

Canadian Agency for
Drugs and Technologies
in Health



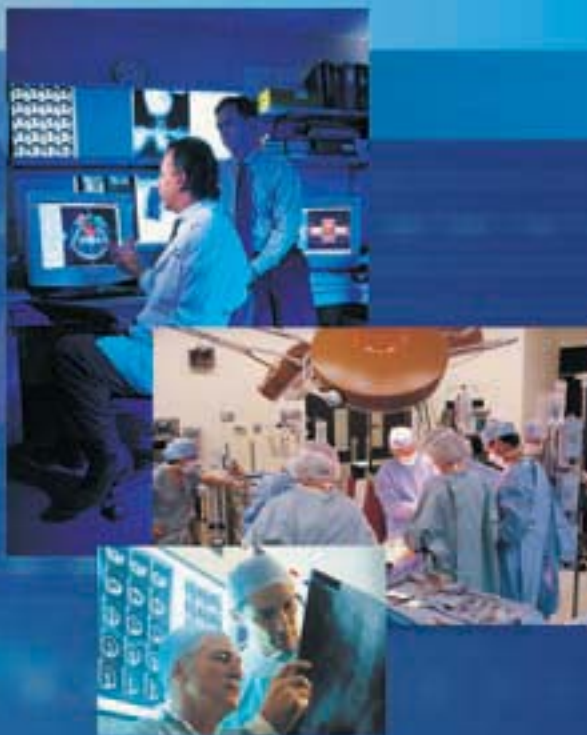
Agence canadienne
des médicaments et des
technologies de la santé

T E C H N O L O G Y O V E R V I E W

HTA

Issue 25
March 2007

Overview of Adjunctive Hyperbaric
Oxygen Therapy for Diabetic Foot Ulcer



Supporting Informed Decisions

Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

Publications can be requested from:

CADTH
600-865 Carling Avenue
Ottawa ON Canada K1S 5S8
Tel. (613) 226-2553
Fax. (613) 226-5392
Email: pubs@cadth.ca

or download from CADTH's web site:

<http://www.cadth.ca>

Cite as: Hailey D, Jacobs P, Perry DC, Chuck A, Morrison A, Boudreau R. *Overview of Adjunctive Hyperbaric Oxygen Therapy for Diabetic Foot Ulcer* [Technology overview no 25]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

Reproduction of this document for non-commercial purposes is permitted provided appropriate credit is given to CADTH.

CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2007
National Library of Canada
ISSN: 1203-9012 (print)
ISSN: 1481-4501 (online)
H0470 – March 2007

PUBLICATIONS MAIL AGREEMENT NO. 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH
600-865 CARLING AVENUE
OTTAWA ON K1S 5S8

Canadian Agency for Drugs and Technologies in Health

**Overview of Adjunctive Hyperbaric Oxygen
Therapy for Diabetic Foot Ulcer**

March 2007

We thank Leigh-Ann Topfer for her assistance in creating this overview from a longer report authored by David Hailey *et al.*

This overview is based on a Technology Report by: Hailey D, Jacobs P, Perry DC, Chuck A, Morrison A, Boudreau R. *Adjunctive Hyperbaric Oxygen Therapy for Diabetic Foot Ulcer: An Economic Analysis* [Technology report no 75]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

CADTH takes sole responsibility for the final form and content.

Adjunctive Hyperbaric Oxygen Therapy for Diabetic Foot Ulcer: An Economic Analysis

Technology and Condition

Adjunctive hyperbaric oxygen therapy (HBOT) for diabetic foot ulcer (DFU), a complication of diabetes mellitus, in adults and children.

Issue

An estimated 240,000 to 300,000 Canadians will have a DFU in their lifetime. DFU is associated with major morbidity, in many cases leading to lower extremity amputation (LEA). Use of HBOT may increase the success of healing DFU, and decrease the risk of infection and LEA. There is uncertainty regarding the cost-effectiveness of using this technology versus standard care.

Methods

Controlled studies that compared adjunctive HBOT for DFU with standard wound care in patients of all ages were identified through a literature search. Summary estimates were derived for the proportion of LEAs and healed ulcers in patients who received adjunctive HBOT, and those who had standard care only. Using a decision model, the cost-effectiveness of adjunctive HBOT was compared with that of standard care alone for the treatment of 65-year-old patients. A health services budget impact analysis was conducted using prevalence data from the literature, and utilization data from Alberta and Canada.

