Economic outcomes in clinical studies assessing hyperbaric oxygen in the treatment of acute and chronic wounds

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Abstract

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Introduction: Hyperbaric oxygen treatment (HBOT) is used to treat acute and chronic wounds. This systematic review was conducted to summarise and evaluate existing evidence on the costs associated with HBOT in the treatment of wounds.

Methods: We searched multiple electronic databases in March 2015 for cohort studies and randomised clinical trials (RCTs) that reported on the clinical effectiveness and treatment costs of HBOT in the treatment of acute or chronic wounds.

Results: One RCT and three cohort studies reported on economic as well as clinical outcomes. These studies comprised different disorders (ischaemic diabetic foot ulcers, thermal burns, Fournier's gangrene and necrotising soft tissue infections) and employed different clinical and economic outcome measures. Only the RCT had a good methodological quality. Three of the included studies reported that their primary clinical outcomes (wound healing, hospital stay, complications) improved in the HBOT group. The effects of HBOT on costs were variable.

Conclusions: Currently, there is little direct evidence on the cost-effectiveness of HBOT in the treatment of acute and chronic wounds. Although there is some evidence suggesting effectiveness of HBOT, further studies should include economic outcomes in order to make recommendations on the cost-effectiveness of applying HBOT in wound care.

Key words

Hyperbaric oxygen therapy; wounds; outcome; cost-effectiveness; systematic review

Introduction

Chronic and acute wounds pose a major healthcare problem and put a substantial burden on the healthcare budget. In the United Kingdom, approximately £2.3–3.1 billion or 3% of the total National Health Service (NHS) budget, is spent annually on the treatment of chronic wounds.[1] Therefore, the evaluation of the cost-effectiveness of established and novel treatment options for such conditions is of great importance. Wounds can result from surgery, trauma or underlying diseases such as diabetes, venous insufficiency or peripheral arterial disease. During normal wound healing, anatomical and functional integrity will be restored. However, normal wound healing can be disrupted and healing subsequently delayed. If wounds do not adequately heal with standard wound care (e.g., infection control, wound dressings, foot care education), more advanced wound care treatments can be considered, such as hyperbaric oxygen.

Hyperbaric oxygen treatment (HBOT) is currently used in the treatment of acute and chronic wounds, such as diabetic foot ulcers, radiation injury and necrotising fasciitis.[2–5] HBOT regimens for the treatment of wounds typically involve repeated sessions of 60 to 120 minutes in a compression chamber with a pressure between 203 and 304 kPa. During the session, the patient inhales 100% oxygen through a mask. Tissue oxygenation is improved mainly as a result of the increased driving partial pressure into tissues caused by HBOT. Furthermore, angiogenesis may be stimulated due to the promotion of oxygen-dependent collagen matrix formation and the mobilisation of stem cells by oxidative stress and their role in wound healing.[6,7]

Multiple review articles have reported on clinical outcomes of HBOT in wound treatment, with mixed results.[2,3,8,9] However, the economic aspects were not considered in these review articles. Yet cost-effectiveness is of key importance in evaluating the benefit of implementing interventions in practice,[10] particularly regarding a time-consuming treatment option like HBOT. This systematic review was conducted to evaluate existing evidence on the costs associated with HBOT in the treatment of acute and chronic wounds in clinical studies and to guide clinical decision-making and further research on this topic.

Methods

We performed a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11]

SEARCH STRATEGY

A comprehensive review of the literature was performed to identify all studies that evaluated both the clinical effectiveness and the economic impact of HBOT in the treatment of acute and chronic wounds published up to March 2015. The searched databases included MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), the NHS Economic Evaluation

Table 1
Flow chart of study inclusions and exclusions

References identified and screened for retrieval after removing duplicates (*n* = 1,040)
↓
Not eligible based on title and abstract (*n* = 1,018)
↓
Full-text articles retrieved for more detailed evaluation (*n* = 22)
↓
Not eligible based on full text (*n* = 18)
– no economic assessment (*n* = 9)
– no original study data (*n* = 7)
– no HBOT (*n* = 2)
↓
Included studies (*n* = 4)

Database and the Health Economic Evaluations Database (HEED). A clinical librarian assisted in formulating an appropriate search strategy. Medical Subject Headings (MeSH) terms were used in combination with key terms and their synonyms such as 'wounds', 'hyperbaric oxygen', 'HBOT' and 'costs'. Additional publications were identified by reviewing the reference lists of retrieved studies. No language restrictions were applied.

