

Hyperbaric oxygen therapy in the treatment of diabetic foot ulcers and late radiation tissue injuries of the pelvis

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Table of content

Summary of the Health Technology Assessment	4
Which health technology or method will be assessed?	6
Disease/disorder of Interest and Present Treatment	7
Present Health Technology	10
Review of the Level of Evidence	13
Ethical aspects	17
Organisation	18
Economy	19
Unanswered Questions	21

Statement from the HTA-centre 2011-10-26

Appendix 1	Outcome tables
Appendix 2	Excluded articles
Appendix 3	Search strategy, study selection and references
Appendix 4	SoF –table

Summary of the Health Technology Assessment

Method and patient group:

Chronic non-healing diabetic foot ulcers and late radiation proctitis and cystitis are medical conditions associated with high comorbidity and impaired quality of life. The pathophysiology of these conditions share some characteristic features such as hypoxia, ischemia and angiopathy. Hyperbaric oxygen therapy (HBOT) stimulates neovascularization and increase oxygen delivery in hypoxic tissues, and thereby may be effective in promoting healing and symptom reduction in these patient categories.

Question at issue

Is hyperbaric oxygen therapy effective in healing diabetic foot ulcers and treating radiation induced cystitis and proctitis?

PICO

PICO1

- P = Patients with diabetic foot ulcers of at least 4 weeks duration, who have received optimal conventional treatment, and in whom revascularisation intervention is not possible.
- I = Hyperbaric oxygen therapy (HBOT) in addition to conventional treatment
- C = Conventional treatment or placebo
- O = Ulcer healing, ulcer size, amputation rate, quality of life, complications

PICO2

- P = Patients with symptomatic proctitis as a delayed or persistent injury due to radiation therapy.
- I = Hyperbaric oxygen therapy (HBOT) in addition to conventional treatment
- C = No treatment, other conventional treatment or placebo.
- O = Mucosal healing, quality of life, complications

PICO3

- P = Patients with symptomatic cystitis as a delayed or persistent injury due to radiation therapy.
- I = Hyperbaric oxygen therapy (HBOT) in addition to conventional treatment
- C = No treatment, other conventional treatment or placebo.
- O = Haemorrhage (macrohematuria), quality of life, complications

Studied benefit and risk for patients of the new health technology

The systematic literature search identified four randomised, controlled trials (RCTs) and five non-randomised, controlled observational studies reporting the effects of HBOT in patients with diabetic foot ulcers. Only one RCT has reported the effects of HBOT in patients with radiation proctitis and one non-randomised, controlled study has reported the effects of HBOT in patients with radiation radiation cystitis. All the studies had some uncertainty with regard to external validity

Diabetic foot ulcer

During 3 – 36 months follow-up the studies have reported an almost doubled rate of complete ulcer healing, and during observation periods from 4 weeks to 6 months a greater decrease in ulcer size in comparison to standard treatment only. According to the GRADE system the quality of evidence of improved ulcer healing by HBOT is moderate (GRADE ⊕⊕⊕O).

Radiation proctitis

The only study (an RCT) reported a significant higher rate of healed mucosa, but the absolute healing rate during three months was rather low. According to the GRADE system the quality of evidence of improved mucosal healing by HBOT is low (GRADE ⊕⊕OO).

Radiation cystitis

The only study (a non-randomised study) of patients with radiation cystitis was a small one of low quality. According to the GRADE system the quality of evidence of any effect of HBOT on bleeding from radiation cystitis is very low (GRADE ⊕OOO).

Ethical considerations

Since HBOT improves healing of diabetic foot ulcers it would not be ethical not to provide this treatment for this patient group.

Economical aspects

The cost of HBOT in patients with non-healing diabetic foot ulcer is estimated to be 3.9-5.9 million SEK per year in region Västra Götaland, and in patients with radiation cystitis and proctitis 2.3-3.1 million SEK per year. Cost-effectiveness analyses indicate that adjunctive HBOT for diabetic foot ulcers is cost-effective compared to standard care. No cost-effectiveness analyses are available for post-radiation tissue injuries.

Which health technology or method will be assessed?

1a Who will lead the project?

Per Arnell, MD, Senior Consultant, Head of the Hyperbaric Chamber, Department of Anaesthesiology and Intensive Care, Sahlgrenska University Hospital/Eastern hospital, Göteborg, Sweden

1b Who posed the question?

Olof Ekre, MD, PhD, Senior Consultant, Former Head of Department of Anaesthesiology and Intensive care, Sahlgrenska University Hospital/ Eastern hospital, Göteborg, Sweden

Additional parties who posed the question?

None

1c Work group:

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1d Other participants, from the HTA centre

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1e Are there any conflicts of interest for the proposer or any of the participants in the work group?

No

Disease/disorder of Interest and Present Treatment

2a Disease/disorder of interest and its degree of severity

Diabetic foot ulcers

Many patients with diabetes mellitus of type 1 or type 2 develop characteristic long-term complications. The “diabetic foot” is characterized by sensory, motor and autonomic neuropathies, which could lead to deformities and alteration of pressure when walking. Typically, it also exhibits disturbances in the macro- and microcirculation that may cause local ischemia. These changes predispose to the development of foot ulcers, some of which heal very slowly or not at all. This could, at least partly, be related to impaired oxygenation of the surrounding tissue and to impaired cellular function secondary to hyperglycemia.

Revascularisation interventions can sometimes improve the circulation in the affected foot and lead to wound healing. However, many patients exhibit non-reconstructable vascular disease, and, thus, are not eligible for surgery or other vascular interventions. Even at “centres of excellence” 19-35% of diabetic foot ulcers are reported as non-healing (Oyibo et al., 2001; Gershater et al., 2009; Reiber et al., 2009), causing suffering for the patient and great costs for the health care system. A diabetic foot ulcer can ultimately lead to amputation, which is associated with significant morbidity and premature death (Eliasson et al., 2004)

- √ Risk of premature death
- √ Risk of permanent illness or damage, or reduced quality of life
- √ Risk of disability and health-related quality of life

Radiation proctitis and cystitis

Radiotherapy is commonly used in the management of malignant diseases. Despite a continuous improvement of the technique, with improved efficacy and tolerance, adverse effects is still rather common. The urinary bladder and rectum are the major organs most commonly affected by radiotherapy to the pelvis area.

Radiation injuries can be classified as acute or delayed. The acute injury is caused by cellular toxicity mediated via free radicals that damages the cellular DNA. This injury is often self-limited and treated symptomatically. In contrast, the delayed injury is chronic and the clinical manifestation often progressive in nature. The time interval between radiotherapy and the onset of late injury is usually long, but may vary from a few months to more than ten years.

The commonly accepted explanation of the delayed injury caused by radiotherapy is the development of obliterative endarteritis. However, new findings suggest that a release of fibrinogenic cytokines, and a depletion of parenchymal and stem cells, play critical roles in the pathophysiology (Fleckenstein et al., 2007). The end result in the tissue of these events is a pathological condition with hypovascularity, hypocellularity and hypoxia.

