Cochrane corner

Recompression and adjunctive therapy for decompression illness: a systematic review of randomised controlled trials

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Key words
Decompression illness, decompression sickness, recompression, non-steroidal anti-inflammatories, helium, Cochrane library

Abstract
(Bennett M, Mitchell SJ, Lehm JP, Wasiak J. Recompression and adjunctive therapy for decompression illness: a systematic review of randomised controlled trials. *Diving and Hyperbaric Medicine*. 2008; 38: 91-8.)
Introduction: Decompression illness (DCI) results from bubble formation in the blood or tissues following the breathing of compressed gas. Recompression is the universally accepted standard for the treatment of DCI, but a number of strategies have been suggested in order to improve the outcome.
Methods: We performed a systematic search of the literature in December 2007 for randomised controlled trials of DCI therapy, and made an analysis of pre-determined clinical outcomes.
Results: Two randomised controlled trials satisfied the inclusion criteria. Pooling of data was not possible. There was a reduction in the number of compressions required with the addition of the non-steroidal anti-inflammatory drug (NSAID) tenoxicam to routine recompression therapy (P = 0.01) but no evidence of improved effectiveness (relative risk (RR) of residual symptoms 1.04, P = 0.58). The risk of multiple recompressions was lower with heliox than with an oxygen treatment table (RR 0.56, 95% CI 0.31 to 1.00, P = 0.05).
Conclusions: There is no randomised evidence concerning the effectiveness of recompression for DCI. Either the addition of an NSAID or the use of heliox may reduce the number of recompressions required, but neither strategy is shown to improve the chance of recovery. The application of either of these strategies may be justified. The modest number of patients studied demands a cautious interpretation of the findings. There is a case for large randomised trials of high methodological rigour in order to define any benefit from the use of different breathing gases during recompression therapy.

Introduction

Decompression illness (DCI) is the term given to the clinical manifestations of bubble formation in the blood or tissues following a reduction in ambient pressure.[1] DCI most commonly occurs in relation to compressed-air or mixed-gas diving, but it may also arise in aviators following rapid ascent to altitude or cabin decompression, and in astronauts participating in 'space walks'.[2] The term covers two different problems: arterial gas embolism (AGE) caused by the presence of bubbles in the arterial blood vessels; and decompression sickness (DCS) caused by bubbles in the veins and tissues.

Bubbles may cause harm through mechanical distortion of tissues, vascular obstruction or stimulation of immune mechanisms that lead to tissue oedema, haemoconcentration and hypoxia. Arterial blood vessels are a particular target for damage by intravascular bubbles, where they disrupt the luminal surfactant layers, damage the endothelium and stimulate intraluminal blood elements (particularly white blood cells and platelets) to clump together and obstruct the flow within the vessel. Secondary interactions between these elements result in leaking vessels and further reductions to flow.[3–5]

The two pathological entities (AGE and DCS) are difficult to distinguish clinically and are treated with similar strategies.[6,7] It is, therefore, accepted practice to make the clinical diagnosis of 'DCI' in the understanding that one or both of the two pathologies may be operating. We will use the generic term DCI in this review except when we refer to the specific pathological mechanisms that cause AGE and DCS.

Clinically, DCI has many possible manifestations, from mild, vague constitutional symptoms to sudden loss of consciousness, paralysis or death.[8] The most important

target tissues are the central nervous system and the musculoskeletal system, with musculoskeletal pain and constitutional symptoms similar to those of a viral illness being the most common complaints.[8,9] Without an objective method of determining whether they are the result of bubble formation, these mild symptoms will sometimes result in misdiagnosis.

Severe DCI is now uncommon in the developed world, but remains a significant problem for poorly trained indigenous commercial divers around the developing world.[2,8] While the overall incidence of DCI has not been determined, a number of studies have reported both incidence and prevalence of DCI and its long-term effects in individual diving populations. In one prospective study involving indigenous sea harvesters the proportion of divers who reported ever having DCI was 94.4%, and 10% had residual signs of spinal injury. In another indigenous group mortality was estimated at four per cent of divers per year.[10,11] In contrast, the incidence of DCI among recreational divers in Canada was estimated at 0.01% of dives over 14 months.[12]

