Recompression and Adjunctive Therapy for Decompression Illness: A Systematic Review of Randomized Controlled Trials

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INTRODUCTION: Decompression illness (DCI) is caused by bubble formation in the blood or tissues after a reduction in ambient pressure. Clinically, DCI may range from a trivial illness to paralysis, loss of consciousness, cardiovascular collapse, and death. Recompression is the universally accepted standard for the treatment of DCI. When recompression is delayed, a number of strategies have been suggested to improve the outcome. We examined the effectiveness and safety of both recompression and adjunctive therapies in the treatment of DCI.

METHODS: We searched CENTRAL (Cochrane Central Register of Controlled Trials) (The Cochrane Library 2009, Issue 2); MEDLINE (Medical Literature Analysis and Retrieval System Online) (1966 to July 2009); CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to July 2009); EMBASE (Excerpta Medica Database) (1980 to July 2009); the Database of Randomized Controlled Trials (RCTs) in Hyperbaric Medicine (July 2009); and hand-searched journals and texts. We included RCTs that compared the effect of any recompression schedule or adjunctive therapy with a standard recompression schedule and applied no language restrictions. Three authors extracted the data independently. We assessed each trial for internal validity and resolved differences by discussion. Data were entered into RevMan 5.0 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

RESULTS: Two RCTs satisfied the inclusion criteria. Pooling of data was not possible. In one study, there was no evidence of improved effectiveness with the addition of a nonsteroidal antiinflammatory drug to routine recompression therapy (at 6 weeks: relative risk 1.04, 95% confidence interval [CI]: 0.90–1.20, P = 0.58), but there was a reduction in the number of recompression treatments required when tenoxicam was added (P = 0.01, 95% CI: 0–1). In the other study, the odds of multiple recompressions were lower with a helium and oxygen (heliox) table compared with an oxygen treatment table (relative risk 0.56, 95% CI: 0.31–1.00, P = 0.05).

DISCUSSION: Recompression therapy is the standard for treatment of DCI, but there is no RCT evidence. The addition of a nonsteroidal antiinflammatory drug (tenoxicam) or the use of heliox may reduce the number of recompressions required, but neither improves the odds of recovery. The application of either of these strategies may be justified. The modest number of patients studied demands a cautious interpretation. Benefits may be largely economic, and an economic analysis should be undertaken. There is a case for large randomized trials of high methodological rigor to define any benefit from the use of different breathing gases and pressure profiles during recompression. (Anesth Analg 2010;X:●●●–●●●)
inert gas out of bubbles down a steep diffusion gradient as well as to deliver a greatly increased PO$_2$ to the tissues. At the same time, the volume of those bubbles is directly reduced in accordance with Boyle law (volume of a given mass of gas is inversely proportional to the ambient pressure). Typically, treatments involve pressurization to between 2 and 6 atmospheres absolute (ATA) (203–608 kPa), for periods ranging from 2 hours to several days. The optimal treatment strategy for differing clinical presentations has not been determined. However, by far, the most frequently used regimen is the United States Navy Treatment Table 6: a 2.8 ATA (284 kPa) maximal pressure, 100% oxygen breathing schedule lasting 4 hours and 45 minutes.\(^4\)

A review of the effectiveness of the United States Navy oxygen treatment tables suggests complete relief of symptoms in 50% to 98% of individuals, apparently depending on the severity of illness and period of time that has elapsed between development of DCI and recompression.\(^5\) In addition, a number of “first aid” and adjunctive therapies have been applied in the hope of improving rates of complete resolution.

The most important target tissues for DCI are the central nervous system and the musculoskeletal system, with musculoskeletal pain being the most common symptom in the early series. More recently, it has been suggested that constitutional symptoms similar to those experienced during viral illness may be a manifestation of DCI.\(^2,6\) Without an objective method of determining whether symptoms are caused by bubble formation, mild symptoms will sometimes result in misdiagnosis. The annual incidence of DCI is not clear but probably varies widely, from low (perhaps 1 in 10,000 dives)\(^7\) among trained recreational divers to high but severe DCI leading to permanent disability or death.\(^8\) Severe illness is now uncommon in the developed world, but severe DCI leading to permanent disability or death remains a significant problem for poorly trained indigenous commercial divers in the developing world.\(^2,3\) In one prospective study, 94.4% of divers reported ever having DCI and 10% had residual signs of spinal injury. Mortality was estimated at 4% of indigenous divers per year in another group.\(^9,10\)

The objective of this review was to examine the effectiveness and safety of both recompression and adjunctive therapies in the treatment of DCI. Further details can be found in the full review, published in The Cochrane Database of Systematic Reviews.\(^11\) We assessed effectiveness by using a number of clinically important outcomes, including mortality, residual functional disability, and severity scoring systems.