Implications for Decision Making

- **Adjunctive HBOT for DFU is more effective than standard care alone.** The proportion of major LEAs can decrease from 32% among patients receiving standard care to 11% among those receiving adjunctive HBOT. There was a decrease in the proportion of unhealed wounds with HBOT; the reverse was true for minor LEAs.
- **HBOT for DFU is cost-effective compared with standard care.** The 12-year cost for a patient receiving HBOT was C\$40,695 compared to C\$49,786 for standard care alone, with an associated increase of 0.63 quality-adjusted life years (QALYs) (3.01 QALYs for standard care versus 3.64 QALYs for those receiving HBOT).
- **HBOT requires additional resources and planning.** The estimated costs to treat all prevalent DFU cases in Canada is C\$14 million per year for four years. An estimated 179 additional monoplace chambers or 19 seven-person multiplace HBOT chambers would be required.
- **Optimal use will require additional considerations.** Guidelines would need to be applied to identify those patients most appropriately treated with HBOT. As standard care evolves and better quality studies become available, the estimated comparative advantage of HBOT may change.

This summary is based on a health technology assessment available from CADTH's web site (www.cadth.ca): Hailey D, Jacobs P, Perry DC, Chuck A, Morrison A, Boudreau R. *Adjunctive Hyperbaric Oxygen Therapy for Diabetic Foot Ulcer: An Economic Analysis*.

1 Introduction

Diabetes mellitus (DM) is a widespread chronic disease caused by the body's inability to sufficiently produce or properly use insulin. Type 1 diabetes, in which the pancreas can no longer produce insulin, affects approximately 10% of individuals with diabetes. Type 2 diabetes results when the pancreas cannot produce enough insulin or when the body is not effectively using the insulin that is produced. Most Canadians with diabetes have type 2 diabetes. Both types of diabetes are associated with health complications, and diabetes is a leading cause of death in Canada. The number of Canadians with diabetes is expected to reach three million by 2010.¹

Diabetic foot ulcer (DFU) is a common manifestation of diabetes. A DFU is an open sore that exposes the underlying tissue, most commonly on the sole. Diabetes affects the body's ability to heal such wounds, and chronic foot ulcers may become infected or turn gangrenous. In the US, the prevalence of DFUs in adults with diabetes is reported to range from 12% to 15%.^{2,3} About 12% of patients with DFUs will need lower extremity amputation (LEA). Major LEAs are amputations of the leg above or below the knee. Minor LEAs involve amputation of the toes or the forefoot.² A study of diabetes-related LEAs in Ontario from 1987 to 1988 found a crude annual rate of 40 LEAs per 10,000 patients with diabetes.⁴ There was a wide regional variation across Ontario (i.e., 30 to 60 per 10,000 annually).⁴ Major LEAs accounted for 45% of the total.⁴ LEA is a major adverse event for those with DM and is associated with considerable costs for the health care system.

Standard care for DFUs includes optimal blood glucose control, debridement, use of antibacterial treatments and dressings, administration of antibiotics to control infection, and pressure relief in the areas of the foot that are most subject to weight bearing.

Hyperbaric oxygen therapy (HBOT) has been used as an adjunctive treatment for DFUs. It has been suggested that the use of HBOT will improve healing and decrease the risk of LEA.

HBOT is an established technology that has been used to treat various medical conditions. It involves the inhalation of 100% oxygen while the patient is in a compression chamber. Single-place compression chambers are pressurized with 100% oxygen, while multiplace chambers are pressurized with air, and the patient breathes 100% oxygen through a mask or a hood. The increased pressure, which is associated with the inspiration of high levels of oxygen, increases the level of oxygen dissolved in the blood plasma. The immune system, wound healing, and vascular tone are all affected by the oxygen supply.⁵

In wound healing applications, HBOT sessions are typically conducted during a 45- to 120-minute period, once or twice daily. Usually 20 to 30 sessions are needed to treat a chronic wound.⁶

2 Objective

There is limited information on the economic aspects of adjunctive HBOT for the management of DFUs, particularly in the Canadian population. An assessment of the cost-effectiveness of HBOT for DFUs will provide information to health care decision makers for policy formulation.