SELECTION OF INCLUDED STUDIES

Eligible studies were either cohort studies or randomised clinical trials (RCTs) that reported on both the clinical effectiveness and treatment costs of HBOT. Furthermore, eligible RCTs should deal with the treatment of open wounds of any type and aetiology, including soft tissue infections. Only studies that compared HBOT with standard care or placebo treatment were included in this study. RCTs on the topical application of HBOT were excluded. Two of the authors (TS and RS) independently screened titles and abstracts of potentially eligible studies. Subsequently, full-text versions of these publications were retrieved.

ASSESSMENT OF STUDY QUALITY

The risk of bias and methodological quality of the included studies was assessed by two review authors (TS and RS) using the Downs-Black instrument and the Drummond checklist.[12,13] The Downs-Black instrument is validated for the assessment of quality of randomised and non-randomised studies and consists of 27 items categorised in five subscales. These subscales are divided into the themes 'reporting' (10 items), 'external validity' (three items), 'bias' (seven items), 'confounding' (six items) and 'power' (one item). The maximum total score using the original instrument is 32, but we modified the score for the items 'confounding' and 'power'. The original scale ranged from 0 to 2 for 'confounding' and 0 to 5 for 'power', but we changed these items into dichotomous variables (i.e., scoring '1' if a power or sample size calculation was present and '0' if not). Each study could therefore score a maximum of 27 points on the modified Downs-Black instrument.

The Drummond checklist is a tool for the assessment of quality of the economic evaluation conducted alongside a clinical effectiveness study and consists of 35 items categorised in three subscales. These subscales are 'study design', 'data collection' and 'analysis and interpretation of results'. Scores that can be obtained for each item are, 'yes', 'no', 'not clear' and 'not appropriate'. We recoded these scores into dichotomous variables, 'yes' scoring '1' and 'no' or 'unclear' scoring '0'. Because no meta-analyses were included in this review, one item was not applicable to the studies. The maximum score could therefore be 34 (instead of 35) on the Drummonds checklist.

DATA COLLECTION AND EXTRACTION

Data extraction was performed by the same two authors independently using a standard extraction form. Extracted study information included research design and setting, year of publication, inclusion criteria, number of included participants, method of allocating patients, details about the HBOT therapeutic regimen and treatment in the control group, clinical outcome measures, and economic outcome measures, as defined by the authors of the papers. Discrepancies were resolved by discussion among the review authors.

DATA ANALYSIS

For dichotomous outcomes, differences between treatment groups are expressed as risk differences (RD) and numbers needed to treat or harm (NNT or NNH), along with their 95% confidence intervals (CIs). For continuous outcomes, differences are expressed as mean differences (MDs), along with 95% CIs. We planned to do a meta-analysis only in case of limited clinical and statistical heterogeneity (i.e., if the I^2 was less than 50%).

Results

The initial search identified 1,040 potentially relevant publications. Full-text articles were retrieved for 22 publications which were deemed potentially eligible based on their titles and abstracts. Eighteen of these articles were subsequently excluded. Reasons for exclusion are shown in Table 1. Eventually, only four articles were considered eligible for inclusion in this review.

STUDY CHARACTERISTICS

The four included studies comprised various categories of patients. Abidia et al. performed a RCT which included 18 patients with ischaemic diabetic foot ulcers.[14] Cianci et al.