**METHODS**

It was our intention to include and review all randomized controlled trials (RCTs) and quasi-RCTs that examined the effectiveness and safety of therapy for DCI. We defined DCI as any symptom or sign arising after breathing compressed gas (including brief exposures such as during submarine escape training) and assessed clinically as likely to represent bubble injury. We excluded participants who had other causes of AGE (e.g., iatrogenic) and included patients of any age or sex with DCI.

We accepted trials comparing interventions that included recompression or an adjunctive therapy of interest (vide infra), compared with a standard therapeutic regimen such as the United States Navy Treatment Table 6. Adjunctive therapies of interest were the administration of IV or oral fluids, corticosteroids, anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), sodium channel blockers such as lidocaine, or benzodiazepines such as diazepam.

We predetermined the following clinically important outcomes and only included studies that reported at least 1 of these: mortality, severe functional disability, complete recovery rate, a functional recovery scale score, the number of recompressions required, time taken to complete recovery or return to diving, and any assessment of the activities of daily living or quality of life. We also examined any reported adverse effects of therapy.

Specific search strategies were developed to identify eligible reports from database inception to July 2009 in MEDLINE (Medical Literature Analysis and Retrieval System Online), EMBASE, CENTRAL (the Cochrane Central Register of Controlled Trials), and DORCTIHM (the Database of Randomized Controlled Trials in Hyperbaric Medicine). The latter is a specifically targeted database of clinical evidence in the field (http://www.hboevidence.com).

Medical subject headings and main key words used were “decompression sickness,” “air embolism,” “diving,” “decompression,” “hyperbaric oxygenation,” and “recompression,” with variants of the main key words and free text terms also applied. No restrictions to language were applied. Relevant hyperbaric textbooks, journals, and conference proceedings were hand searched. Experts in the field were contacted for published, unpublished, and continuing RCTs. We also sought additional trials from the citations within obtained articles.

Each reviewer independently assessed the electronic search results and selected potentially relevant studies. Disagreements were settled by examination of the full article and consensus. To assess methodological quality and detect potential sources of bias, we used the risk of bias table in the Review Manager (RevMan) computer program, Version 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). To allow an intention-to-treat analysis, we extracted the data reflecting the original allocation group where possible.

For proportions (dichotomous outcomes), we calculated relative risk (RR) with 95% confidence intervals (CIs). All analyses were made on an intention-to-treat basis where possible; where not possible, this is clearly stated. Where the 95% CI for the absolute risk difference did not cross 0, we calculated the number needed to treat (NNT) from the standard recompression event rate and the experimental group rate. The 95% CI was calculated from the 95% CI for the absolute risk difference.

Where appropriate, we intended to perform sensitivity analyses for missing data by comparing best and worst case scenarios at discharge and 6 weeks. If there were appropriate data, we had also planned to consider subgroup analysis based on subtype of DCI (mild DCS, severe DCS, and AGE); severity grade; gas burden; and the time that elapsed between completion of last dive and treatment.
RESULTS
The Included Studies
We identified 14 publications describing the use of recompression or adjunctive therapy for the treatment of DCI. Initial examination confirmed that 6 were investigations concerning divers but for problems other than DCI, 2 were reviews without new data, 1 was a comparative trial with retrospective reviews without new data, 1 was a treatment guideline, 1 was a comparative trial with retrospective reviews without new data, and 1 was a treatment guideline. One proposed the investigation of helium-oxygen mixtures have been abandoned at the time of writing. Two were reviews without new data.

We are aware of 2 planned RCTs but believe that both have been abandoned at the time of writing. One proposed the investigation of helium-oxygen mixtures versus oxygen-only recompression and one of a planned (and subsequently abandoned) trial. These reports were excluded, leaving 2 publications of possible randomized comparative trials. After appraisal of the full reports, we included both of these trials.