The objective of this economic assessment was to determine if adjunctive HBOT is a cost-effective option compared with standard care for treating patients with DFUs in Canada. The objective was achieved by:

- synthesizing data on the clinical efficacy of HBOT as an adjunctive treatment for DFUs
- undertaking a cost-effectiveness analysis of HBOT for DFUs, using Canadian data where possible.

3 Clinical and Economic Review Methods

Methods

Published and unpublished literature was searched to identify controlled studies that compared adjunctive HBOT for DFUs with standard wound care only, in patients of any age with type 1 or type 2 diabetes. The search included electronic databases, hand searching selected journals, CADTH's health technology assessment checklist, and Internet sources.

Two reviewers independently selected abstracts and relevant articles, and used a data extraction form to record clinical data from selected studies. The study quality was evaluated using an approach that appraises study design and performance, and links these to judgments on study reliability.⁷ Disagreements were resolved by consensus.

A decision model was developed to determine the cost-effectiveness of adjunctive HBOT compared with standard care alone for the treatment of DFUs. The model used a 65-year-old patient cohort with DFUs, and included inpatient and outpatient care. The time horizon was 12 years, and the perspective was that of a ministry of health. The health states were a healed wound with or without a minor LEA, an unhealed wound with no related surgery, and a major LEA. Two sensitivity analyses were conducted to assess the stability of the model.

A health services budget impact analysis was conducted for Alberta and for Canada. Using prevalence data from the literature, and utilization data from an Alberta hospital and from an assessment conducted in Québec,⁸ we estimated the cost and capacity needs for treating all eligible DFU patients in Alberta and in Canada, over a period of one to four years.

4 Results

Clinical Review

The literature searches retrieved 977 citations, from which seven relevant studies were identified. Three of the seven studies were randomized controlled trials, and four were non-randomized comparative studies (Table 1).

Fewer major LEAs occurred in patients who received adjunctive HBOT, compared with those who received standard care alone (11% versus 32%). Wound healing occurred in 83% of patients who had HBOT, compared with 43% of those who did not. The proportion of patients with wounds that remained unhealed, without the patient requiring amputation, was 6% (HBOT) and 24% (controls). The evaluation of study design and performance found that the available evidence of efficacy was of fair quality, with limitations that should be considered in any implementation of study findings.

Table 1: Characteristics of selected studies

Study	Study Design	Study Quality	Patients	Comments
Baroni ⁹	NRCT	C	28 DM patients with foot gangrene (23) or perforating ulcer (5); consecutive series admitted to hospital; HBOT 18, controls 10	controls were patients who refused HBOT; 5 controls were stable (unhealed) in hospital, but lost to follow-up after discharge
Doctor ¹⁰	RCT	D	30 DM patients with chronic foot lesions; all in this category admitted to hospital for treatment; HBOT 15, controls 15	no information on randomization method; specific wound healing details for 12 HBOT patients and 11 controls
Faglia ¹¹	RCT	B	68 consecutive DM patients hospitalized for foot ulcer; Wagner grade 2*, HBOT 4, controls 5; grade 3*, HBOT 9, controls 8; grade 4*, HBOT 22, controls 20	no information on randomization method
Zamboni ¹²	NRCT	C	10 consecutive patients with long-term DM; non-healing lower extremity wounds; treated as outpatients; HBOT 5, controls 5	controls were patients who refused HBOT
Faglia ¹³	NRCT	D	115 consecutive patients with DM, hospitalized with foot ulcers; HBOT 51, controls 64	controls were patients who refused HBOT; brief details of HBOT; only major LEA data presented
Kalani ¹⁴	NRCT	C	38 patients with DM; chronic non-healing foot ulcers, treated as outpatients; HBOT 17, controls 21	started as RCT (first 14 patients) but completed as non-randomized study; 2 deaths in HBOT group, and 3 in controls group, unrelated to treatment
Abidia ¹⁵	RCT	B	16 patients with DM; ischemic ulcers >1 cm and <10 cm maximum diameter with no signs of healing despite optimum management for >6 weeks since presenting; treated as outpatients; HBOT 8, controls 8; Wagner grades HBOT: all grade 2*; controls: 7 grade 2*, and 1 grade 1*	randomized to 100% oxygen or 100% air; sealed envelope, single blind; 2 dropouts, 1 from each group

NRCT=non-randomized controlled trial; RCT=randomized controlled trial; DM=diabetes mellitus; HBOT=hyperbaric oxygen therapy. *Grade refers to Wagner grading system for diabetic foot ulcer classification. Study quality ratings: A=high quality (high degree of confidence in study findings); B=good quality (some uncertainty regarding study findings); C=fair quality (some limitations that should be considered in any implementation of study findings); D=poor to fair quality (substantial limitations in study, findings should be used cautiously); E=poor quality (study findings have unacceptable uncertainty).