Table 2
Characteristics of included studies; HBOT – hyperbaric oxygen treatment; * – not specified

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Wound type	Ischaemic diabetic foot ulcers	Thermal burns	Fournier's gangrene	Necrotising soft tissue infections
Study design	Randomised trial	Prospective cohort	Retrospective cohort	Retrospective cohort
Country	UK	USA	USA	USA
Participants (*n*)	18	21	42	45,913
- HBOT group	9	10	26	405
- control group	9	11	16	45,508
HBOT sessions				
- Total sessions	30	*	2–26 (median 6)	*
- Duration	90 minutes	90 minutes	30–90 minutes	*
- Pressure (kPa)	243	203	243–304	*
Control treatment	Sham HBOT	Standard treatment	Standard treatment	No HBOT
Follow-up period	1 year	13–81 days	9 months–10 years	*

Table 3
Quality assessment using the Downs and Black instrument

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Reporting				
Objective	+	+	+	+
Main outcomes	+	+	+	+
Patient characteristics	+	+	+	+
Intervention	+	–	+	–
Confounders	+	+	+	–
Main findings	+	+	+	–
Variability	+	–	+	–
Adverse events	+	–	–	–
Loss to follow-up	+	–	–	–
Probability values	+	–	+	+
External validity				
Representative subjects invited	+	–	–	–
Representative subjects participated	+	–	–	–
Representative treatment	+	+	+	+
Internal validity – bias				
Blinding subjects	+	–	–	–
Blinding outcome assessors	+	–	–	–
Data dredging	+	+	+	–
Length of follow up	+	–	–	–
Statistical tests	+	–	+	+
Compliance	+	–	–	+
Accurate main outcome measures	+	+	+	+
Internal validity – confounding				
Selection bias	+	–	+	+
Period of time	+	–	+	+
Randomisation	+	–	–	–
Concealment	+	–	–	–
Confounding	+	–	–	–
Loss to follow up	+	–	–	–
Power				
Sample size	–	–	–	–
Total score	26/27	8/27	14/27	10/27

Table 4
Quality assessmentusingtheDrummondchecklist; * only original clinical studiesareincluded in thisreview, sothisitem isnot applicable

Study	Abidia et al[14]	Cianci et al[15]	Mindrup et al[16]	Soh et al[17]
Study design				
Research question	−	+	−	−
Economic importance	−	+	−	−
Viewpoint(s) of the analysis	−	−	−	−
Rational alternative treatment	−	−	−	−
Alternative treatment	+	−	−	−
Form of economic evaluation	−	−	−	−
Form justified	−	−	−	−
Data Collection				
Sources	+	+	+	+
Design	+	+	+	+
Meta-analysis	*	*	*	*
Primary outcome	±	−	−	−
Value benefits	−	−	−	−
Subjects	−	−	−	−
Productivity	−	−	−	−
Relevanceproductivity	−	−	−	−
Resource use	−	−	−	−
Estimation quantities	±	−	−	−
Currency and prize data	±	−	−	−
Inflation	−	±	±	±
Model	−	−	−	−
Model justified	−	−	−	−
Analysis and interpretation of results				
Time horizon	+	−	−	−
Discount rate	−	−	−	−
Choice of rate	−	−	−	−
Explanation if not discounted	−	−	−	−
Statistical tests for stochastic data	−	−	−	−
Sensitivity analysis	−	−	−	−
Choice of variables	−	−	−	−
Rangesvariables	−	−	−	−
Alternatives	−	−	−	−
Incremental analysis	−	−	−	−
Disaggregated and aggregated	−	−	−	−
Answer study question	−	−	−	−
Conclusion from data reported	−	−	−	−
Conclusions with caveats	−	−	−	−
Total score	4/34	4/34	2/34	2/34

included 21 patients with thermal burns in a prospective cohort study.[15] The retrospective cohort study by Mindrup et al. included 42 patients with Fournier's gangrene.[16] The retrospective study by Soh et al. described a cohort of 45,913 patients with necrotising soft tissue infections (NSTIs) taken from the United States Nationwide Inpatient Sample.[17]

HBOT therapeutic regimes, as well as treatment pressure and session duration, were quite different among the studies. Only Abidia et al. employed sham HBOT with 100% oxygen in the control group, while other studies compared HBOT to wound care without HBOT.[14] A complete overview of the study characteristics is shown in Table 2.