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In the study by Bennett et al., 180 participants presenting for management of DCI (excluding AGE) were randomized to either routine recompression therapy or routine recompression therapy with the addition of an NSAID (tenoxicam). The randomization schedule stratified those enrolled into 5 groups by disease severity using a clinical scoring system described by Bond et al. The recompression schedule was not specified in the protocol but prescribed at the discretion of the treating physician. In the active therapy arm, tenoxicam 20 mg was administered at the first air break during recompression and daily for 7 days, whereas in the control arm, a placebo medication was administered on the same schedule. Ninety-one percent of participants enrolled reached final analysis. The primary outcome variable in this trial was complete recovery of symptoms and signs measured at completion of recompression therapy and at 6 weeks. Any mortality was also reported, as was the number of recompression sessions administered. This study involved allocation concealment and blinding of all participants, treating staff, and outcome evaluators. Analysis was by intention to treat (Table 1).

In the study by Drewry and Gorman, 88 patients with a clinical diagnosis of DCI were randomized to an initial recompression schedule of 100% oxygen breathing at 2.8 ATA or a schedule involving breathing 50% oxygen with 50% helium at 2.8 ATA. Both initial schedules could be modified if response was estimated to be <80% clinical resolution. No details were given as to how an 80% improvement was calculated. This trial has been reported as interim results in an abstract only, and appraisal is hampered by a lack of methodological detail. Eighteen of the 88 participants (20.5%) were withdrawn from analysis because of failure to meet entry criteria (retrospectively) or because of protocol violations, and a further 14 had not been reached for final follow-up. Therefore, only 56 participants (64% of those enrolled) had outcomes reported in the abstract, and this significantly reduces confidence in the published results. Furthermore, although allocation was by sealed envelope, the operational staff members were aware of allocation during therapy, and blinding of any treating physician present must have been very difficult because of voice timbre changes when breathing the different compressed gases in the 2 groups. This trial reported the proportion of participants who required multiple compressions before discharge. There were multiple violations of protocol, and it may not have been analyzed by intention to treat (Table 1).

Clinical Outcomes
Data from the 2 included studies could not be pooled and are described individually.

Bennett et al. reported no difference in the proportion of participants who completely recovered by discharge or 6 weeks later (at discharge: 59 of 84 [70%] in the placebo group versus 53 of 84 [63%] in the tenoxicam group; at 6 weeks: 64 of 80 [80%] with placebo versus 70 of 84 [83%] with tenoxicam). Analysis in this review confirmed the lack of a significant effect (at discharge: RR for recovery with...
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Table 2. Results Stratified by Presentation Severity from Bennett

<table>
<thead>
<tr>
<th>Presentation Grade</th>
<th>Placebo/Tenoxicam</th>
<th>Placebo (%)</th>
<th>Tenoxicam (%)</th>
<th>P (95% CI for Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>Discharge status &gt;1</td>
<td>2 (13%)</td>
<td>5 (28%)</td>
<td>0.41 (41% to 15%)</td>
</tr>
<tr>
<td>15 (8.3)/19 (10.6)</td>
<td>Final health status &gt;1</td>
<td>2 (14%)</td>
<td>1 (5%)</td>
<td>0.57 (36% to 29%)</td>
</tr>
<tr>
<td></td>
<td>Median treatments (range)</td>
<td>3 (1–3)</td>
<td>2 (1–4)</td>
<td>0.20 (0–1)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 treatments</td>
<td>8 (53%)</td>
<td>4 (21%)</td>
<td>0.08 (60% to 1%)</td>
</tr>
<tr>
<td>Two</td>
<td>Discharge status &gt;1</td>
<td>10 (22%)</td>
<td>20 (36%)</td>
<td>0.19 (31% to 4%)</td>
</tr>
<tr>
<td>57 (31.7)/56 (31.1)</td>
<td>Final health status &gt;1</td>
<td>10 (20%)</td>
<td>11 (20%)</td>
<td>0.92 (15% to 16%)</td>
</tr>
<tr>
<td></td>
<td>Median treatments (range)</td>
<td>3 (1–6)</td>
<td>2 (1–6)</td>
<td>0.15 (0–1)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 treatments</td>
<td>34 (60%)</td>
<td>25 (45%)</td>
<td>0.19 (48% to 18%)</td>
</tr>
<tr>
<td>Three, four, and five</td>
<td>Discharge status &gt;1</td>
<td>9 (53%)</td>
<td>5 (36%)</td>
<td>0.27 (37% to 21%)</td>
</tr>
<tr>
<td>18 (9.9)/15 (8.3)</td>
<td>Final health status &gt;1</td>
<td>4 (31%)</td>
<td>2 (14%)</td>
<td>0.66 (37% to 21%)</td>
</tr>
<tr>
<td></td>
<td>Median treatments (range)</td>
<td>4 (1–8)</td>
<td>2 (1–6)</td>
<td>0.14 (0–2)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 treatments</td>
<td>13 (72%)</td>
<td>6 (43%)</td>
<td>0.15 (58% to 5%)</td>
</tr>
</tbody>
</table>