The dysfunction of the mucosa in the urinary bladder and in the rectum leads to symptoms that can be severely disabling. Both micro- and macroscopically detectable bleedings are common, and sometimes require blood transfusions. Other symptoms are due to a reduced capacity of the urinary bladder or rectum with frequent mictations and or defecations, with an imperative and immediate need to use a toilet. Furthermore, pain and discomfort in the pelvis area as well as urinary or fecal incontinence are common. The severity of these symptoms is usually so pronounced that they lead to a severe restriction in the patient's freedom of life, and, thus, to a drastic decrease in quality of life.

Risk of premature death

√ Risk of permanent illness or damage, or reduced quality of life

√ Risk of disability and health-related quality of life

2b Prevalence and incidence of the disease/disorder

Diabetic foot ulcers

Diabetes mellitus is a common disease with a prevalence of about 5% in the Swedish population. It is estimated that about 5-9% of the total diabetic population have any type of foot ulcer. (Apelqvist, 2005). The incidence increases with age. Some of these ulcers will not heal by conventional treatment. The exact prevalence of non-healing diabetic foot ulcers is not known. The clinical experience from Lund University Hospital, Sweden, indicates an annual incidence of non-healing ulcers of at least 9 per 100 000 residents. (Löndahl, personal communication).

The incidence of lower limb amputations among diabetics varies widely in studied populations. This is thought to reflect different standards of ulcer care among Swedish hospitals. Probably, the readiness to perform an amputation also differs among orthopaedic surgeons. A study from Västra Götaland showed an annual amputation frequency of 12/100,000 residents during the period 1987-2002 (Eliasson et al., 2004). The majority of the amputations are preceded by a period with a non-healing ulcer (Apelqvist, 2005).

Radiation proctitis and cystitis

There is a scarcity of data regarding both prevalence and incidence of proctitis and cystitis caused by radiation. Some of these patients are handled by their general practitioner, others by general surgeons at local hospitals, and some by specialists in urology, colorectal surgery or oncology. Thus, it is difficult to assess the overall prevalence and incidence.

One of the most common forms of cancer treated with radiotherapy of the pelvis area is prostate cancer. The annual incidence of prostate cancer in Sweden is over 10,000 (Socialstyrelsen, 2010). This means approximately 195 men per 100,000 residents (Socialstyrelsen, 2009). Approximately 20 % of all prostate cancer patients are treated with radiotherapy as monotherapy, or in combination with other treatment modalities.

The incidence of late rectal and urinary bladder complications after curative doses of radiotherapy for cervical, prostate or rectal cancer is reported to be about 5-10 %

(Barillot et al., 2000; Boersma et al., 1998; Borghede et al., 1997). This would correspond to an annual incidence of 100-200 patients in Sweden.

The number of patients treated with radiotherapy for cervix, urinary bladder or rectal cancer in region Västra Götaland is estimated to be approximately 100 per year. This estimation is based on The National Board of Health and Welfare report over cancer statistics (Socialstyrelsen, 2010).

2c Present treatment of the disease/disorder in the outpatient setting/ in-patient setting.

Diabetic foot ulcers

All diabetic patients with ulcers should have access to qualified foot-care either at their primary care facility or at a hospital. This often involves nurses that are specialized in diabetes and wound care, professional foot-technicians, and podiatric treatment. A vascular surgeon should assess the lower limb circulation and revascularization should be performed when indicated. Orthopaedic surgeons should be consulted when appropriate.

Radiation proctitis and cystitis

The conventional treatment is symptomatic. It includes different means of surgical coagulation, installation of substances such as formalin, alun and steroids in the rectum or the urinary bladder in order to stop bleeding or to reduce inflammation. Medical treatment in order to reduce urge, pain and discomfort are often tried. Surgical intervention to reduce leakage of urine is tested in selected patients. If the symptoms progress into more severe forms, the final solution is usually a rectal or a urinary deviation into a stoma.

2d Number of patients who undergo current treatment regimen?

Diabetic foot ulcers

It is estimated that about 100-150 patients are currently treated for non-healing diabetic foot ulcers in region Västra Götaland.

Radiation proctitis and cystitis

In region Västra Götaland approximately 130 patients with the diagnosis radiation induced proctitis and/or cystitis receive health care.

2e The normal pathway of a patient through the health care system

Diabetic foot ulcers

Diabetic patients with foot ulcers living in the Göteborg area could be referred to a multidisciplinary foot-team at the department of Orthopaedics at Sahlgrenska University Hospital/Mölndal hospital. Patients from other parts of region Västra Götaland with foot ulcers are either treated at their local hospital, including orthopaedic evaluation when necessary, or are referred to the foot-team at Sahlgrenska University Hospital/Mölndal Hospital. Some cases are presently referred to hyperbaric oxygen therapy (HBOT).

Radiation proctitis and cystitis

Most patients who develop late radiation injuries are initially handled and treated by their general practitioner. If the symptoms aggravate, patients are referred to the Oncologic centre where they were initially treated for their malignancy. Severe cases with hemorrhage as the predominant symptom are directly referred to a urological or colo-rectal clinic. Some cases are referred to HBOT

2f Actual wait time in days for medical assessment /treatment

The time from referral to the hyperbaric unit to initiation of HBOT is usually less than three months.

Present Health Technology

3a Name/description of the health technology at issue

Hyperbaric oxygen therapy (HBOT) is defined as the breathing of oxygen in a hyperbaric chamber at higher pressure than the normal atmospheric pressure (100 kPa). The HBOT-dose, i.e., the overall effect of the treatment pressure, duration and frequency, is limited by the risk of oxygen toxicity in the CNS and the lungs. HBOT is typically given as 100% oxygen at 240-280 kPa pressure for 60-90 minutes, 1-3 times daily. The treatment leads to an up to 20-fold increase in the amount of oxygen dissolved in plasma. This leads to a series of various physiological effects.

HBOT is mainly given to patients with localized or generalized hypoxia. Hypoxia in threatened tissues can be reversed in acute conditions such as decompression sickness in divers, gas embolism, life-threatening carbon monoxide poisoning and soft tissue infection (Swedish Society of Anesthesiology and Intensive Care Medicine, SFAI, 2011).

Repeated treatments stimulate neovascularization and can accelerate wound healing in hypoxic tissues (Marx et al., 1990; Brismar et al., 1997; Reng et al., 1998).

For diabetic foot ulcers and late radiation injury in soft tissues HBOT is given once a day, 5 days a week for 6 to 8 weeks (30 to 40 treatments sessions). The treatment can be given in two different types of hyperbaric chambers; multi- and mono-place chambers.