The historical development of recompression treatment tables is well described by Moon and Gorman.[2] Pol and Wattelle first proposed recompression (whilst breathing air) as a treatment for DCI in 1854, but it was not used systematically in practice until 1896 during the construction of the Hudson River Tunnel.[13] The mortality of 25% of cases recorded prior to institution of recompression was dramatically reduced with recompression. In a subsequent tunnel project in New York, Keays demonstrated a symptom recurrence rate of 13.7% in workers with DCI who were treated with analgesics and 'stimulants' compared to 0.5% in those treated with recompression.[14] Recompression on air became the standard therapy for DCI until the introduction of 100% oxygen breathing during recompression in 1944, following the work of Yarbrough and Behnke.[15]

Many variations of recompression on oxygen, air and helium–oxygen mixtures have been proposed and used since; and indeed, recompression in some form remains the mainstay of treatment for DCI. 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 elapsed between development of DCI and recompression.[16] In addition, a number of 'first aid' and adjunctive therapies have been applied in the hope of improving rates of complete resolution. Strategies suggested include the maintenance of a horizontal position (to discourage distribution of intravascular bubbles into the cerebral circulation), 100% oxygen administration at one atmosphere and the administration of intravenous or oral fluids, corticosteroids, anticoagulants, non-steroidal anti-inflammatory drugs, lignocaine and diazepam. These strategies (and others) have been summarized by Moon.[2] It is important to consider that any one of these strategies might modify the outcome of DCS and AGE in either direction.

Recompression whilst breathing nitrogen-free mixtures greatly enhances the movement of nitrogen out of any bubbles down a steep diffusion gradient as well as directly reducing bubble volume in accordance with Boyle's Law. The use of high oxygen fractions also delivers a greatly increased partial pressure of oxygen to the tissues. Typically, recompression involves pressurization to between two and six atmospheres absolute (ATA; 203–608 kPa), for periods between two hours and several days. The optimal treatment strategy for differing clinical presentations is not apparent. By far the most commonly used regimen is the United States Navy Treatment Table 6 (USN T6), which involves compression to 2.8 ATA (284 kPa) breathing 100% oxygen, followed by a stepwise decompression over four hours and 45 minutes.[17]

We present here a systematic review of the randomised clinical evidence for the benefits and harms of all therapies used in the treatment of DCI.

Methods

It was our intention to identify and review all randomised and quasi-randomised controlled trials concerning the use of any strategy for the treatment of DCI. Specific search strategies were developed to identify eligible reports from database inception to August 2005 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). All searches were re-run in December 2007, and a further search was conducted of the Rubicon Foundation database (http://www.rubicon-foundation.org) at that time, but no further studies were identified.

Medical subject headings (MeSH) and main key words used were 'decompression sickness', 'embolism, air' and 'hyperbaric oxygenation' with variants of the main key words, free-text terms and all adjuvant treatments mentioned above also applied. No restrictions to language were made. Relevant hyperbaric textbooks, journals and conference proceedings were searched by hand. Experts in the field were contacted for published, unpublished and ongoing randomised controlled trials (RCTs). Additional trials were sought 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: mortality at any time, severe functional disability rate, complete recovery rate, a functional recovery scale (e.g., Royal New Zealand Navy (RNZN) Recovery Score,[18] Dick and Massey Score,[19] functional outcome scale[20]) or the number of recompression sessions required. We also recorded the time to complete recovery, time to return to diving, activities of daily living (ADL), quality of life and any adverse events following therapy when reported.

Two reviewers independently assessed the electronic search results and selected potentially relevant studies. Disagreements were settled by examination of the full paper and the opinion of a third reviewer. To assess methodological quality and detect potential sources of bias we followed the guidelines set out by the Cochrane Handbook for Systematic Reviews of Interventions.[21] This method assesses factors related to applicability of findings, validity of individual studies, and study design characteristics such as double blinding and adherence. Two authors independently assessed the methodological quality of the selected studies and ranked allocation concealment as A (adequate), B (unclear), C (inadequate) or D (not used). We resolved any differences of opinion by discussion and consensus.

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 mortality at a single time point, 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.

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 zero, 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 of the risk difference between the groups.

