Strength of evidence in hyperbaric medicine

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What is hyperbaric medicine?

- A therapy in search of a disease (Tibbles, NEJM 1996).

- The therapeutic administration of respirable gases (usually oxygen) at pressures greater than 1 atmosphere.
  - Not topical

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For the authority providing funding, it is appropriate to apply the principles of EBM to assist in allocation of the health budget.

It is very tempting to use EBM as a mantra to justify cost containment objectives.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.
# Levels of Evidence (NHMRC)

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from a systematic review of all relevant randomised controlled trials</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one properly designed randomised controlled trial.</td>
</tr>
<tr>
<td>III-1</td>
<td>Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).</td>
</tr>
<tr>
<td>III-2</td>
<td>Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.</td>
</tr>
<tr>
<td>III-3</td>
<td>Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from case series, either post-treatment or pre- and post-treatment.</td>
</tr>
<tr>
<td>V</td>
<td>Evidence obtained from a single case report.</td>
</tr>
</tbody>
</table>

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Systematic reviews

- Explicit search and appraisal methodology
- Strict design minimises the chance of bias
- Quantitative where randomised evidence exists
- Of relevance to practitioners, researchers and patients

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Summary of meta-analyses

- All being done under the auspices of the Cochrane Collaboration

- Completed:
  - Multiple sclerosis
  - Chronic wounds
  - Traumatic brain injury
  - Thermal burns
  - Acute coronary syndrome
  - Fracture non-union

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Summary of meta-analyses

- Underway
  - Idiopathic Sudden Sensorineural Hearing Loss
  - Sports Injuries and DOMS
  - Enhancement of radiotherapy
  - Radiation tissue injury
  - Decompression illness
  - Headache
  - Stroke
  - Osteomyelitis
  - Intracranial abcess

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## Current approved indications

<table>
<thead>
<tr>
<th>UHMS Approved Indications for Hyperbaric Oxygen Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Air or gas embolism</td>
</tr>
<tr>
<td>2. Carbon monoxide poisoning</td>
</tr>
<tr>
<td>Carbon monoxide poisoning complicated by cyanide poisoning</td>
</tr>
<tr>
<td>3. Clostridial myositis and myonecrosis (gas gangrene)</td>
</tr>
<tr>
<td>4. Crush injury, compartment syndrome and other acute traumatic ischaemias</td>
</tr>
<tr>
<td>5. Decompression sickness</td>
</tr>
<tr>
<td>6. Enhancement of healing in selected problem wounds</td>
</tr>
<tr>
<td>7. Exceptional blood loss (anaemia)</td>
</tr>
<tr>
<td>8. Intracranial abscess</td>
</tr>
<tr>
<td>9. Necrotising soft tissue infections</td>
</tr>
<tr>
<td>10. Osteomyelitis (refractory)</td>
</tr>
<tr>
<td>11. Delayed radiation injury (soft tissue and bony necrosis)</td>
</tr>
<tr>
<td>12. Skin grafts and flaps (compromised)</td>
</tr>
<tr>
<td>13. Thermal burns</td>
</tr>
</tbody>
</table>

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Strength of evidence - three examples

1. Sports injuries
2. Myocardial infarction
3. Chronic wounds

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Example one: Sports injuries
Possible areas of interest

- Crush injury/compartment syndromes
- Acute tissue injuries
- Delayed onset muscle soreness (DOMS)
- Overuse injuries
- Exercise recovery
- Enhanced performance
### Examples of sports injuries

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Acute</th>
<th>Overuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>bone</td>
<td>fracture</td>
<td>stress fracture</td>
</tr>
<tr>
<td>ligament</td>
<td>sprain (tear)</td>
<td>inflammation</td>
</tr>
<tr>
<td>tendon</td>
<td>tear</td>
<td>tendinitis, tendinosis</td>
</tr>
<tr>
<td>skin</td>
<td>laceration</td>
<td>blister</td>
</tr>
<tr>
<td>muscle</td>
<td>strain (tear)</td>
<td>chronic compartment syndrome</td>
</tr>
</tbody>
</table>

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The theoretical basis for HBO in sports injuries
The 3 phases of healing

• inflammatory
• repair
• maturation / remodelling

HBO has effects during the inflammatory and repair phases

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[The effects of hyperbaric oxygen and surgical decompression in experimental compartment syndrome]


METHODS: Twenty rats were divided into four groups as: Control, Fasciotomy, HBO and HBO-Fasciotomy. Rear legs of all animals were strangulated with a tourniquet for 4 hours. Fasciotomy was performed by double incisions. HBO protocol was set as: 6 sessions/day in the first two days, 4 sessions/day in the 3rd and 4th days. The intra-compartmental pressure and leg volume in all groups were measured daily.

