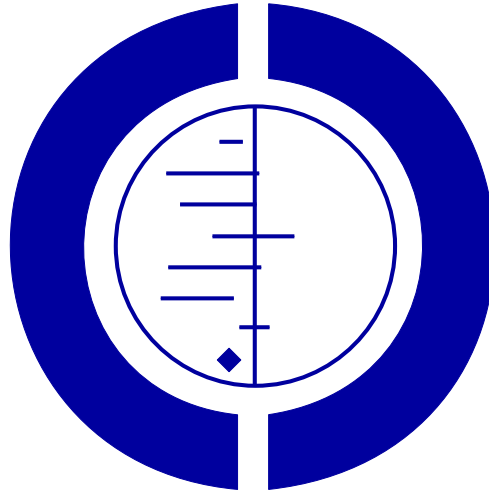


# Hyperbaric oxygen therapy for thermal burns (Review)

Villanueva E, Bennett MH, Wasiak J, Lehm JP



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## ABSTRACT

### Background

Hyperbaric oxygen therapy (HBOT) consists of intermittently administering 100% oxygen at pressures greater than 1 atmosphere in a pressure vessel. This technology has been used to treat a variety of disease states and has been described as helping patients who have sustained burns.

### Objectives

The aim of this review was to assess the evidence for the benefit of hyperbaric oxygen treatment (HBOT) for the treatment of thermal burns.

### Search strategy

We searched the Cochrane Controlled Trials Register (The Cochrane Library, Issue 3, 2002), MEDLINE (Ovid 1966 to November Week 2, 2003), CINAHL (Ovid 1982 to December Week 2 2003), EMBASE (Ovid 1980 to September 2003), DORCTHIM (Database of Randomised Controlled Trials in Hyperbaric Medicine) from inception to 2003, and reference lists of articles.

### Selection criteria

We included all randomised controlled trials that compared the effect of HBOT with no HBOT (no treatment or sham).

### Data collection and analysis

Two authors using standardised forms extracted the data independently. Each trial was assessed for internal validity with differences resolved by discussion. Data was extracted and entered into RevMan 4.2.3.

### Main results

Four randomised controlled trials were identified, of which two satisfied the inclusion criteria. The trials were of poor methodological quality. As a result, it was difficult to have confidence in the individual results and it would not have been appropriate to attempt to pool the data.

One trial reported no difference in length of stay, mortality, or number of surgeries between the control and HBO-treated groups once these variables were adjusted for the patient's condition. The second trial reported mean healing times that were shorter in patients exposed to HBOT (mean: 19.7 days versus 43.8 days).

### Authors' conclusions

This systematic review has not found sufficient evidence to support or refute the effectiveness of HBOT for the management of thermal burns. Evidence from the two randomised controlled trials is insufficient to provide clear guidelines for practice. Further research is needed to better define the role of HBOT in the treatment of thermal burns.

## SYNOPSIS

Little evidence that burns patients benefit from hyperbaric oxygen therapy

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Hyperbaric oxygen therapy for thermal burns (Review)

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Burns are very common, sometimes fatal, and have a high impact on the wellbeing of those affected. Recovery is often slow and complicated by infection and scarring. Hyperbaric oxygen therapy (HBOT) is a treatment designed to increase the supply of oxygen to the burnt area and improve healing. HBOT involves people breathing pure oxygen in a specially designed chamber (such as those used for deep sea divers suffering pressure problems after resurfacing). The review found only two randomised trials, with only a limited number of patients. There was no consistent benefit from HBOT, but one trial did suggest an improvement in healing time. Overall, there is little evidence to support or refute the use of HBOT for burns patients. More research is needed.