We performed sensitivity analyses for missing data from the outcome 'complete recovery' in Bennett et al[22] by comparing best- and worst-case scenarios at discharge and six weeks. For the best-case scenario, all missing patients in the tenoxicam group were assumed to have recovered while all those in the placebo group were assumed not to have recovered. The worst-case scenario employed the reverse assumptions. We also considered subgroup analysis based on the subtype of DCI, severity grade, gas burden, time elapsed between completion of last dive and treatment, time elapsed from appearance of first symptom to treatment and dose of oxygen received.

Results

THE INCLUDED STUDIES

We identified 14 publications apparently dealing with the use of recompression or adjunctive therapy for the treatment of DCI. Initial examination confirmed six were investigations concerning divers, but for problems other than DCI; two were reviews without new data; one was a treatment guideline; one was a comparative trial with retrospective controls; one was a trial involving pre-dive treatment with a range of adjunctive agents intended to modify any subsequent illness; and one was a report of a planned trial. These reports were excluded, leaving two publications of possible randomised comparative trials. After appraisal of the full reports we included both these trials.[22,23] No new studies were found on a repeat search in December 2007.

The authors were aware of two planned RCTs but both have been abandoned at the time of writing the original review. One proposed the investigation of helium–oxygen mixtures versus oxygen-only recompression (Jonas Hink, personal communication, 2006), whilst the other proposed investigation of the addition of intravenous lignocaine to recompression for serious neurological DCI (James Francis, personal communication, 2004). The details of the two included trials are summarised in Table 1.

Bennett et al enrolled 180 divers presenting for management of DCI, but excluded those with a clinical diagnosis of AGE. They were randomised with stratification by clinical disease severity to either routine recompression therapy or routine recompression therapy with the addition of a non-steroidal anti-inflammatory drug (tenoxicam). In the active therapy arm, tenoxicam 20 mg was administered at the first air break during the first recompression treatment and daily for seven days, while in the control arm a placebo medication was administered on the same schedule. In the absence of complete recovery with the initial treatment, once-daily recompressions were continued until either complete recovery was achieved, or there was no sustained improvement over two consecutive days. Results were given for 164 of the 180 enrolled (91%). This trial reported complete recovery of symptoms and signs measured at completion of recompression therapy and at six weeks, mortality and the number of recompressions administered.

Drewry et al enrolled 88 patients with a clinical diagnosis of DCI and randomised them either to an initial recompression schedule of 100% oxygen breathing at 2.8 ATA or to a schedule involving breathing 50% oxygen with 50% helium at 2.8 ATA. Both arms had treatment option available if initial response was less than 80% improvement. This study utilised the same criteria for cessation of repeat recompression therapy as outlined above for the Bennett et al trial. This trial has been reported to date only in the form of interim results in an abstract. Eighteen of the 88 participants (20.5%) were withdrawn from analysis due to failure to meet entry criteria (retrospectively) or because of protocol violations, and a further 14 had not reached final follow up. Therefore only 56 participants (64% of those enrolled) had outcomes reported in the abstract. This trial reported the proportion of participants who required multiple compressions prior to discharge.

Table 1. Summary of included trials

Study	Methods	Participants	Interventions	Outcomes	Notes
Drewry 1994	Randomised controlled trial with blinding of investigators and participants. Sealed envelope method with stratification for presentation within 48 hours or at more than 48 hours.	88 patients presenting with DCI (clinical diagnosis) and requiring recompression therapy.	Control: intravenous hydration and recompression breathing 100% oxygen at 18 msw. • If 80% or more improvement after 45 minutes, then USN T6 recompression table is completed. • If less than 80% improvement, then proceed to 30 msw breathing 50% oxygen with 50% nitrogen. Complex aglorithm if there is still poor response, with maximum compression to 50 msw. Active: intravenous hydration and recompression breathing 50% oxygen and 50% helium at 18 msw. • If 80% or more improvement after 45 minutes, then completed 18 msw maximum depth table breathing heliox with no air breaks. • If less than 80% improvement, then proceed to 30 msw breathing 50% oxygen with 50% helium. Complex algorithm if there is still poor response, with maximum compression to 50 msw breathing 20% oxygen and 80% helium.	Proportion of participants requiring second recompression due to incomplete resolution of clinical symptoms or signs.	Trial only reported in an abstract. Not analysed by intention to treat (18 withdrawals due to protocol violations and 14 others with results not reported). The first report did not give any results. Allocation concealment: B
Bennett 2003	Randomised controlled trial with blinding of all participants. Analysed by intention to treat. Central computer code held by pharmacy.	180 participants with 'clinical' DCI (excluding CAGE) from three centres.	Control: recompression on physician choice table (88% had USN T6), placebo medication at first air break and daily for seven days, recompression as clinically indicated to plateau of symptoms or complete resolution plus one further treatment. Active: as above, but active medication with tenoxicam 20 mg per dose.	Death; outcome functional score 1 to 4; number of compression cycles required.	High methodological quality. Allocation concealment: A

CLINICAL OUTCOMES

Major clinical outcomes of interest are summarised in Table 2 and those of greatest interest are discussed below. Data from the two included studies could not be pooled and are described individually.