*Modern square hyperbaric chamber.
(Karolinska Hospital, Stockholm, Sweden)*



*Traditional cylindrical hyperbaric chamber
(SU/Eastern Hospital, Göteborg, Sweden)*

3b The work group's understanding of the potential value of the health technology

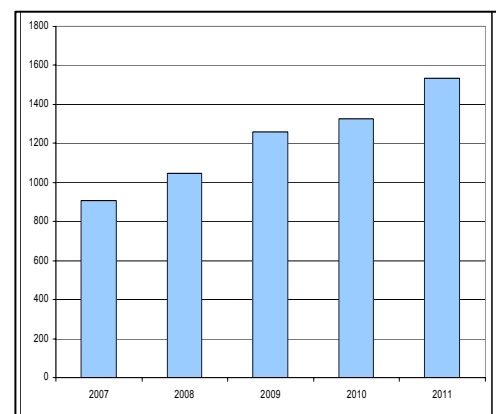
HBOT for diabetic foot ulcers has been used for decades, but is a relatively new therapy for late radiation injury. Published trials suggest that HBOT is effective in these pathological conditions (Löndahl et al., 2010; Clark, 2008; Marx et al., 1990). Both the The European and American Hyperbaric Medical Societies (ECHM and UHMS) list diabetic foot ulcers and late radiation injuries as conditions in which HBOT can be recommended. In a review from Karolinska Hospital 2010 the same recommendations are given (Lind et al., 2010).

Currently, 5 centers in Sweden (Göteborg, Stockholm, Karlskrona, Helsingborg, Uddevalla) use HBOT as a treatment modality for diabetic foot ulcers and late radiation injury.

In 1986 a unit for HBOT was established at Sahlgrenska University Hospital. It is situated at and administered by the Department of Anaesthesiology and Intensive care, Sahlgrenska University Hospital/ Eastern Hospital.



Elective hyperbaric session



Number of elective treatment sessions/yr

During 2011 1,534 elective HBOT sessions were given in the hyperbaric chamber at Sahlgrenska University Hospital/ Eastern hospital.(see figure above). Seven patients were treated for non-healing diabetic foot ulcers and 21 patients for late radiation injuries to soft tissues (proctitis, cystitis).

As previously discussed, it is difficult to estimate the total number of patients eligible for HBOT in region Västra Götaland (see 2b). If half of the patients with non-healing diabetic foot ulcers will receive HBOT, the number of patients is estimated to be 50-75 patients per year. As for radiation proctitis and cystitis it is reasonable to assume that about 30-40 patients are eligible for treatment every year (see 2b). In addition to these estimates there is an additional number of patients living outside Region Västra Götaland that is referred to the unit.

Patients with non-healing diabetic foot ulcers and late radiation injuries have a markedly reduced quality of life. Interventions such as repeated surgical debridement of ulcers, amputations, blood transfusions, repeated urological and proctological surgical procedures carry a high medical cost, and expose the patients to risk of

adverse effects and discomfort. If HBOT can improve wound healing and reduce symptoms the quality of life will be greatly improved. Furthermore, medical resources can be re-allocated.

3c The central question for the current HTA project in one sentence

Is hyperbaric oxygen therapy more effective in healing diabetic foot ulcers and to treat radiation induced cystitis and proctitis compared to standard care?

3d PICO

P= Patients, I= Intervention, C= Comparison, O=Outcome

PICO1

P = Patients with diabetic foot ulcers of at least 4 weeks duration, who have received optimal conventional treatment, and in whom revascularisation intervention is not possible.

I = HBOT in addition to conventional treatment.

C = Conventional treatment or placebo.

O = Ulcer healing, amputation rate, quality of life, complications.

PICO2

P = Patients with symptomatic proctitis as a delayed or persistent injury due to radiation therapy.

I = HBOT in addition to conventional treatment.

C = No treatment, other conventional treatment or placebo.

O = Mucosal healing, quality of life, complications.

PICO3

P = Patients with symptomatic cystitis as a delayed or persistent injury due to radiation therapy.

I = HBOT in addition to conventional treatment.

C = No treatment, other conventional treatment or placebo.

O= Haemorrhage (macrohematuria), quality of life, complications

3e Key words

Hyperbaric Oxygenation; Diabetic Foot; Radiation Injuries; Cystitis; Proctitis

4 Search strategy, study selection and references – appendix 3 (Search strategy, Eligibility criteria, Selection process – flow diagram, References)

During April, 2011, the library performed searches in PubMed, the Cochrane Library, CINAHL, EMBASE and a number of HTA-databases. Reference lists of relevant articles were also scanned for additional references. A total of 607 articles were identified after removal of duplicates, of which 549 abstracts were excluded by the library. Another 18 articles were excluded by the library after having been read in full text.

40 articles were sent to the work group for assessment. Articles with patients who had less than 20 HBO treatment sessions were excluded.

28 of these articles are included in the report; 5 are randomized controlled trials, and 5 are controlled studies. Two of the articles, (Löndahl et al., 2010; Löndahl et al., 2010) refers to the same study. They have all been critically appraised. The 11 case-series have only been used in the outcome rate tables in Appendix 1. Three systematic reviews and two cost-effectiveness studies are commented upon.

The appraisal of articles is based on checklists from SBU regarding randomized controlled trials, and other checklists developed by Olle Nyrén, professor, Karolinska Institutet, Stockholm.

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in appendix 3. The literature search and exclusion of abstracts were made by two librarians (TS, ME) in consultation with the HTA-centre and the work group.

5a Describe briefly the present knowledge of the health technology

In 2004 Kranke et al. published a systematic review of HBOT for chronic wounds in the Cochrane Database of Systemic Reviews (Kranke et al., 2004). The literature search covered published reports until the end of 2003. Based on pooled data of three trials, two of which also are included also in the present HTA report, they concluded that adjunctive HBOT reduced in the risk of major amputation. Healing rates were reported in one trial (also included in the present HTA report), and the authors merely stated that it reported a significant improvement in the chance of healing 1 year after therapy.

The Canadian Agency for Drugs and Technologies in Health published an HTA-report on “Adjunctive Hyperbaric Therapy for Diabetic Foot Ulcer: An Economic Analysis” in 2007 (Hailey et al., 2007). The literature search identified seven controlled studies. The conclusion was that adjunctive HBOT for diabetic foot ulcer is more effective than standard care (lower proportion of lower limb amputation, higher rate of complete ulcer healing and better outcome of patients with wounds that remained unhealed), although the available evidence remained limited.

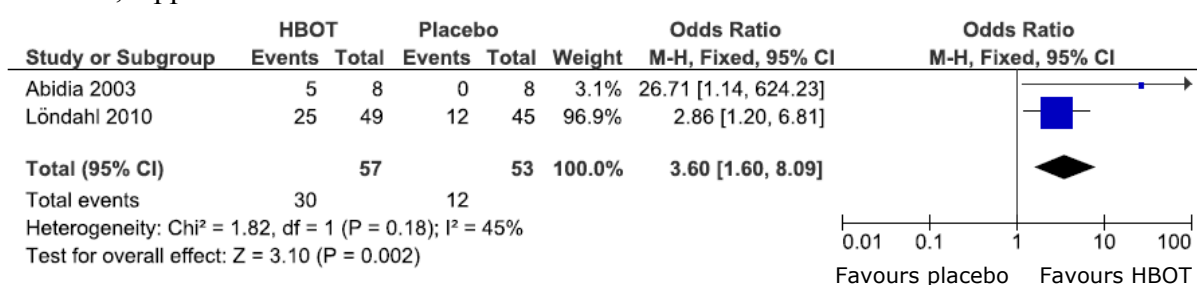
Goldman published a systematic review on HBOT for wound healing and limb salvage in 2009 (Goldman, 2009). Based on five studies, of which two were RCTs and also are included in the present HTA report, he concluded that there is a high level of evidence that HBOT reduces risk of amputation for patients with diabetic foot ulcer complicated by surgical infection. Furthermore, based on six studies (two were RCTs) he concluded that the level of evidence was also high that HBOT promotes partial or complete healing of problem wounds.