## BACKGROUND

Thermal burns remain an important source of morbidity and mortality. Every year, approximately two million people are burned, 80,000 are hospitalised, and 6,500 die in the USA (Brigham 1996). Globally there were 238,000 fire-related deaths in 2000, with low and middle-income countries bearing 95% of the global burden. Mortality per 100,000 population is 1.3 in North America but 5.5 in Africa (WHO 2002). Burns are a complex and evolving injury, with both local and systemic consequences - the latter manifesting once the burn area is greater than about 20% of the body surface area (BSA) (Sheridan 2002). Locally, the burn wound tends to extend in the acute phase of the injury secondary to microvascular changes, profound activation of white cells and platelets, and the development of oedema. Many small vessels are directly coagulated by the application of heat, while others will thrombose late and develop tissue dehydration (Boykin 1980). The systemic response to burning is characterised by interstitial oedema in distant organs, secondary to a combination of wound-released mediators and hypoproteinaemia (Demling 1980; Youn 1992).

Burns are a difficult treatment challenge and ideally the province of specialised units with high-volume workloads. Such units do not exist in most parts of the world. Early treatment can positively influence mortality rate. It involves appropriate fluid resuscitation, usually involving attainment of resuscitation targets using consensus formulas for initial fluid administration (Sheridan 2002), together with topical agents to control pain, limit direct fluid losses and slow bacterial growth. Over the past two decades, early closure of full-thickness wounds has improved the outcome from extensive burns through the prevention of wound colonisation and infection (Sheridan 2002). Temporary skin substitutes are widely employed on a similar rationale when formal closure is not an option.

Hyperbaric oxygen therapy (HBOT) is an adjunctive therapy that has been proposed to improve outcome in thermal burns. HBOT is the therapeutic administration of 100% oxygen at environmental pressures greater than 1 atmosphere absolute (ATA). Administration involves placing the patient in an airtight vessel, increasing the pressure within that vessel, and administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased partial pressure of oxygen to the tissues. Typically, treatments involve pressurisation to between 1.5 and 3.0 ATA, for periods between 60 and 120 minutes once or more daily.

It has been suggested since 1965 that HBOT might improve the outcome following thermal burns (Wada 1965). HBOT has been shown to reduce oedema and preserve microcirculation in a number of injury models, including burns, through vasoconstriction with enhanced oxygen delivery, a direct osmotic effect and the inactivation of white cell adhesion (Nylander 1985; Thom 1994; Hills 1999). HBOT also exerts beneficial effects on infections in hypoxic tissues through a variety of mechanisms (Knighton 1984).

Despite nearly 40 years of interest in the delivery of HBOT in these patients, little clinical evidence of effectiveness exists. An experimental model of burn injury suggested some reduction in hyperaemia, exudate and wound size, but no overall improvement in healing (Niezgoda 1982), while small, non-random, comparative trials have reported lower mortality and shorter hospital stays following HBOT in significantly burnt individuals (Grossman 1978; Niu 1987; Cianci 1988). On the other hand, a comparative study of 72 matched patients suggested more renal failure and sepsis (although fewer grafts) in the HBO group (Waisbren 1982).

HBOT is associated with some risk of adverse effects, including damage to the ears, sinuses and lungs from the effects of pressure, temporary worsening of short-sightedness, claustrophobia and oxygen poisoning. Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention.

## OBJECTIVES

The aim of this review was to assess the evidence for the benefit of hyperbaric oxygen treatment (HBOT) for the treatment of thermal burns.

Specifically, we aimed to address whether HBOT:

- reduced mortality and morbidity following thermal burns
- reduced the time required to heal thermal burns
- reduced the degree of scarring following thermal burns
- reduced the requirement for debridements and/or grafts in the treatment of thermal burns
- reduced the requirement for fluid therapy in the acute treatment phase.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

We included all randomised controlled trials that compared the effect of HBOT with no HBOT (no treatment or sham).

### Types of participants

We focused on patients with thermal injuries to the epidermis, subcutaneous tissues, vessels, nerve, tendons, or bone. No restrictions on age or sex were made.

### Types of intervention

We compared treatment regimens that 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 once or more often daily were eligible for inclusion. We accepted any standard treatment regimen designed to promote burn healing as the comparator.