Bennett et al reported no significant difference in the proportion of participants who were completely recovered at discharge or six weeks later (80% with placebo versus 83% with tenoxicam at six weeks).[22] However, the result at six weeks was sensitive to the outcome of those lost to follow up, with a best-case analysis suggesting that the chance of recovering completely at six weeks was improved with tenoxicam: relative risk (RR) of complete recovery with tenoxicam was 1.19, 95% CI 1.01 to 1.39, P = 0.03.

In order to achieve these outcomes, the placebo group required a median of three recompression treatments (range one to eight), while the tenoxicam group required a median of two treatments (range one to six), and this difference was reported as significant (P = 0.01, 95% CI 0 to 1). Of the placebo group, 61% required more than two treatments whilst only 39% of the treatment group required more than two treatments. A stratified analysis by the severity grade of DCI on presentation suggested this treatment effect was present across the range of severities tested. The analysis suggested a need to treat five patients in order to reduce the number of compressions required by one patient (NNT 5, 95% CI 3 to 18).

Drewry et al similarly reported that the proportion of participants requiring multiple recompressions was significantly smaller in the oxygen and helium group (heliox) versus the oxygen group (36% versus 65%, P = 0.03).[23] Analysis in this review suggests the chance of multiple recompressions may be lower with heliox (RR 0.56, 95% CI 0.31 to 1.00, P = 0.05) and that we would need to treat four individuals with helium and oxygen in order to have one extra individual requiring only a single recompression (NNT = 4, 95% CI 2 to 31).

Adverse events were reported by Bennett et al. Six participants had problems during initial recompression: three (one on tenoxicam, two on placebo) complained of aural barotrauma, two (one on tenoxicam, one on placebo) developed premonitory signs of cerebral oxygen toxicity and one tenoxicam patient complained of nausea not resolved by removal from oxygen breathing at depth (pressure).

Discussion

This review has included data from two trials investigating the treatment of DCI, and we believe these represent all randomised human trials in this area, both published and unpublished, at the time of searching the databases. Unsurprisingly, we did not find randomised controlled trial 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 most unlikely to be subject to randomised investigation against sham therapy in the future. The two trials considered in this review involved a modest total of 268 patients and investigated alternative recompression strategies [23] and an NSAID drug as an adjunctive therapy to standard recompression [22] respectively. The results could not therefore be pooled for meta-analysis.

The Drewry et al trial was never reported at completion and is probably underpowered to find a clinically significant difference between the two recompression strategies.

Table 2
Summary of outcomes (RR = relative risk, MD = median difference, *statistically significant outcomes)

Study; outcome measure	N		Outcome rate		Efficacy data#	95% CI	P-value	NNT
Drewry 1994	**Heliox**	**Nitrox**	**Heliox**	**Nitrox**	**RR**			
Need for more than one recompression	25	31	9 (36%)	20 (65%)	*0.56	0.31 to 1.00	0.05	4 [2 to 31]
Bennett 2003	**Tenoxicam**	**Placebo**	**Tenoxicam**	**Placebo**	**RR**			
Complete recovery at discharge	84	84	53 (63%)	59 (70%)	0.90	0.72 to 1.11	0.33	
Complete recovery at 6 weeks	84	80	70 (83%)	64 (80%)	1.04	0.90 to 1.20	0.58	
Need for more than one recompression	90	90	35 (39%)	55 (61%)	*0.65	0.48 to 0.88	0.005	5 [3 to 18]
Median number of treatments administered	90	90	2 (1–6)	3 (1–8)	MD 1	0 to 1	0.01	

There is a significant difference in the reported number of participants enrolled in each arm of this study (25 versus 31) and although this may be due to chance we consider the potential for selection bias to be high. While a preliminary 1992 report on trial methodology described a sequential analysis strategy with a stopping rule based on a significant difference in health outcome between the groups at one month (P = 0.05 or less), it is not clear this rule was invoked.[24] Indeed, only the proportion of participants who required multiple recompressions was reported and there are no data describing health outcomes at any stage.