Diabetic foot ulcers

Ulcer healing

Three randomised, controlled trials (RCTs) and three non-randomised, controlled studies were identified in the present literature search that have reported the effect of HBOT on ulcer healing. The total number of patients in these studies was 340 of which 212 were included in the RCTs. Two RCTs had follow-up of one year, and one non-randomised, controlled study of three years. All the six studies had some uncertainty with regard to external validity.

All studies reported a higher rate of complete ulcer healing in the HBOT group, with about two out of three completely healed ulcers in the RCTs. This was an almost doubled frequency in comparison to conventional therapy (Table 1:1, Appendix 1). A meta-analysis of the two RCTs with moderate to high quality yielded an odds ratio of 3.60 (95 % confidence limit 1.60, 8.09) as illustrated below. With regard to data from the study by Löndahl et al. 2010 see comment in Table 1:1, Appendix 1.



It should be pointed out that the study subjects were selected patients with chronic ulcer that have not healed with conventional treatment for many months (average duration 6-10 months) prior to entry of the studies (Abidia et al. 2003, Löndahl et al. 2010).

HBOT improves ulcer healing in patients with a diabetic foot ulcer. The quality of evidence of this effect is moderate according to the GRADE system (GRADE ⊕⊕⊕○)

Ulcer size

Two RCTs and two non-randomised, controlled studies have reported the effect of HBOT on ulcer size. The total number of patients in these studies was 94. The RCTs had a follow-up time of six months and 4 weeks, respectively. The time of follow-up was 7 and 8 weeks, respectively, in the non-randomised, controlled studies. All studies reported a greater decrease of the size of the ulcer in the patient groups treated with HBOT, ranging from a reduction of 30 – 100 % in comparison to 15 – 95 % in the control groups (Table 1:2, Appendix 1)

All the studies had some uncertainty with regard to external validity. There was some heterogeneity between the RCTs (see SoF-table).

HBOT is more effective to decrease ulcer size than standard treatment in patients with a diabetic foot ulcer. The quality of evidence of this effect is low according to the GRADE system (GRADE ⊕⊕○○).

Amputation

Three RCTs and two non-randomised, controlled studies have reported the effect of HBOT on the frequency of amputation due to a diabetic foot ulcer. The total number of patients in these studies was 407. The RCTs had a follow-up time of one year. The non-randomised, controlled studies did not specify the time of follow-up. Two RCTs reported no difference in the

amputation frequency between the treatment groups (Table 1:3, Appendix 1). The other studies reported a reduced frequency of amputations in the HBOT group, but all three of them had methodological flaws.

All the studies had some uncertainty with regard to external validity. There was some heterogeneity between the RCTs (see SoF-table).

A possible beneficial effect of HBOT on the need for amputation in patients with a diabetic foot ulcer has not been shown. The quality of evidence of the effect of HBOT with regard to need for amputation is very low according to the GRADE system (GRADE ⊕○○○).

Quality of life

Two RCTs reported the effect of HBOT on quality of life. The total number of patients was 91, and the time of follow-up was one year. The larger RCT reported an improvement in two SF-36 domain scores within the subset of patients in the HBOT group who healed their ulcers (Table 1:4, Appendix 1). However, there were no differences in quality of life scores after 12 months between the HBOT group and the placebo group in either study.

The external validity of the study is uncertain.

An improvement of quality of life by HBOT in patients with a diabetic foot ulcer has not been shown. The quality of evidence of the effect of HBOT on quality of life is low according to the GRADE system (GRADE ⊕⊕○○).

Radiation proctitis

Mucosal healing

One RCT reported the effect of HBOT on mucosal healing.

The study was designed with a cross-over component where the patients that received placebo were offered to cross-over to active treatment 6 weeks after the end of the placebo session. This makes it impossible to compare the long-term effects between the placebo and the active group. The total number of patients was 120. After 6 weeks the study reported a significant result in favour of treatment. Five patients out of 63 healed completely in the HBOT group in comparison to none in the control group. (Table 1:5, Appendix 1).

The external validity of the study is uncertain and there is some imprecision of the data (SoF table).

HBOT improves mucosal healing in patients with radiation proctitis. The quality of evidence of this effect is low according to the GRADE system (GRADE ⊕⊕○○).

Quality of life

One RCT reported the effect of HBOT on quality of life.

Due to imbalance of the baseline data, the group randomised for active treatment had a lower QoL-score than the placebo group. The total number of patients was 120. An improvement in the quality of life between baseline and 6 weeks follow-up was reported in the group treated with HBOT (Table 1:6, Appendix 1).

The external validity of the study is uncertain and there is some imprecision of the data (SoF table).

An improvement of quality of life by HBOT in patients with a radiation proctitis has not been unequivocally shown. The quality of evidence of the effect of HBOT on quality of life is very low according to the GRADE system (GRADE ⊕○○○).

Radiation cystitis

Bleeding

One non-randomised, controlled study with 14 patients has reported the effect of HBOT on bleeding (macrohematuria) in patients with radiation cystitis (Table 1:7, Appendix 1). The study is of uncertain external validity and has serious study limitations with imprecise data (SoF table).

The quality of evidence of the effect of HBOT on bleeding (macrohematuria) is very low according to the GRADE system (GRADE ⊕○○○).

Complications and adverse effects:

Hyperbaric oxygen treatment has some well known side effects which are independent on the underlying reason for such therapy. Such side effects are middle ear barotraumas, sinus squeeze, claustrophobia, myopia, oxygen induced pulmonary injury, pulmonary barotraumas and oxygen-induced seizures.

Middle ear barotraumas are the most common side effects. The incidence is reported to be between 1 - 45 % depending on how it is defined. Sinus squeeze is the second most common side effect. Progressive myopia may occur during repeated HBO sessions, usually after more than 20 sessions. The exact mechanism is not fully understood, but it appears to be of lenticular in origin, and usually regresses completely within weeks after the last session. Oxygen induced seizures are rare, and it is estimated to occur in less than 0.1% of HBO sessions. (Clark, 2008; Banham, 2011). Our own experience is one episode of seizures per year in about 1500 treatments.