The rate of minor LEAs was higher in HBOT-treated patients when compared with controls in three studies where such amputations occurred.^{10,11,15} Zamboni *et al.* found that over seven weeks, the reduction in wound surface area was significantly greater in the HBOT group than in the control group ($p<0.05$).¹² Abidia *et al.* reported a 100% reduction in wound size with HBOT at six weeks, compared with 52% at six weeks in controls, and 95% at six months in controls.¹⁵ Kalani *et al.* found that the mean healing time was 15 months in the HBOT and the control groups.¹⁴

A summary of reported outcomes, using the means of the values reported for each study, appears in Table 2.

The results of the clinical review corroborate the findings in previous assessments that adjunctive HBOT for DFU is more effective than standard care, although the available evidence remains limited. Good quality studies are needed to confirm the comparative benefits of the technology in this application.

Outcomes	Number of Studies	HBOT	Controls
major LEAs (%)	7	11	32
minor LEAs (%)	6	27	15
wounds healed, no minor LEA (%)	6	56	27
total with wounds healed (%)	6	83	43
total with wounds unhealed (%)	6	6	24
hospital stay (range) in days	3	47.1 (43.2 to 57.6)	56.9 (50.8 to 72.8)

LEAs=lower extremity amputations; HBOT=hyperbaric oxygen therapy.

Economic Analysis

The 12-year cost for patients receiving HBOT was C\$40,695, compared with C\$49,786 for standard care alone. Outcomes were 3.64 quality-adjusted life-years (QALYs) for those in the HBOT arm, and 3.01 QALYs for controls. Because outcomes were better, and costs were less in the HBOT arm, adjunctive HBOT used with standard care is the dominant strategy. This remained the case in the sensitivity analyses.

The results of our economic evaluation show that, based on available data, adjunctive HBOT for DFU is cost-effective compared with standard care.

5 Health System Implications

The estimated cost to treat all DFU cases in Canada was \$57 million in one year or \$14 million per year over four years. About 179 additional monoplace HBOT chambers would be required nationally for the four-year scenario (Table 4).

Most patients with DFU are managed successfully using standard care. Guidelines should be used to identify those patients for whom HBOT would be the most appropriate treatment. The severity of ulceration and delayed response to treatment using standard care are important considerations.

Variables	Canada	Alberta	Data source
number of patients with diabetes	1,195,000	86,000	National Diabetes Surveillance Strategy ¹⁶
prevalence of DFU in patients with diabetes	6%	6%	Ramsey <i>et al.</i> ¹⁷
percentage of patients with DFU whose condition warrants HBOT	22% to 30%	22% to 30%	Reiber <i>et al.</i> , ¹⁸ AÉT MIS ⁸
demand for prevalent cases	15,774 to 21,510	1,135 to 1,548	not applicable

DFU=diabetic foot ulcer; HBOT=hyperbaric oxygen therapy.

Table 4: Budget impact of expanding HBOT

Scenario	Total Number of Patients	Years to Complete Backlog	Monoplace Machines Needed	Total Annual Cost (C\$)
Alberta Costs				
all patients treated in 1 year*	1,135	1	51	\$4,145
all patients treated in 1 year*	1,548	1	70	\$5,653
all patients treated in 2 years*	1,135	2	26	\$2,072
all patients treated in 3 years*	1,135	3	17	\$1,381
all patients treated in 4 years*	1,135	4	13	\$1,036
Canada Costs				
all patients treated in 1 year*	15,774	1	717	\$57,606
all patients treated in 1 year*	21,510	1	977	\$78,554
all patients treated in 2 years*	15,774	2	358	\$28,803
all patients treated in 3 years*	15,774	3	239	\$19,202
all patients treated in 4 years*	15,774	4	179	\$14,401

* Alberta cost of \$3,652 per treatment, and 22 patients treated annually per monoplace machine; HBOT=hyperbaric oxygen therapy.

6 Limitations

There is clinical evidence in the included studies that HBOT is effective in the treatment of DFU, but there are few comparative studies, and all of them have limitations. The summary of outcomes (Table 2) must be regarded as provisional, given the disparate nature of the studies that were reviewed.