### Types of outcome measures

Studies were eligible for inclusion if they reported any of the following outcome measures.

#### Primary outcomes

1. Mortality rate.
2. Major morbidity rate (wound infection, haemodynamic instability).

#### Secondary outcomes

3. Acute fluid requirement.
4. Time to healing.
5. Requirement for grafts and/or debridement.
5. Length of stay.
6. Scar quality (hypertrophic, retracted).
7. Pain scores.
8. Activities of daily living.
9. Adverse effects of HBOT: proportion of patients with visual disturbance (short and long-term), barotrauma (aural, sinus, pulmonary in the short and long-term) and oxygen toxicity (short-term) with respect to HBOT obtained from the included studies. Any other recorded adverse effects were reported and discussed.

## SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Injuries Group search strategy

We searched the Cochrane Controlled Trials Register (The Cochrane Library, Issue 3, 2002), MEDLINE (Ovid 1966 to November Week 2, 2003), CINAHL (Ovid 1982 to December Week 2, 2003), EMBASE (Ovid 1980 to September 2003) and

DORCTHIM (The Database of Randomised Controlled Trials in Hyperbaric Medicine) at [www.hboevidence.com](http://www.hboevidence.com) (Bennett 2002) from inception to 2003. This database was compiled from an unfocused search of PubMed using "hyperbaric oxygenation" as a MeSH term, along with handsearching of primarily hyperbaric journals (see below) since first publication and checking references in identified RCTs. The site is now interactive and receives citations for formal review from health care professionals in the field.

In MEDLINE, the following search strategy was combined with the optimal trial search strategy described in the Cochrane Reviewer's Handbook (Clarke 2000). The strategy was modified to search other databases. No language or publication restrictions were applied.

MEDLINE(Ovid)

1. hyperbari\$.tw
2. hbo\$.tw
3. mutliplace chamber.tw
4. monoplace chamber.tw
5. or/1-4
6. exp Burns
7. burn\$.tw
8. or/6-7
9. 5 and 8

We also handsearched relevant hyperbaric textbooks (Kindwall, Jain, Marroni, Bakker, Bennett and Elliot), journals (Undersea and Hyperbaric Medicine, Hyperbaric Medicine Review, South Pacific Underwater Medicine Society (SPUMS) Journal, European Journal of Hyperbaric Medicine and Aviation, Space and Environmental Medicine Journal) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published from 1980 to 2003. We checked the reference lists of the trials and reviews. We contacted current researchers in the field for unpublished data and ongoing trials but was unable to contact the authors of the two included RCTs.

## METHODS OF THE REVIEW

### Trial identification

Two reviewers (JW and MB) independently reviewed titles and abstracts of articles retrieved using the aforementioned search strategy. Trials that clearly failed to meet the inclusion criteria were not reviewed. Those that could not be excluded were retrieved and reviewed in full-text by two reviewers. In all instances, differences of opinion were resolved by discussion.

### Data extraction

Two reviewers using a paper pro forma extracted data independently from the trials. Disagreements were resolved by discussion.

#### *Quality assessment*

Study quality was assessed using an adaptation of the method outlined in Schulz 1995. The following characteristics were presented in a descriptive and tabular manner:

#### *Adequacy of the randomisation process*

A - Adequate sequence generation is reported using random number tables, computer random number generator, coin tossing, or shuffling.

B - Did not specify one of the adequate reported methods in (A) but mentioned randomisation method.

C - Other methods of allocation that appear to be unbiased.

#### *Adequacy of the allocation concealment process*

A - Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment.

B - Unclearly concealed trials in which the author either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in (A).

C - Inadequately concealed trials in which method of allocation is not concealed such as alteration methods or use of case record numbers.

#### *Potential for selection bias after allocation*

A - Trials where an intention to treat analysis is possible and few losses to follow-up are noted.

B - Trials which reported exclusions (as listed in A but exclusions were less than 10%).