Many HBOT studies do not report any data on complications, and some studies give only a vague description of complications, such as “some mild effects”. In the controlled studies and case series of HBOT for diabetic foot ulcers, radiation proctitis and radiation cystitis that have been appraised in the present report the incidences of complications do not differ from what has been reported in the literature for other indications of HBOT (Table 1:8, Appendix 1). The role of HBOT in six reported fatal cases (3 multiorgan failure, 2 myocardial infarctions and 1 sepsis) is unclear.

5b Outcome tables – appendix 1

5c Excluded articles – appendix 2

5d Ongoing research?

A search in Clinicaltrials.gov (October 21st, 2011) using the search strategy; diabetic AND ulcer AND hyperbaric AND oxygen, identified six registered trials in the database. Only one of them is of interest for the specific question at issue of this report. This is a prospective, double-blind, randomised, controlled clinical trial from Toronto, Canada, in which standard wound care combined with adjunctive HBOT is compared to standard wound care only for the treatment of chronic, non-healing ulcers of the lower limb in patients with diabetes mellitus (“Hyperbaric Oxygen Therapy (HBOT) for Chronic Diabetic Lower Limb Ulcers”; NCT00621608).

A search in Clinicaltrials.gov (October 21st, 2011) using the search strategy; cystitis AND proctitis AND hyperbaric AND oxygen; identified two registered trials in the database. None of them are of interest for the specific question at issue of this report.

6 Which medical societies or health authorities recommend the new health technology?

- The National Board of Health and Welfare
- Medical societies
- Other health authority

Which medical society or health authority?

SFAI (Swedish Society of Anaesthesiology and Intensive Care Medicine)

ECHM (European Committee of Hyperbaric Medicine)

UHMS (Undersea and Hyperbaric Medical Soc.)

Ethical aspects

7 Ethical consequences

There is substantial suffering among patients with diabetic foot ulcers, radiation proctitis and radiation cystitis. HBOT improves healing of diabetic foot ulcers with few and manageable side effects. Therefore it would be unethical to deny HBOT for this patient group.

If HBOT is made a routine treatment it is not likely that other patient groups, or other treatments, will be negatively affected.

Organisation

8a When can this new health technology be put into practice?

Hyperbaric oxygen therapy is already in use. However, the treatment facility at the Department of Anaesthesiology and Intensive Care, Sahlgrenska University Hospital/ Eastern hospital, Göteborg, is soon outdated.

The treatment capacity of the hyperbaric unit is sufficient for the current number of referred patients. If the number of referred patients continues to increase with 10 - 20% per year the full capacity will be reached within a few years.

8b Is this technology used in other hospitals in region Västra Götaland or Sweden?

Yes, in;

Uddevalla Hospital, Uddevalla

Karolinska University Hospital, Solna

Blekinge Hospital, Karlskrona

Helsingborg Hospital, Helsingborg

8c According to the work group, will there be any consequences of the new health technology for personnel?

The Hyperbaric unit at Sahlgrenska University Hospital/ Eastern hospital can manage a minor increase in the number of patients without any major consequences for the personnel. If this increase leads to more than 2,000 treatments a year it would require an increase of the nursing staff. With a new larger hyperbaric chamber, the number of patients treated in each session can be increased from five to maximum 10 subjects. This would not require an increase in the staff.

8d Will there be any consequences for other clinics or supporting functions at the hospital or in the whole region Västra Götaland?

There may be a decrease in the current demand of both outpatient and hospital care for patients that are successfully treated with conventional care for their diabetic foot ulcers or late radiation proctitis and cystitis.

9a **Present costs of currently used technologies.**

In a Swedish review the average direct costs of conventional treatment of an infected diabetic ulcer until its healing was calculated to be about SEK 139 000 and the cost for an ulcer leading to a lower-extremity amputation about SEK 238 000-266 000 (Ragnarsson Tennvall et al., 2004). In the recently published Eurodial study the corresponding costs were reported to be EUR 7 722 (SEK 72 600; healed within one year), EUR 20 064 (SEK 188 600; not healed within one year), and EUR 25 222 (SEK 237 000; ulcer leading to major amputation) respectively (Prompers et al., 2008).

It is assumed that the incidence of non-healing diabetic foot ulcers in Västra Götaland is 100-150 patients per year (see section 2d), and that 50-75 of these would be eligible for HBO treatment. If we assume that these patients will heal with conventional treatment within one year (i.e. best case according to the previous paragraph), at a cost of SEK 72 600 per patient (see above), the total annual cost for these 50-75 patients would be about 3,6-5,4 million SEK in the region, using standard treatment [$(50 \times 72\,600) \approx 3.6$ million ; $(75 \times 72\,600) \approx 5.4$ million]. As some of these patients are likely to suffer an amputation and/or will not heal within one year, the actual cost is probably higher.

There are no published cost estimations for standard treatment of post-radiation cystitis and post-radiation proctitis.

The actual costs of conventional treatment, and other associated costs, of non-healing diabetic foot ulcers and of post-radiation cystitis/proctitis in the Region Västra Götaland have not been calculated in this report. However, it is unlikely that the costs concerning non-healing diabetic foot ulcers would differ substantially from the reported costs in the two studies referred above.

9b **Expected costs of the new health technology?**

The cost for one elective HBO treatment session in Göteborg is currently SEK 2 600 per patient. The cost of a normal series of 30 treatment sessions (6 weeks) will then be SEK 78 000 per patient.

It is assumed that every year 50-75 patients with non-healing diabetic foot ulcers in Västra Götaland will be eligible for HBO treatment. Thus, the HBOT of this group of patients will cost 3.9-5.9 million SEK per year.

The estimated annual incidence of severe post-radiation cystitis and post-radiation proctitis in Västra Götaland eligible for HBO treatment is 30-40 patients. HBO treatment for these patients would thus cost 2.3-3.1 million SEK per year.

9c Total change of cost.

According to the calculations above (standard treatment at least 3.6 – 5.4 million SEK) the total estimated costs of HBO treatment (3.9 – 5.9 million SEK) are probably only moderately increasing the total costs with regard to diabetic foot ulcers. The healing rate is increased and thereby, the total time needed for complete ulcer healing is greatly reduced. Parts of the costs will be transferred from primary care and out-patient diabetic clinics to the HBOT unit at the hospital. However, it is still uncertain how the economical effects will be distributed on various sectors of health care.

9d Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?

No

9e Are there any available analyses of health economy? Cost advantages or disadvantages?

Chuck et al. reported in their cost-effectiveness analysis that the 12-year cost for patients receiving HBOT was lower compared with standard care alone (Chuck et al. 2008). Moreover, the HBOT patients had a better outcome in terms of quality-adjusted life-years. Thus, the authors conclude that adjunctive HBOT for diabetic foot ulcers is cost-effective compared to standard care. The additional cost for a quality adjusted life year gained by HBOT is estimated to be moderate to high in the short term but low in the long-term.

Another cost-effectiveness analysis has also indicated that HBO therapy is cost-effective in the treatment of diabetic ulcers, particularly in a long-term perspective (Guo et al., 2003).