METHODOLOGICAL QUALITY

The methodological quality of the RCT by Abidia et al. was very good (26 out of 27 points).[14] The observational nature of the other studies limited their validity, which is reflected by their relatively low scores on the Downs and Black quality assessment tool (Table 3). The quality of the economic evaluations was poor in all four studies. This is reflected by lower scores on the Drummonds checklist (Table 4).

Table 5
Primary clinical outcomes; CI – Confidence interval; HBOT – Hyperbaric oxygen treatment; MD – mean difference; NNT – number needed to treat; RD – risk difference; * not applicable

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Main outcome	Ulcers healed after one year	Length of hospital stay (days)	Disease specific mortality	In-hospital mortality
HBOT group	5/9	Mean 28.4 (range 13–60 ± 16.1)	7/26	18/405
Control group	0/9	Mean 43.2 (range 20–81 ± 19.4)	2/16	4,289/45,508
RD (95% CI)	56% (22 to 89%)	MD 14.8 (-1.6 to 31.2)	-14% (-36 to 13%)	47% (30 to 74%)
NNT (95% CI)	NNT 2 (1 to 5)	*	*	20 (15 to 50)

Table 6
Primary economic outcomes; CI: confidence interval; HBOT: Hyperbaric oxygen treatment; * statistically non-significant; † averaged daily hospital charges were statistically higher in the HBOT treated group

Study	**Abidia et al**[14]	**Cianci et al**[15]	**Mindrup et al**[16]	**Soh et al**[17]
Main outcome	Costs of treatment per year	Costs of burn care	Total hospital charges	Hospitalisation costs
Monetary unit	GBP	USD	USD	USD
HBOT group	Mean 4,972	Mean 60,350 (± 9,250)	Median 63,199 (range 31,858–256,741)	Median 52,205 (95% CI 46,397–58,012)
Control group	Mean 7,946	Mean 91,960 (± 12,590)	Median 51,185 (range 8,691–$427,283)	Median 45,464 (95% CI 44,7867–46,060)
Cost benefit?	37% cost reduction	34% cost reduction*	23% cost increase*†	15% cost increase

CLINICAL OUTCOMES

Three of the included studies reported that HBOT positively affected clinical outcomes (Table 5). The RCT by Abidia et al. demonstrated improved healing of ischaemic diabetic ulcers at one year of follow-up.[14] Cianci et al. reported a reduced length of hospital stay in HBOT-treated patients with thermal burns.[15] Soh et al. reported a longer length of hospital stay, but lower complications and in-hospital mortality in patients with NSTI who were treated with HBOT.[17] Nevertheless, Mindrup et al. demonstrated a non-significant increase in disease-specific mortality among patients with Fournier's gangrene who received HBOT.[16]

ECONOMIC OUTCOMES

The depth of the economic analyses varied widely among the four included studies. An overview of all economic outcome findings is shown in Table 6.

Abidia et al. assessed the costs of hospital visits for wound care and HBOT costs during the one-year follow-up period using unit costs as obtained from the NHS (*pounds sterling,* £) £58 for an outpatient visit and £100 for an HBOT-session), and reported lower overall costs in HBOT-treated patients (£4,972 vs. £7,946).[14] The extra costs for HBOT were compensated by a substantial reduction in the number of outpatient visits (33.75 visits in the HBOT group vs. 136.5 in the control group).

Cianci et al. reported a non-significant reduction in the costs of hospitalisation for HBOT-treated patients by reviewing all hospital bills.[15] The authors corrected the costs of inflation by standardising prices to 1987 levels but did not use appropriate statistical tests for non-parametric cost data.

In the study by Mindrup et al. the primary economic outcome was the total hospital costs.[16] Median total hospital costs were higher in the HBOT group, but this difference was not statistically significant (median costs USD $63,199 vs. $51,185). However, they reported statistically significant higher average daily hospital expenditures for HBOT-treated patients ($3,384 vs. $2,552) compared with non-HBOT treated patients.

Also, in the retrospective cohort study by Soh et al., the main economic outcome parameter was the total hospital charges during hospitalisation.[17] After adjustments for inflation, the authors reported statistically significantly higher median hospital costs in the HBOT group.