C - No reporting on exclusions or exclusions greater than 10% or wide differences in exclusions between groups.

#### *Level of masking (treatment provider, patient, outcome assessor)*

A - Double or triple-blind.

B - Single-blind.

C - Non-blind.

#### *Analyses*

There were no outcome measures in common with the two included trials so pooling of data was impossible. We had planned to perform a subgroup analyses with respect to age i.e.: adults versus children, oxygen received (pressure <2.0 ATA versus  $\geq$  2.0ATA), time (<60 mins versus  $\geq$  60 mins) and length of treatment course (<5 sessions versus  $\geq$  5 sessions), nature of the comparative treatment modalities and severity of injury but the paucity of eligible trials did not permit this approach.

## **DESCRIPTION OF STUDIES**

A total of 113 references were identified. Independent scrutiny of

the titles and abstracts identified 22 potentially relevant articles. Of the 22 articles assessed in full text form, 18 were excluded because they failed to meet the pre-defined methodological criteria. Two further trials were excluded as they did not report on clinical outcomes, nor could they contribute data to the review. The remaining two trials formed the basis of the review.

In Brannen 1997, 125 acutely burned patients (range of body surface area burnt not given), with or without inhalation injury and admitted within 24 hours of injury were randomised to either routine burn management or routine burn management with the addition of HBOT. The routine burn management employed was not specified. HBOT consisted of 100% oxygen at 2 ATA for 90 minutes twice a day for at least 10 treatments and a maximum of one treatment per percent total body surface area. The primary outcome variable, in this trial was length of stay, and it also reported mortality, acute fluid requirements and the number of operations required.

In Hart 1974, 16 patients with thermal burns to between 10 and 50% of the total body surface area and admitted within 24 hours of injury were randomised to either routine burn management and HBOT or routine burn management with sham HBOT. Routine management included administration of Ringer's lactate solution titrated against central venous pressure and urine output (colloids after 24 hours as indicated), daily dressing with silver sulphadiazine cream, vitamin-B complex, vitamin C, alpha-tocopherol and antibiotics (unspecified). HBOT in the intervention arm consisted of 100% oxygen at 2 ATA for 90 minutes every 8 hours for 24 hours, then every 12 hours until healed. The controls were placed in the same chamber at equivalent times and compressed rapidly to a trivial pressure breathing air to simulate HBOT. This trial reported mortality, mean time to healing, acute fluid requirements and the number of grafts required.

## **METHODOLOGICAL QUALITY**

Components of the study design relating to the quality of the included studies are presented in Table 01.

Methodological quality was assessed using criteria suggested by Schulz (Schulz 1995). Overall, the reported quality of the studies was poor. Hart 1974 used the expression 'the envelope method' to describe randomisation, while Brannen 1997 did not elaborate on the method used. Neither study commented on allocation concealment, while double blinding was reported by Hart 1974 but not by Brannen 1997.

Neither trial reported any losses to follow-up or withdrawals from treatment.

## RESULTS

Data from the two studies (Brannen 1997; Hart 1974) comparing routine burn management versus HBOT or sham HBOT could not be pooled, and thus, are described individually.

Brannen 1997 reported no difference in length of stay (reported as a regression against age, %BSA, presence of inhalational injury and number of operations- actual length of stay in each group not reported), mortality (seven patients (11%) in each group), or number of surgeries (again only reported after regression) between the control and HBOT groups, once these outcomes were adjusted for the patient's condition.

Hart 1974 reported that mean healing times were significantly shorter in patients exposed to HBOT (Mean: 19.7 days versus 43.8 days,  $P < 0.001$ ) and that fluid requirements were also smaller in the HBOT group (Mean: 2.2 ml/kg versus 3.4 ml/kg, no statistical analysis reported). No standard deviations or errors were recorded. One of two grafts required in the sham group did not succeed, while three of three required in the HBOT group succeeded: relative risk (RR) for failed graft without HBOT 2.0, 95% confidence interval (CI) 0.5 to 8.0.