In the Canadian HTA-report a decision model was developed to determine the cost effectiveness of adjunctive HBOT for the treatment of diabetic foot ulcer with a time horizon of 12 years (Hailey et al., 2007). Based on the available data the conclusion was that adjunctive HBOT is cost effective when compared with standard care.

Thus, the available health economic evidence point in the direction that it is cost-effective to provide HBOT to diabetic patients with non-healing foot ulcers. The costs for foot-ulcers are high (Ragnarson Tennvall et al., 2004) and the impact on the patients' health related quality of life is substantial. The additional cost for a quality adjusted life year gained by HBOT is estimated to be moderate to high in the short term but low in the long-term (Chuck et al., 2008). However, the evidence for this is sparse.

No cost-effectiveness study has been identified within the systematic review for HBOT for delayed or persistent injury due to radiation therapy. From a health economic perspective further data is required regarding patient reported outcomes and health care utilization due to chronic injury, in order to estimate the cost-effectiveness.

Thus, the available health economic analyses indicate that HBOT is cost-effective in diabetic patients with non-healing foot ulcers.

Unanswered Questions

10a **Important gaps in scientific knowledge?**

There is a need for further clinical studies regarding the effects of HBOT on the healing of diabetic foot ulcers as well as its role in the treatment of radiotherapy induced cystitis and proctitis.

There is also a need for further studies regarding the specific physiological effects of HBOT.

10b **Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?**

Dr Magnus Löndahl at Lund University hospital, Sweden, is currently planning a randomised, controlled, double-blind, multicenter study of the effects of HBOT on diabetic foot ulcers. The Department of Anaesthesiology and Intensive care, Sahlgrenska University Hospital/ Eastern hospital, Göteborg will participate in this study.

We have recently started the planning of a prospective, controlled, randomised, multi-center, clinical trial of the effect of HBOT in patients with radiotherapy induced cystitis. The study will have a cross-over design and a blinded evaluation of the primary outcome variable. The study will be collaboration between the Nordic countries co-ordinated by us.

Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Hyperbar oxygenerapi av kroniska fotsår hos patienter med diabetes mellitus och av sena strålskador i lilla bäckenet hos patienter som tidigare genomgått radioterapi

Frågeställning:

Är hyperbar oxygenerapi en effektivare behandling av diabetiska fotsår och strålningsorsakad cystit och proktit än konventionell standardbehandling?

PICO

P1 = Patienter med diabetes mellitus och med ett fotsår som funnits i minst 4 veckor trots optimal standardbehandling, och där revaskularisering inte är möjlig.

P2 = Patienter med symtomatisk proktit till följd av tidigare genomgången strålterapi.

P3 = Patienter med symtomatisk cystit till följd av tidigare genomgången strålterapi.

I = Hyperbar oxygenerapi (HBOT) som tillägg till konventionell standardbehandling.

C1 = Konventionell standardbehandling eller placebo.

C2 = Ingen behandling, konventionell standardbehandling eller placebo.

C3 = Ingen behandling, konventionell standardbehandling eller placebo.

O1= Sårsläkning, amputationsfrekvens, livskvalitet, komplikationer.

O2= Läkning av slemhinna, livskvalitet, komplikationer.

O3= Blödning (makrohematuri), livskvalitet, komplikationer.

Resultat av HTA-processen:

Metod och målgrupp:

Patienter med diabetes mellitus kan utveckla sensorisk, motorisk och autonom neuropati. I kombination med mikro- och makrovaskulära komplikationer kan detta leda till en så kallad "diabetesfot", som i sin tur ofta kompliceras av ett kronisk svårläkt sår.

Patienter som behandlats med radioterapi mot en malign sjukdom i det lilla bäckenet utvecklar ibland lång tid efter behandlingen sena strålskador i form av kronisk proktit eller cystit.

Det "diabetiska fotsåret", strålproktit och strålcystit har vissa gemensamma karakteristika. Typiskt för samtliga är hypoxi i de drabbade vävnaderna. HBOT är en behandling som markant kan öka syretillförseln till de drabbade hypoxiska vävnaderna. Genom förbättrad syresättning har HBOT därmed möjlighet att förbättra sårsläkningen och strålningsorsakad proktit och cystit.

Evidensläge:

Kroniska fotsår hos diabetiker

Den systematiska litteratursökningen identifierade fyra randomiserade, kontrollerade studier (RCT) och fyra icke-randomiserade, kontrollerade studier som har rapporterat behandlingseffekter av HBOT hos diabetespatienter med kroniska fotsår som inte läker".

Sårsläkning, sårtyta, amputationer och livskvalitet

Studierna har rapporterat en högre frekvens av läkta sår i de HBO-behandlade studiegrupperna med vartannat upp till två av tre läkta sår efter genomgången behandlingsserie. Det är en nästan dubbelt så hög läkningsfrekvens jämfört med konventionell standardbehandling. Även en större reduktion i sårtyta observerades i patienterna som fick HBO behandling med en minskad sårtyta från 30 -100 % jämfört med 15 – 95 % i kontrollpatienterna.

Det föreligger ett måttligt stöd för att HBOT leder till förbättrad sårsläkning hos patienter med långvariga kroniska "diabetiska fotsår" (Måttligt starkt vetenskapligt underlag GRADE ⊕⊕⊕○).

Två RCT:er fann ingen positiv effekt med avseende på amputationsfrekvens. Två icke-randomiserade studier rapporterade däremot detta. Båda dessa studier hade dock metodologiska svagheter.

Det vetenskapliga underlaget för effekterna av HBOT på behovet av amputation är otillräckligt (Otillräckligt vetenskapligt underlag Grade ⊕○○○).

Två RCT har studerat effekterna på livskvalitet. Man fann en förbättrad livskvalitet hos de HBO-behandlade patienterna som helt läkte ut sina sår. Emellertid visar ingen studie någon skillnad i livskvalitet för hela HBOT-grupperna jämfört med kontrollgrupperna efter 12 månader. Man har inte påvisat någon skillnad i livskvalitet mellan HBO-behandlade och konventionellt behandlade patienter (Begränsat vetenskapligt underlag GRADE ⊕⊕OO).

Strålproktit

Den systematiska litteratursökningen identifierade en RCT som har rapporterat behandlingseffekter av HBOT hos patienter med proktit efter radioterapi.

Läkning av slemhinna och livskvalitet

I studien fann man en signifikant behandlingseffekt. Under en behandlingsperiod på tre månader läkte slemhinnan i ändtarmen helt hos sex av 63 patienter i HBOT gruppen jämfört med hos ingen patient i kontrollgruppen. Även en förbättrad livskvalitet observerades i de HBO-behandlade patienterna. Det föreligger ett visst stöd för att HBOT leder till bättre läkning av skadad slemhinna och till en förbättrad livskvalitet hos patienter med strålproktit (Begränsat vetenskapligt underlag GRADE ⊕⊕OO).