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RESULTS: Fasciotomy was more effective than HBO to decrease leg volume and intra-compartmental pressure. The combination of HBO and fasciotomy was more effective than either. The findings of inflammation and necrosis were less in the HBO group when compared with the fasciotomy and HBO-fasciotomy groups.

CONCLUSION: Adjuvant HBO is beneficial in the treatment of compartment syndrome.

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Muscle – acute tears

- Torn rat muscles did not heal better, but increased collagen metabolism in the HBO group (Ishii 1998).
- Stretched rabbits. Functional deficit (percent ankle isometric torque; injured side versus uninjured side) 14.9% in HBO group versus 47.5% in sham, $P = 0.001$ (Best 1998).
A: untreated muscle 7 days after stretch injury showing persistent muscle fiber rupture and retraction from the tendon.

B: HBO-treated muscle 7 days after stretch injury showing less fiber disruption and more complete healing. Note the relative lack of cellularity. T, tendon; M, intact muscle fibers.
DOMS

- Subjective complaint (not entirely)
- Attractive to study because:
  - Established, reproducible human model
  - Injury is self-limiting
- Several human studies, 6 randomised
  - Included subjective and objective outcomes
  - Different muscle groups

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Systematic review


- Covers DOMS (6 RCTs) and tendon/ligament strain (2 RCTs)
Review

- Trials were published between 1996 and 2003, included data on 198 participants, 108 receiving HBOT and 90 control.
- 5 of 6 DOMS trials involved multiple repetitions of resistance to lengthening of the target muscle group (eccentric exercise). Three studies exercised the quadriceps, two exercised the forearm flexors.
- The remaining study involved bilateral calf muscles raises against an 80% of maximal load - five repetitions to failure

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Review

- sham exposure breathing air at a trivial pressure in five trials
- All used between 2.0 and 2.5 ATA as a maximum oxygen pressure for 3 to 10 sessions.
- Followed for around three days
- Generally well planned and conducted

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Review: Hyperbaric oxygen therapy for delayed onset muscle soreness and closed soft tissue injury

Comparison: 05 Pain and swelling

Outcome: 01 Pain score change at 24 hours after exercise (Immediate treatment)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>HBCT Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staples 1999</td>
<td>9</td>
<td>44.50 (6.50)</td>
<td>18 40.50 (4.60)</td>
<td>56.57 4.00 [-0.75, 8.75]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staples 1999a</td>
<td>20</td>
<td>32.30 (8.00)</td>
<td>10 32.50 (8.20)</td>
<td>33.46 -0.20 [-6.37, 5.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mekjavic 2000</td>
<td>12</td>
<td>44.00 (19.00)</td>
<td>12 34.00 (12.00)</td>
<td>7.89 10.00 [-2.71, 22.71]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harrison 2001</td>
<td>5</td>
<td>46.00 (23.50)</td>
<td>6 41.70 (17.20)</td>
<td>2.08 4.30 [-20.47, 29.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babul 2003</td>
<td>8</td>
<td>0.00 (0.00)</td>
<td>8 0.00 (0.00)</td>
<td>Not estimable</td>
<td></td>
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<tr>
<td>Germa 2003</td>
<td>8</td>
<td>29.00 (0.00)</td>
<td>8 29.00 (0.00)</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 62 62

Test for heterogeneity: Chi² = 2.38, df = 3 (P = 0.60), I² = 0%

Test for overall effect: Z = 1.69 (P = 0.09)
**Review:** Hyperbaric oxygen therapy for delayed onset muscle soreness and closed soft tissue injury