Severity grade at presentation (from Bond et al.26): One: Musculoskeletal pain, rash, itching; Two: pain and/or mild neurologic symptoms; Three: Severe pain and/or neurologic symptoms and signs; Four: Clear neurologic symptoms with objective signs such as numbness, weakness, dyscoordination, and cognitive dysfunction; Five: Severe neurologic dysfunction such as marked weakness/paralysis, speech or visual disturbance, and bladder or bowel dysfunction.

Discharge status >1 indicates less than complete recovery.

tenoxicam 0.90, 95% CI: 0.72–1.11, P = 0.33; at 6 weeks: RR for recovery with tenoxicam 1.04, 95% CI: 0.90–1.20, P = 0.58). However, this result was sensitive to the outcome of those lost to follow-up, with a best case analysis suggesting that the chance of recovering completely at 6 weeks was improved with tenoxicam (RR 1.19, 95% CI: 1.01–1.39, P = 0.03). There were no fatalities in either group.

This trial reported a difference in the number of recompressions required to reach these outcomes. The placebo group required a median of 3 treatments (range, 1–8), whereas the tenoxicam group required a median of 2 treatments (range, 1–6), and this difference was statistically significant (P = 0.01, 95% CI: 0–1). Analysis of the proportion of participants requiring >2 recompressions suggested a benefit from the administration of tenoxicam (55 of 90 [61%] of the placebo group versus 35 of 90 [39%] of the tenoxicam group). The RR for requiring >2 treatments with tenoxicam was 0.65 (95% CI: 0.48–0.88, P = 0.005). Overall, this analysis suggested a need to treat 5 patients to reduce the number of compressions required for 1 extra patient (NNT 5, 95% CI: 3–18). A stratified analysis by the severity grade of DCI on presentation suggested that this treatment effect was present across the range of severities tested, although no individual group reached statistical significance (Table 2).

Drewry and Gorman25 reported that the proportion of participants requiring multiple recompressions was significantly smaller in the oxygen and helium group (heliox) (9 of 25 [36%] versus 20 of 31 [65%], P = 0.03). Analysis in this review suggests that the chance of multiple recompressions may indeed be lower with heliox (RR 0.56, 95% CI: 0.31–1.00, P = 0.05) and suggests the need to treat 4 individuals with heliox and oxygen to have 1 extra individual requiring only a single recompression (NNT = 4, 95% CI: 2–31).

Adverse events were reported by Bennett et al.24 Six participants had problems during initial recompression, 3 (1 receiving tenoxicam and 2 receiving placebo) complained of aural barotrauma, 2 (1 taking tenoxicam and 1 taking placebo) developed premonitory signs of cerebral oxygen toxicity, and 1 tenoxicam patient complained of nausea not resolved by removal from oxygen breathing at depth (pressure).

DISCUSSION

We did not find RCT evidence to support or refute the effectiveness of recompression versus no recompression for the management of DCI. Recompression is a universally accepted therapy for DCI and for ethical reasons is not likely to be compared with sham therapy in any future study.

The 2 trials involved a modest total of 268 patients. The trial by Drewry and Gorman was never reported at completion and was probably underpowered to find a significant difference in clinical outcome between the 2 recompression strategies. We understand the trial was abandoned shortly after the 1994 report because of continuing protocol violations (personal communication). There is a substantial difference in the reported number of participants enrolled in each arm of this study (25 vs 31) and although this may have been due to chance, the potential for selection bias is high. One further problem is that only the proportion of participants who required multiple recompressions were reported in this trial, and there were no available data on the clinical health outcomes at any stage. The trial by Bennett et al. was powered to detect a 10% improvement in the proportion of participants with complete resolution (30% placebo versus 20% tenoxicam), and we can be reasonably confident that the addition of tenoxicam to recompression does not result in an improvement in the effectiveness of therapy.