The proportion of participants requiring more than one recompression was significantly reduced by the use of an aggressive helium and oxygen recompression regimen in which treatment depth and duration was determined by symptom response.[23] The impact of the heliox regimen should be interpreted carefully in the context of local patient characteristics and the expected rate of multiple compressions. While calculation of the NNT with heliox using the control event rate in this study (65% required multiple compression) is four, 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 Network in 2001 suggested the proportion receiving multiple compressions was 50%.[17] Using this as the control event rate and an RR of 0.56 as our best estimate of effect suggests an NNT of five.

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. More information is needed on the actual profiles used and the clinical outcome of participants in this trial. This is important because it is possible that any benefit for heliox treatment may have arisen from an interaction with complex, long, high-pressure recompression protocols that might be impractical in many facilities.

The trial by Bennett et al was powered to detect a difference between groups in the proportion of participants with incomplete resolution (30% placebo versus 20% tenoxicam predicted). We can therefore be reasonably confident that the addition of tenoxicam to recompression does not in fact result in a clinically significant improvement in the effectiveness of therapy.

The proportion of participants requiring more than two recompressions before discharge was significantly reduced by the addition of the NSAID tenoxicam to a standard recompression treatment. Bennett et al chose the dichotomous outcome 'one or two treatments versus more than two treatments' because the standard practice in many Australasian institutions is to continue recompression treatments until resolution of symptoms plus one further recompression session, or until symptoms plateau for two consecutive recompression sessions. Thus, for many physicians, two recompression sessions is a minimal treatment course. Analysis suggested a modest treatment-sparing effect with an NNT of five patients to reduce the number of recompression treatments required by at least one. Similar considerations concerning the interpretation of NNT apply here, particularly as world practice suggests that single recompression therapy remains common. Once again, using the DAN data for comparison and the effect estimate from the study (RR 0.65), only 30% of patients received more than two compressions, suggesting an NNT with tenoxicam of 10 rather than five.

An informal economic analysis based on the results of Bennett et al[22] and using data from a contemporaneous cost analysis in the main contributing hyperbaric facility, suggests there may be modest cost savings associated with the administration of tenoxicam as an adjunctive measure for DCI.[25] These data suggest a saving of $AUD 720 (one session of HBOT for DCI) for every five patients treated for DCI (95% CI every 3 to 18 patients), whilst the cost of a single week course of tenoxicam is estimated at $AUD 6.50 for each patient.[26]

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 suffer from a bubble-related injury. In general, this will tend to minimize the apparent effectiveness of specific, targeted therapies while magnifying the effect of symptomatic therapies with broad, non-specific activity. The included studies are both pragmatic and likely to reflect the efficacy of interventions in the presence of this diagnostic uncertainty.

There are a few major adverse effects of recompression (pulmonary barotrauma, acute cerebral oxygen toxicity or death related to chamber fire) and short courses of non-steroidal drugs (renal failure or significant gastric bleeding), and while 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. There are, however, a number of more minor complications that may occur commonly and Bennett et al reported six individuals with minor adverse effects.[22] None of the six was withdrawn from therapy.

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.

Conclusions

Recompression therapy is universally accepted as standard

practice for the treatment of DCI. While there is considerable evidence for good outcomes following recompression, this practice is not based on any RCT evidence. There is some evidence that the addition of an NSAID to breathing 100% oxygen during recompression 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, though the methodological problems in the single trial examining the use of helium and oxygen breathing should be 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 numbers of patients included in this review demand a cautious interpretation.

Given the natural history of severe DCI and the well-documented clinical response to recompression, 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 rigour in order 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. The diagnosis and classification of DCI is particularly problematic with the milder forms of the disease. Formal economic analysis is required to quantify the cost benefit of treatment with NSAIDs and heliox. Any future trials would need to consider adequate sample sizes to detect important differences in clinical outcome, careful definition of target cases, appropriate adjunctive therapies and the careful elucidation of any adverse effects.

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Conflicts of interest

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