Adverse events reported by Hart 1974 indicated three patients in the HBOT group experienced sinus barotrauma and one patient in the control group had transient viraemia during the course of therapy. No information was provided by Brannen 1997.

## DISCUSSION

This systematic review did not find evidence to support or refute the effectiveness of HBOT for the management of thermal burns. Important methodological problems existed with both studies and there were also potentially important methodological differences between the studies. In addition, the two trials were published 23 years apart and we presume the comparator therapy to be significantly different. As a result, it was difficult to ascribe sufficient validity to either the individual results or any attempt to pool results across the studies.

The two trials involved a modest total of only 141 patients, of which 125 were in the Brannen 1997 trial. The Hart 1974 trial was particularly constrained by a lack of power to detect useful clinical differences, and the finding that HBOT was no more effective than placebo in regards to length of stay, mortality or number of surgeries may have been erroneous for this reason alone. Furthermore, the sample sizes of these studies may have precluded any definitive statement on safety or frequency of adverse events.

Allocation concealment was not described in either study, while neither the method of randomisation or blinding was described by Brannen 1997. As a result, the potential for selection bias was considered high, and particularly so considering entry into one

trial was dependent on the availability of HBO facilities at the time of presentation (Brannen 1997).

Mean healing times were reported by Hart 1974 and showed promising results, with times being shorter in patients exposed to HBOT. However, no definition of 'healing' was given, nor was a description given as to the extent of wound size and depth at presentation. Acute fluid requirements and other outcomes such as successful skin-grafting were reported 'better' in those receiving HBOT, but no formal analysis was made. Neither trial measured long-term outcomes. In an accompanying analysis of a series of 191 patients treated at their facility (138 with HBOT), Hart 1974 reported that the overall death rate for those treated with HBOT was 9% (less than predicted on the basis of a national series rate), and that 92/138 patients also survived to undergo autografting, with an average of 1.35 grafts per patient.

We had planned to perform subgroup analyses with respect to age, oxygen dose (treatment profile and number of treatments) and comparator therapy. However, the paucity of eligible trials did not permit this approach. Patient inclusion criteria were not standard (Hart did not report burn size or depth), nor was the dose of oxygen administered.

There are a few major adverse effects of HBOT (pulmonary barotrauma, drug reactions, injuries or death related to chamber fire), and while these are all rare enough not to expect to see them in the trials included in this review, they should be included in consideration of any benefit of this therapy.

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 Hart reported three individuals as experiencing sinus barotrauma requiring symptomatic therapy. There is no indication that these individuals were withdrawn from treatment.

While HBOT is advocated as an adjunctive treatment for thermal burns in some centres, there are surprisingly few comparative reports that support its use. Given the substantial cost associated with these treatments, the routine use HBOT for thermal burns cannot be justified by the findings of this review.

## AUTHORS' CONCLUSIONS

### Implications for practice

Although there are some promising results from one small RCT, there is insufficient evidence from this review to support the routine use of HBOT for patients with thermal burns.

### Implications for research

Given the routine use in some centres, there is a case for further randomised trials of high methodological rigour in order to de-

fine the true extent of benefit from the administration of HBOT to patients with thermal burns. Specifically, more information is required on the subset of burn severity or size most likely to benefit from this therapy 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
- appropriate outcome measures including all those listed in this review
- careful elucidation of any adverse effects
- the cost-utility of the therapy.

## POTENTIAL CONFLICT OF INTEREST

None known. The authors of this article are responsible for its contents. Statements contained herein should be constructed as reflecting the views of the authors and not of the agencies or organisations involved in the work.

## SOURCES OF SUPPORT

### External sources of support

- No sources of support supplied

### Internal sources of support

- No sources of support supplied

## REFERENCES

### References to studies included in this review

#### Brannen 1997 *{published data only}*

\* Brannen AL, Still J, Haynes M. A randomized prospective trial of hyperbaric oxygen in a referral burn center population. *American Surgeon* 1997;**63**(205-8).