The effect of the heliox regimen used in the trial by Drewry and Gorman should be interpreted carefully in the context of local patient characteristics and the expected rate of multiple recompressions. Although calculation of the NNT with heliox using the control event rate in this study (65% required multiple compression) is 4, this estimate is sensitive to the actual event rate in practice at other treatment facilities. For example, data from 591 cases of DCI reported by the Divers Alert Network4 in 2001 suggest that the proportion receiving multiple compressions is 50%. Using this as the control event rate and an RR of 0.56 as our best estimate would suggest that the addition of heliox has no effect on reducing the number of multiple recompressions.
estimate of effect suggests an NNT of 5. Also of potential importance is the consideration that the treatment protocol was quite complex for both arms of the study and ultimately allowed for the participants to enter a saturation treatment that may have lasted for several days. This mode of treatment is unlikely to be a realistic prospect for most treatment facilities, and the clinical relevance of this finding is therefore unclear. Any benefit for heliox treatment may have arisen from an interaction with complex, long, high pressure recompression protocols that might be impractical in many hyperbaric units.

Similar considerations concerning the interpretation of NNT apply to the trial by Bennett et al., particularly because world practice suggests that single recompression therapy remains common. Once again using the Divers Alert Network4 data for comparison and the effect estimate from the study (RR 0.65), only 30% of patients received >2 compressions, suggesting an NNT with tenoxicam of 10 rather than 5.

An informal economic analysis based on the results of the trial by Bennett et al., using cost data from a contemporaneous cost analysis in the main contributing hyperbaric facility involved,27 and the current cost of similar NSAIDs in Australia,28 suggests there may be modest cost savings associated with the administration of tenoxicam as an adjunctive measure for DCI. These data suggest a savings of $AUD 720 (one session of hyperbaric oxygen therapy for DCI) for every 5 patients treated for DCI.

One problem with research in this area is diagnostic uncertainty. There are no reliable diagnostic tests or clinical criteria for DCI, and it is likely that all clinical trials will be contaminated by an unknown number of “cases” that do not, in fact, involve a bubble-related injury. This is particularly likely for those with mild, nonspecific symptoms. In general, this will tend to minimize the apparent effectiveness of specific, targeted therapies while magnifying the effect of symptomatic therapies with broad, nonspecific activity. For the clinician, the studies included here are both pragmatic and likely to reflect the efficacy of interventions in the presence of this diagnostic uncertainty.

There are a few uncommon major adverse effects of both recompression (pulmonary barotrauma, acute cerebral oxygen toxicity, or death related to chamber fire) and short courses of NSAIDs (renal failure or significant gastric bleeding), and although these are all rare enough not to be seen in the trials included in this review, they should be included in consideration of any benefit of these therapies. In practice, it is likely that a beneficial effect strong enough to be clearly identified in clinical trials would overwhelm the consideration of such rare events.

CONCLUSIONS
Recompression therapy is universally accepted as standard practice for the treatment of DCI. Although there is considerable evidence for good outcomes after recompression, this practice is not based on any RCT evidence. There is some evidence that the addition of an NSAID reduces the number of recompression sessions required to treat DCI, but no evidence for an improvement in the rate of complete recovery. Similarly, there is some evidence that helium and oxygen breathing during recompression may reduce recompression requirements, although the methodological problems in the single trial examining the use of helium and oxygen breathing are noted. The use of an NSAID is likely to be associated with a modest reduction in the cost of therapy. Thus, the application of either of these strategies may be justified. The small number of studies and the modest number of patients included in this review demand a cautious interpretation. Given the lack of evidence for improved outcomes, benefits may be largely economic, and an economic analysis should be undertaken.

It is unlikely that any comparison of recompression therapy against a sham alternative can be justified. There is, however, a strong case for large RCTs of high methodological rigor to define the extent of benefit (if any) from the use of different breathing gases and pressure profiles during recompression therapy. Specifically, information is required on the subset of disease severity that may justify the use of complex and expensive treatment tables.

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