Strålcystit

Den systematiska litteratursökningen identifierade en icke-randomiserad, kontrollerad studie som har rapporterat behandlingseffekter av HBOT hos patienter med cystit efter radioterapi. Studien har osäker extern validitet, allvarliga studiebegränsningar och har oprecisa data. Det vetenskapliga underlaget för effekterna av HBOT på strålcystit är otillräckligt. (Otillräckligt vetenskapligt underlag Grade ⊕OOO).

Komplikationer och biverkningar:

Allvarliga biverkningar som syreutlösta kramper, medvetslöshet eller död har rapporterats i en frekvens mellan 0 - 5 %, och mindre allvarliga biverkningar i en frekvens som varierat mellan 0 – 28 % i olika studier.

Etiska aspekter och frågeställningar:

Kan vi avstå från att behandla patienter med kroniska ”diabetiska fotsår” eller strålproktit med hyperbar oxygenerapi i avvaktan på resultaten i planerade och pågående studier när det redan idag finns ett visst stöd för att behandlingen är till nytta för dessa svårt drabbade patienter?

Economiska aspekter

Kostnaden för HBOT av patienter med svårläkta ”diabetiska fotsår” uppskattas till 3,9-5,9 miljoner kronor per år i Västragötalandsregionen, och till 2,3 – 3,1 miljoner kronor årligen för behandling av patienter med strålproktit och strålcystit. Kostnads-effektanalyser indikerar att tillägg av HBOT till vanlig sårbehandling av ”diabetiska fotsår” är kostnadseffektivt jämfört med standardbehandling. Det saknas kostnads-effektanalyser avseende strålproktit och strålcystit.

Sammanfattning och slutsats

Det föreligger ett måttligt stöd för att hyperbar oxygenerapi leder till förbättrad sårhäkning hos patienter med långvariga kroniska ”diabetiska fotsår” (Måttligt starkt vetenskapligt underlag (GRADE ⊕⊕⊕O), och ett visst stöd för att HBOT leder till bättre läkning av skadad slemhinna och till en förbättrad livskvalitet hos patienter med strålproktit (Begränsat vetenskapligt underlag GRADE ⊕⊕OO). Det vetenskapliga underlaget för effekterna av HBOT på strålcystit är otillräckligt (Otillräckligt vetenskapligt underlag GRADE ⊕OOO).

För HTA-kvalitetssäkringsgruppen
Göteborg, 2012-02-10

Christina Bergh, Professor.
HTA-chef

Statement from HTA-Centre, Region Västra Götaland

Hyperbaric oxygen therapy in the treatment of diabetic foot ulcers and late radiation tissue injuries of the pelvis

Question at issue:

Is hyperbaric oxygen therapy more effective in healing diabetic foot ulcers and to treat radiation induced cystitis and proctitis compared to standard care?

PICO

- P1 = Patients with diabetic foot ulcers of at least 4 weeks duration, who have received optimal conventional treatment, and in whom revascularisation intervention is not possible.
P2 = Patients with symptomatic proctitis as a delayed or persistent injury due to radiation therapy.
P3 = Patients with symptomatic cystitis as a delayed or persistent injury due to radiation therapy.
- I = Hyperbaric oxygen therapy (HBOT) in addition to conventional treatment.
- C1 = Conventional treatment or placebo.
C2 = No treatment, other conventional treatment or placebo.
C3 = No treatment, other conventional treatment or placebo.
- O1= Ulcer healing, amputation frequency, quality of life, complications.
O2= Mucosal healing, quality of life, complications.
O3= Haemorrhage (macrohematuria), quality of life, complications.

Summary of the health technology assessment:

Method and patient category:

Patients with diabetes mellitus can develop sensory, motor and autonomic neuropathies. Combined with micro- and macrovascular complications these pathophysiological consequences may result in a “diabetic foot”, which can lead to a chronic, non-healing ulcer.

Patients with malignant diseases in the pelvis region treated with radiotherapy can develop late radiation tissue injuries resulting in a chronic proctitis or cystitis.

The “diabetic foot ulcer” and the radiation proctitis and cystitis share same characteristics, one of which being hypoxia in the affected tissues. Hyperbaric oxygen therapy is a treatment in which oxygen delivery to hypoxic tissues can be substantially increased. This has the potential to enhance ulcer healing and cure hypoxia-induced proctitis and cystitis.

Level of evidence:

Diabetic foot ulcers

The systematic literature search identified four randomised, controlled trials (RCT) and four non-randomised, controlled cohort studies, which have reported the effects of HBOT on chronic non-healing diabetic foot ulcers.

Ulcer healing, ulcer size, amputations and quality of life

The studies have reported a higher rate of complete ulcer healing in the HBOT groups with about two out of three completely healed ulcers. This was an almost doubled healing rate compared to conventional therapy. The studies have also reported a greater decrease of the ulcer size in the patient groups treated with adjunctive HBOT.

It is concluded that HBOT improves ulcer healing in patients with a chronic diabetic foot ulcer. The quality of evidence of this effect is moderate according to the GRADE system (GRADE ⊕⊕⊕O).

Two RCTs reported that there was no beneficial effect with regard to the amputation rate. Two non-randomised studies reported a reduced need of amputations in HBOT patients, but both these studies had methodological flaws.

It is concluded that a possible beneficial effect of HBOT on the need for amputation in patients with a diabetic foot ulcer has not been shown. The quality of evidence of the effect of HBOT with regard to need for amputation is very low according to the GRADE system (GRADE ⊕OOO).

Two randomised, controlled trials have reported the effect on quality of life. The larger RCT reported an improvement of quality of life in the HBO-treated patients who healed their ulcers. However, there were no

differences in quality of life scores after 12 months between the HBOT group and the placebo group in either study.

It is concluded that an improvement of quality of life by HBOT in patients with a diabetic foot ulcer has not been shown. The quality of evidence of the effect of HBOT on quality of life is low according to the GRADE system (GRADE ⊕ ⊕OO).

Radiation proctitis

The systematic literature search identified one randomised, controlled trial, which has reported the effect of HBOT on late radiation proctitis.

Mucosal healing and quality of life

The study reported a significant result in favour of treatment. During a treatment period of three months five patients out of 63 healed the proctitis completely in the HBOT group in comparison to none in the control group. An improvement of the quality of life score was also observed in the HBO-treated patients.

It is concluded that HBOT improves mucosal healing in patients with radiation proctitis. The quality of evidence of this effect is low according to the GRADE system (GRADE ⊕ ⊕OO).

Radiation cystitis

The systematic literature search identified one non-randomised, controlled study, which has reported the effect of HBOT on late radiation cystitis. The study is of uncertain external validity, has serious study limitations and has imprecise data.

It is concluded that a reduction of bleeding in patients with radiation cystitis by HBOT has not been shown. The quality of evidence of the effect of HBOT on bleeding (macrohematuria) is very low according to the GRADE system (GRADE ⊕OOO).

Side effects and complications:

Serious adverse events such as oxygen seizures, unconsciousness or death have been reported to occur at a rate ranging from 0 - 5 %, and non-serious adverse events with a rate between 0 - 28 %.