**Comparison:** D5 Pain and swelling

**Outcome:** D2 Pain score change at 48 hours after exercise (immediate treatment)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>HBCT Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>VMD (random) 95% CI</th>
<th>Weight %</th>
<th>VMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D1 Quadriceps exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staples 1999</td>
<td>9</td>
<td>44.50 (4.50)</td>
<td>30.00 (4.70)</td>
<td>45.39</td>
<td>14.50 [10.85, 18.15]</td>
<td></td>
</tr>
<tr>
<td>Staples 1999a</td>
<td>20</td>
<td>29.80 (9.00)</td>
<td>24.50 (8.60)</td>
<td>35.75</td>
<td>5.30 [-1.33, 11.93]</td>
<td></td>
</tr>
<tr>
<td>Babul 2003</td>
<td>8</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>German 2003</td>
<td>8</td>
<td>17.50 (0.00)</td>
<td>31.00 (0.00)</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>45</td>
<td>44</td>
<td></td>
<td>81.14</td>
<td>10.33 [1.36, 19.31]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 5.67, df = 1 (P = 0.02), I² = 82.4%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.26 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>D2 Forearm flexors exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meijavic 2000</td>
<td>12</td>
<td>68.00 (19.00)</td>
<td>56.00 (23.00)</td>
<td>13.38</td>
<td>12.00 [-4.88, 28.88]</td>
<td></td>
</tr>
<tr>
<td>Harrison 2001</td>
<td>5</td>
<td>52.00 (26.10)</td>
<td>58.30 (22.30)</td>
<td>5.47</td>
<td>-6.30 [-35.31, 22.71]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>17</td>
<td>18</td>
<td></td>
<td>16.86</td>
<td>6.81 [-9.36, 22.98]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.4%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.83 (P = 0.41)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td>62</td>
<td></td>
<td>100.00</td>
<td>9.74 [2.56, 16.92]</td>
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</tr>
<tr>
<td>Test for heterogeneity: Chi² = 7.24, df = 3 (P = 0.06), I² = 58.6%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.66 (P = 0.008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Study or sub-category** | **N** | **HBOT Mean (SD)** | **Control Mean (SD)** | **WMD (fixed)** | **Weight %** | **WMD (fixed) 95% CI**
--- | --- | --- | --- | --- | --- | ---
Mekjavic 2000 | 12 | 5.60 (1.30) | 3.30 (4.30) | | 51.06 | 2.30 [-4.54, 9.14]
Webster 2002 | 6 | 8.00 (5.70) | 8.00 (5.60) | | 48.94 | 0.00 [-6.99, 6.99]
Belou 2003 | 8 | 0.00 (0.00) | 0.00 (0.00) | | Not estimable

Total (95% CI) | 26 |  |  |  | 100.00 | 1.17 [-3.71, 6.06]

Test for heterogeneity: Chi² = 0.21, df = 1 (P = 0.64), P = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
Review: Hyperbaric oxygen therapy for delayed onset muscle soreness and closed soft tissue injury
Comparison: 06 Recovery of muscle strength or function
Outcome: 02 Decrease in maximal eccentric torque (% baseline) at 48 hours after exercise (immediate treatment)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>HBCT Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staples 1999</td>
<td>8</td>
<td>11.10 (5.60)</td>
<td>16.10 (5.00)</td>
<td></td>
<td>52.72</td>
<td>0.80 [-3.79, 5.39]</td>
</tr>
<tr>
<td>Staples 1999a</td>
<td>20</td>
<td>12.00 (7.50)</td>
<td>10.00 (8.30)</td>
<td></td>
<td>25.80</td>
<td>2.00 [-4.10, 8.10]</td>
</tr>
<tr>
<td>Mekjavic 2000</td>
<td>12</td>
<td>46.00 (20.00)</td>
<td>43.70 (18.80)</td>
<td></td>
<td>4.60</td>
<td>2.30 [-13.23, 17.83]</td>
</tr>
<tr>
<td>Harrison 2001</td>
<td>5</td>
<td>26.40 (44.50)</td>
<td>50.30 (12.30)</td>
<td></td>
<td>0.68</td>
<td>-23.90 [-64.21, 16.41]</td>
</tr>
<tr>
<td>Webster 2002</td>
<td>6</td>
<td>7.50 (7.50)</td>
<td>9.00 (10.00)</td>
<td></td>
<td>11.10</td>
<td>-1.50 [-11.50, 8.50]</td>
</tr>
<tr>
<td>Babu 2003</td>
<td>8</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>German 2003</td>
<td>8</td>
<td>-1.30 (33.20)</td>
<td>-2.70 (31.80)</td>
<td></td>
<td>1.09</td>
<td>1.40 [-30.46, 33.26]</td>
</tr>
</tbody>
</table>

Total (95% CI) 67 66 0.81 [-2.52, 4.14]

Test for heterogeneity: Chisq = 1.63, df = 5 (P = 0.87), I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Conclusion

- Good evidence that HBOT does not improve speed or quality of recovery from DOMS
- Little evidence of benefit for ankle sprain or medial collateral ligament strain of the knee
- Little justification for further research in DOMS, great care needed in formulating a trial for ligament or tendon strain

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Example two:
Chronic wounds
TYPES OF PROBLEM WOUND FOR WHICH HBO HAS BEEN UTILIZED

- Ulcers with peripheral vascular insufficiency
- Venous stasis ulcers
- Decubitus ulcers
- Diabetic ulcers
- Crush injuries
- Non-healing surgical incisions
- Frostbite
- Animal bites
Chronic wounds

Does HBOT:
Increase the rate of healing of diabetic foot ulcers, venous leg ulcers, arterial ulcers of the lower limb or pressure ulcers?
Reduce the proportion of people with diabetic foot or arterial ulcers who undergo partial or total amputation of the lower limb?
Is HBOT safe in the short and long term?
Criteria for considering studies for this review

Types of studies

Randomised controlled trials that compare the effect on chronic wound healing of treatment with HBOT with no HBOT.