The data (notably cost) on which the variables in the economic model were based, are not of high quality, and in some cases, estimates from foreign resources had to be used. The cost data for HBOT were based on data from a few centres, and the reporting was not standardized. Nevertheless, because the sensitivity analyses showed the results to be robust, there is confidence in the finding that adjunctive HBOT used for the treatment of DFU is economically attractive.

The immediate impact on the provincial budget is the cost of providing adjunctive HBOT for DFU treatment. Post-HBOT downstream costs, which include treatment costs for unhealed wound care and LEAs, have not been considered in our analysis. We have conducted an immediate budget impact analysis for Alberta and for Canada, and have considered the costs of HBOT only (i.e., costs of acquiring and operating hyperbaric oxygen chambers).

7 Conclusions

The results of our clinical review corroborate findings in previous assessments that adjunctive HBOT for DFU treatment is more effective than standard care alone, although the available evidence remains limited. Data from a few clinical studies suggest that adjunctive HBOT results in a reduction in the proportion of patients with DFUs undergoing a major LEA from 32% to 11%, and in those with continuing non-healed ulcers from 24% to 6%. If such reductions were applicable to the Canadian population, many major amputations would be avoided, with consequent benefits to patients and their families, and to the health care system.

The results of our economic evaluation show that based on available data, adjunctive HBOT for this application is cost-effective when compared with standard care. To achieve the possibility of reductions in major LEAs commensurate with what was found in our clinical review, it would be necessary for health authorities to ensure that there was enough HBOT capacity to cope with the DFU caseload, and that patients had reasonable access to HBOT facilities. To treat all Canadian patients with DFUs during a four-year period with monoplace chambers, we estimate that an additional 179 HBOT machines would be required nationally.

Newer types of dressings and other technologies are becoming available for the treatment of skin ulcers, and the comparative advantage of adjunctive HBOT may change as a result. The consequences of recurring ulceration and the treatment required have not been considered in this analysis.

8 References

1. *The prevalence and costs of diabetes*. Toronto: Canadian Diabetes Association; 2004. Available: http://www.diabetes.ca/Section_about/prevalence.asp .
2. *Foot health and diabetes: prevalence of foot symptoms and complications*. Bethesda (MD): National Diabetes Education Program, National Institutes of Health; 2004. Available: <http://ndep.nih.gov/diabetes/WTMD/foot.htm> .
3. Stillman RM. Diabetic ulcers. In: *eMedicine* [database online]. New York: WebMD; 2006. Available: <http://www.emedicine.com/med/topic551.htm> .
4. Lawee D, et al. *Can J Public Health* 1992;83(4):298-302.
5. Grim PS, et al. *JAMA* 1990;263(16):2216-20.
6. Undersea and Hyperbaric Medical Society. *Hyperbaric chambers North and Central America. A directory of hyperbaric treatment chambers*. Kensington (MD): The Society; 2001.
7. Hailey D, et al. *J Telemed Telecare* 2004;10(6):318-24.
8. Agence d'évaluation des technologies et des modes d'intervention en santé. *Hyperbaric oxygen therapy in Québec* [AÉTMIS 2000-3 RE]. Montréal: L'Agence; 2001. Available: <http://www.aetmis.gouv.qc.ca/site/download.php?2146748a9206c0f6064d7c24de19b4c8> .
9. Baroni G, et al. *Diabetes Care* 1987;10(1):81-6.
10. Doctor N, et al. *J Postgrad Med* 1992;38(3):112-4, 111.
11. Faglia E, et al. *Diabetes Care* 1996;19(12):1338-43.
12. Zamboni WA, et al. *Undersea Hyperb Med* 1997;24(3):175-9.
13. Faglia E, et al. *J Diabetes Complicat* 1998;12(2):96-102.
14. Kalani M, et al. *J Diabetes Complicat* 2002;16(2):153-8.
15. Abidia A, et al. *Eur J Vasc Endovasc Surg* 2003;25(6):513-8.
16. National Diabetes Surveillance Strategy. *Responding to the challenge of diabetes in Canada*. Ottawa: Public Health Agency of Canada; 2000.
17. Ramsey SD, et al. *Diabetes Care* 1999;22(3):382-7.
18. Reiber GE, et al. *J Rehabil Res Dev* 2001;38(3):309-17.