#### Hart 1974 *{published data only}*

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\*Indicates the major publication for the study

## TABLES

### Characteristics of included studies

Study	Brannen 1997
Methods	Randomised controlled trial comparing routine burn management or routine burn management with the addition of HBOT.
Participants	125 acutely burned patients ( 94 male, 31 female; age in years, range of body surface area burnt and dates of enrolment into study not given; location of study - USA) with or without inhalation injury admitted within 24 hours of injury.
Interventions	Routine burn management plus treatment in an unstated chamber HBO device using 100% oxygen at 2 ATA for 90 minutes twice a day for at least 10 treatments and a maximum of 1 treatment per percent total body surface area burn.
Outcomes	Length of stay, mortality, and number of surgeries.
Notes	
Allocation concealment	B

Study	Hart 1974
Methods	Randomised controlled trials comparing routine burn management and HBOT or routine burn management with sham HBOT.
Participants	16 patients (14 male, 2 female; age range - 21.31 to 21.62 years and enrolment into the USA study between Nov 1972 and Jan 1974) with thermal burns amounting to between 10 and 50% of the total body surface area admitted within 24 hours of injury.
Interventions	Routine burn management and HBOT or sham HBOT in a monoplace HBO chamber with 100% oxygen at 2 ATA for 90 minutes every 8 hours for 24 hours, then every 12 hours until healed.
Outcomes	Mean healing time, requirements for grafts, adverse effects, acute fluid requirements.
Notes	
Allocation concealment	B

### Characteristics of excluded studies

Niezgoda Model burn in volunteers. Required little specific therapy - very minor burn.

Xu No clinical outcomes reported. Abstract only available.

## ADDITIONAL TABLES

**Table 01. Methodological quality of randomised controlled trials**

Study	Randomisation	Concealment	Follow up	Blinding
Brannen 1997	B	B	A	C
Hart 1974	B	B	A	A

## GRAPHS

### Comparison 01. Death

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality at last follow-up			Relative Risk (Fixed) 95% CI	Subtotals only

### Comparison 02. Time to heal

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean time to healing (days)	1	16	Weighted Mean Difference (Fixed) 95% CI	Not estimable

### Comparison 03. Fluid requirement

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Intravenous fluid replacement (mls)	1	16	Weighted Mean Difference (Fixed) 95% CI	Not estimable

### Comparison 04. Graft success

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Graft success at final follow-up	1	5	Relative Risk (Fixed) 95% CI	2.00 [0.50, 8.00]

## INDEX TERMS

### Medical Subject Headings (MeSH)

Burns [therapy]; Hyperbaric Oxygenation; Randomized Controlled Trials

### Medical MeSH check words

Humans

## COVER SHEET

<b>Title</b>	Hyperbaric oxygen therapy for thermal burns
<b>Authors</b>	Villanueva E, Bennett MH, Wasiak J, Lehm JP
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Bennett: Conception, background, critical appraisal, hyperbaric medicine content expert, statistical analysis, co-author description and discussion.  
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GRAPHS AND OTHER TABLES