Types of participants

Any person with a chronic wound associated with venous or arterial disease, diabetes mellitus, or external pressure. Chronic wounds were defined as described in the retrieved papers (prolonged healing or healing by secondary intention), but must have had some attempt at treatment by other means prior to the application of HBOT.
Types of interventions

We compared wound care regimens which included HBOT with similar regimens that excluded HBOT.

HBOT administered in a compression chamber between pressures of 1.5ATA and 3.0ATA and treatment times between 30 minutes and 120 minutes daily or twice daily. The comparator group was diverse, we accepted any standard treatment regimen designed to promote wound healing (see background). The salient feature of the comparison group was that these measures had failed before enrolment in the studies.
NNT is 4, 95%CI 2 to 8
There was a significant increase in the proportion of ulcers healed following HBOT (the RR of failing to heal with sham treatment was 2.3, 95%CI 1.1 to 4.7, P=0.03). These efficacy data relate to a NNT to avoid 1 failure to heal of 2, 95%CI 1 to 5.
Reviewers' conclusions

Implications for practice
There is some limited evidence that HBOT reduces the rate of major amputation in people who have chronic foot ulcers as a result of diabetes. Thus, the application of HBOT to these patients may be justified where HBOT facilities are available however an economic evaluation should be undertaken. Furthermore 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. To date no useful information regarding the efficacy or effectiveness of HBOT for chronic wounds with other underlying pathologies can be provided.

Implications for research
There is insufficient evidence to recommend the routine use of HBOT in the clinical treatment schedule for people with diabetes related foot ulcers. There is a strong case for further large randomised trials of high methodological rigour in order to define the true extent of benefit 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, the time for which we can expect any benefits to persist, and the oxygen dose most appropriate. Any future trials would need to consider in particular:

- Appropriate sample sizes with power to detect expected differences
- Careful definition and selection of target patients
- Appropriate oxygen dose per treatment session (pressure and time)
- Appropriate comparator therapy
- Use of an effective sham therapy
- Effective and explicit blinding of outcome assessors and surgeons
- Appropriate outcome measures including all those listed in this review
- Careful elucidation of any adverse effects
Example three:
Acute coronary syndromes
Acute Coronary Syndrome
Acute coronary syndrome (ACS) includes acute myocardial infarction and unstable angina. Hyperbaric oxygen therapy (HBOT) has been suggested to improve oxygen supply to the threatened heart and, therefore, to reduce the volume of heart muscle that will ultimately perish.

It is postulated that the addition of HBOT to the standard intensive regimen (including thrombolysis) may result in a reduction in patient death and other major adverse outcomes as a result of these additional heart-preserving effects.
**Review:** Hyperbaric oxygen therapy for acute coronary syndrome

**Comparison:** 01 Death

**Outcome:** 01 Death at any time

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>HBOT n/N</th>
<th>Control n/N</th>
<th>RR (fixed)</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurston 1973</td>
<td>17/103</td>
<td>24/105</td>
<td></td>
<td>84.70</td>
<td>0.72 [0.41, 1.26]</td>
</tr>
<tr>
<td>Stavitsky 1998</td>
<td>1/59</td>
<td>2/63</td>
<td></td>
<td>6.89</td>
<td>0.53 [0.05, 5.73]</td>
</tr>
<tr>
<td>Sharifi 2002</td>
<td>0/24</td>
<td>2/27</td>
<td></td>
<td>8.40</td>
<td>0.22 [0.01, 4.45]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>186</td>
<td>195</td>
<td></td>
<td>100.00</td>
<td>0.67 [0.39, 1.14]</td>
</tr>
</tbody>
</table>

Total events: 18 (HBOT), 28 (Control)

Test for heterogeneity: Chi² = 0.62, df = 2 (P = 0.73), P = 0%

Test for overall effect: Z = 1.49 (P = 0.14)
Review: Hyperbaric oxygen therapy for acute coronary syndrome

Comparison: 02 Major Adverse Cardiac Events

Outcome: 01 Major Adverse Cardiac Events

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>HBOT n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharifi 2002</td>
<td>1/24</td>
<td>8/27</td>
<td>0.14 [0.02, 1.04]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 24/27

Total events: 1 (HBOT), 8 (Control)

Test for heterogeneity: not applicable

Test for overall effect: Z = 1.92 (P = 0.06)
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 and timing of therapy most likely to result in benefit from this therapy.
In conclusion:

Systematic review of the evidence is capable of bringing together diverse studies that are often difficult to find and interpret.

The purpose of such reviews is not only to guide practice, but to stimulate better clinical research in those areas of greatest potential impact.
Thank you