Discussion

This systematic review demonstrates that there is little direct evidence on the cost-effectiveness of HBOT in the treatment of chronic or acute wounds. Only four clinical studies were found that reported clinical as well as economic outcomes. Each study comprised of patients with different wound types, which prevented pooling of the results. Furthermore, outcome measures were very heterogeneous for both clinical and economic endpoints. Moreover, the economic analyses were of limited quality, failed to include an in-depth analysis, and were conducted in different decades.

A number of recent systematic reviews have reported on the clinical effectiveness of HBOT for patients with chronic ulcers or late radiation tissue injury.[2–4] Most of these reviews focussed on patients with diabetic ulcers and were hampered by between-study heterogeneity and limited methodological quality. Nevertheless, there is some evidence on the effectiveness of HBOT in improving the healing of diabetic foot ulcers and late radiation tissue injury.[3,4] Also, some evidence exists on the effectiveness of additional HBOT for acute wounds.[9]

Given the magnitude of the health problem and its economic impact, evidence for cost-effective treatments is essential in wound care. Prospective clinical studies are required to accurately assess cost-effectiveness, as all relevant and important clinical and cost parameters must be measured simultaneously. Although an economic analysis is rarely the primary purpose of a clinical study, a few adjustments to the study design can ensure that the data can be used in high-quality economic analyses.

None of the included trials in this review stated which economic perspective was taken into account. When performing a cost-effectiveness analysis alongside a clinical trial, the most preferred approach is taking all costs into account from a societal perspective. After this analysis, the perspective can be changed into the standpoint of, e.g., the government, the hospital or the patient.[13]

A cost-utility analysis is the preferred option when a study aims to determine the costs and efficacy of a treatment option, in which quality of life is an important factor. In such analyses, the outcome is often expressed as the effect on the quality-adjusted life years (QALY) that are lost or gained by the use of a specific therapy.[13] The International Society for Pharmacoeconomics and Outcome Research Task Force in Good Research Practices: randomized clinical trials–cost-effectiveness analysis (ISPOR RCT-CEA) has formulated recommendations for the design of economic analyses alongside clinical trials.[18] An important recommendation is that health utilities or QALYs should be measured directly from the study participants. Health utilities are preference-weighted health states on a scale from 0 (death) to 1 (perfect health) that can be measured by using utility questionnaires such as the EuroQol-5D.[19,20] Unfortunately, none of the included studies in the present review measured utilities or expressed their health outcomes as QALYs.

Besides clinical studies assessing economic outcomes, a few economic evaluations have been performed. The results of such evaluations are highly dependent on specific assumptions on treatment costs and clinical outcomes. An example of this kind of evaluation is a budget impact study in which a decision model comparing additional HBOT with standard care alone in the treatment of diabetic foot ulcers was developed.[21] This model included only the costs of the HBOT. Efficacy data were obtained from a review of clinical studies that were of poor methodological quality. They concluded that over a 12-year period, the costs for the treatment of patients with diabetic foot ulcers with HBOT would be lower than the costs for standard care alone in the Canadian setting (CND $40,695 vs. $49,786).

An example of an ongoing clinical trial on HBOT in wound care is the Dutch DAMOCLES trial. The objective of this clinical trial is to investigate the cost-effectiveness of HBOT in patients with ischaemic diabetic ulcers. In the DAMOCLES trial, all medical and direct non-medical costs are assessed and QALYs are measured.[22]

Conclusions

Although HBOT seems effective for various acute and chronic wounds, the lack of available evidence on economic endpoints is striking, given the fact that HBOT is widely applied in these settings and is reimbursed by insurance companies in Europe and the USA for the treatment of chronic wounds. Future research should include economic outcomes in large clinical studies of strong methodological quality to ensure that meaningful results can be used in clinical decision making and economic evaluations.

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The database of randomised controlled trials in hyperbaric medicine maintained by Michael Bennett and his colleagues at the Prince of Wales Hospital Diving and Hyperbaric Medicine Unit, Sydney is at: <http://hboevidence.unsw.wikispaces.net/>

Assistance from interested physicians in preparing critical appraisals is welcomed, indeed needed, as there is a considerable backlog. Guidance on completing a CAT is provided.
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