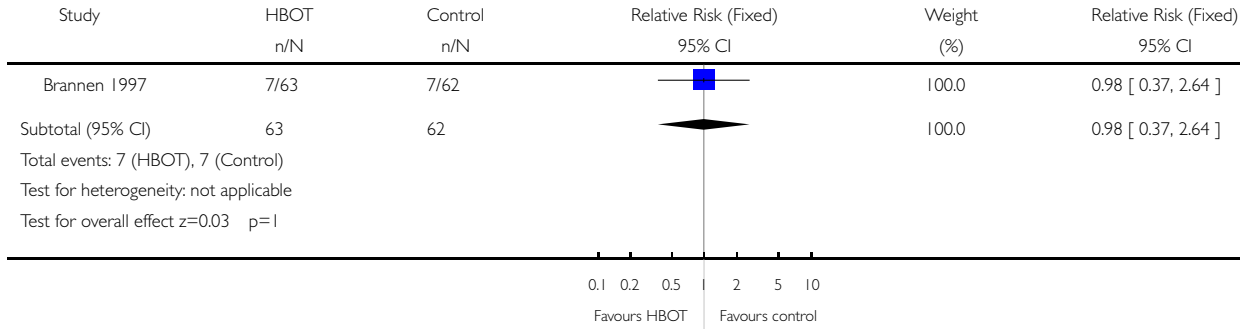
**Fig. 1. Comparison 01. Death**

**01.01 Mortality at last follow-up**

Review: Hyperbaric oxygen therapy for thermal burns

Comparison: 01 Death

Outcome: 01 Mortality at last follow-up



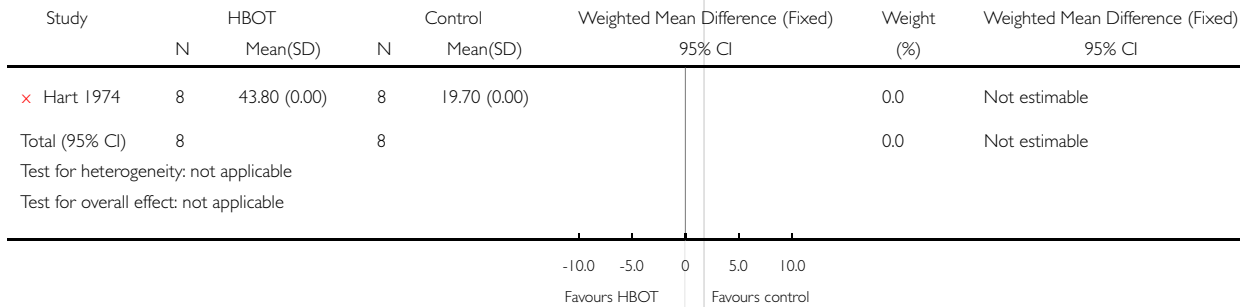
**Fig. 2. Comparison 02. Time to heal**

**02.01 Mean time to healing (days)**

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Comparison: 02 Time to heal

Outcome: 01 Mean time to healing (days)



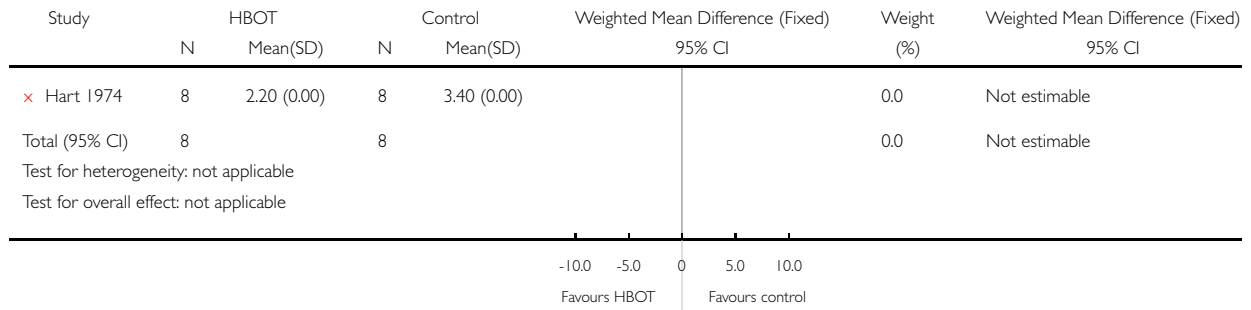
**Fig. 3. Comparison 03. Fluid requirement**

**03.01 Intravenous fluid replacement (mls)**

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Comparison: 03 Fluid requirement

Outcome: 01 Intravenous fluid replacement (mls)



**Fig. 4. Comparison 04. Graft success**

**04.01 Graft success at final follow-up**

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Comparison: 04 Graft success

Outcome: 01 Graft success at final follow-up