Ethical aspects:

It does not seem appropriate to withhold HBOT in patients with diabetic foot ulcers and late radiation proctitis while we await the results of forthcoming and ongoing studies when current evidence indicates that it can help these categories of patients with chronic severely disabling symptoms.

Economical aspects

The cost of HBOT in patients with non-healing diabetic foot ulcer is estimated to be 3.9-5.9 million SEK per year in region Västra Götaland, and in patients with radiation cystitis and proctitis 2.3-3.1 million SEK per year. Cost-effective analyses indicate that adjunctive HBOT for diabetic foot ulcers is cost-effective compared to standard care. No cost-effective analyses are available for post-radiation tissue injuries.

Concluding remarks

Hyperbaric oxygen therapy improves the healing rate of chronic, non-healing diabetic foot ulcers (Moderate quality of evidence, GRADE ⊕ ⊕ ⊕ O). There is some support that HBOT also improves healing of late radiation proctitis with an improved quality of life (Low quality of evidence, GRADE ⊕ ⊕ OO). The documentation of the effects of HBOT on radiation cystitis is of very low (Very low quality of evidence, Grade ⊕ OOO).

On behalf of the Regional HTA Centre, Region Västra Götaland in Sweden

Göteborg, Sweden, 2012-02-10

Christina Bergh, Professor, MD.
Head of Regional HTA Centre

The Regional Health Technology Assessment Centre (HTA-centrum) of the Western Region in Sweden (Region Västra Götaland, VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

The former Head of Department of Anaesthesiology and Intensive care, Sahlgrenska University Hospital/ Eastern hospital, Göteborg, Sweden, Olof Ekre requested the present HTA.

The HTA was accomplished during the period of 2011-02-07 – 2011-10-26. A working group under the chairmanship of Per Arnell, MD, at the Department of Anaesthesiology and Intensive Care, Sahlgrenska University Hospital/ Eastern hospital, Sahlgrenska University Hospital, Göteborg, Sweden, produced the HTA report. The other members of the working group were Nicklas Oscarsson, MD, Department of Otorhinolaryngology, and Anders Rosén, MD, Department of Anaesthesiology and Intensive Care, Sahlgrenska University Hospital/ Eastern hospital, Sahlgrenska University Hospital, Göteborg, Sweden.

The participants from the HTA centre were Ola Samuelsson MD, PhD, Maud Eriksson, librarian, and Therese Svanberg, librarian, Sahlgrenska University Hospital, Göteborg, Sweden.

Ann Thurin Kjellberg, MD, PhD, has critically appraised the report.

Appendix 1:1 Outcome variable: Frequency of completely healed diabetic foot ulcers in patients treated with hyperbaric oxygen therapy (HBOT) and conventional treatment.

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					HBOT n (%)	Conventional treatment n (%)		
Abidia, 2003	UK	Randomised, controlled trial	18	2	6 weeks: 5/8 6 months: 5/8 1 year : 5/8 p = 0.03	6 weeks: 1/8 6 months: 2/8 1 year : 0/8	Absolute difference after 6 months: 38 %	Moderate
Löndahl, 2010	Sweden	Randomised, controlled trial	94	19 ⁱ	<p>“ITT-analysis”ⁱⁱ 1 year : 25/48 (52%) p = 0.03</p> <p>ITT-analysisⁱⁱⁱ 1 year : 25/49 (51%) p = 0.02</p> <p>Per protocol analysis 1 year: 23/38 (61%) p = 0.009</p>	<p>“ITT-analysis” 1 year : 12/42 (29%)</p> <p>ITT-analysisⁱⁱⁱ 1 year : 12/45 (27%)</p> <p>Per protocol analysis 1 year: 10/37 (27 %)</p>	Absolute difference after 12 months: 33 - 34 % The 4 patients who died during FU ^{iv} are added in the respective denominator.	High
Duzgun, 2008	Turkey	Randomised, controlled trial	100	0	FU ^{iv} not reported: 33/50 (66%) p < 0.0001	FU not reported: 0/50 (0%)	Absolute difference: 66 %	Low
Kalani, 2002	Sweden	Non-randomised, controlled study	38	0	3 years: 13/17 (76%) p = 0.10	3 years: 10/21 (48%)	Absolute difference after 36 months: 28 %	Low
Oriani 1990	Italy	Non-randomised, controlled study	80	0	37/62 (60 %) p < 0.001	2/18 (13 %)	Time of follow-up was not reported. Absolute difference: 47 %	Low
Zamboni, 1997	USA	Non-randomised, controlled study	10	0	4 – 6 months: 4/5 (80%) p = 0.20	4 – 6 months 1/5 (20%)	Absolute difference after 4 - 6 months: 60 %	Low

Footnotes:

i. 19 subjects had less than 30 of the planned 40 treatment sessions

ii. Four patients died during the one-year follow-up, i.e. 94 - 4 = 90 patients available for the “ITT-analysis” presented in the publication

iii. Addition of the four patients who died, and who should have been included, in a correct ITT-analysis. iv. FU = follow-up

Appendix 1:2

Outcome variable: Reduction of ulcer size in patients treated with hyperbaric oxygen therapy (HBOT) and conventional treatment.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					HBOT	Conventional treatment		
Abidia, 2003	UK	Randomised, controlled trial	18	2	6 weeks: -100 % 6 months: - 100 %	6 weeks: -52 % 6 months: - 95 %		Moderate
Kessler, 2003	USA	Randomised, controlled trial	28	1	2 weeks: - 42 % p = 0.04 4 weeks: - 48 % nonsign.	2 weeks: - 27 % 4 weeks: - 42 %		Low
Lyon, 2008	USA	Non-randomised, controlled study	38	0	8 weeks: - 30 %	8 weeks: - 15 %		Low
Zamboni, 1997	USA	Non-randomised, controlled study	10	0	7 weeks: - 90 %	7 weeks: - 60 %	Derived from table	Low

Appendix 1:3

Outcome variable: Frequency of amputations due to diabetic foot ulcer in patients treated with hyperbaric oxygen therapy (HBOT) and conventional treatment.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention n (%)	Control n (%)		
Abidia, 2003	UK	Randomised, controlled trial	18	2	2/9 (22 %) non-significant	1/9 (11 %)	Minor and major amputation	Moderate
Löndahl, 2010	Sweden	Randomised, controlled trial	94	19	3/48 (6 %) non-significant	1/42 (2 %)		High
Duzgun, 2008	Turkey	Randomised, controlled trial	100	0	4/50 (8 %) p<0.001	41/50 (72 %)	Proximal and distal amputation	Low
Faglia, 1998	Italy	Non-randomised, controlled study	115	0	7/51 (14 %) p=0.045	20/64 (31 %)		Low
Oriani 1990	Italy	Non-randomised, controlled study	80	0	3/62 (5 %) p<0.001	6/18 (33 %)		Low

Appendix 1:4

Outcome variable: Quality of life in patients with a diabetic foot ulcer in patients treated with hyperbaric oxygen therapy (HBOT) and conventional treatment.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					HBOT score	Conventional treatment score		
Löndahl, 2010	Sweden	Randomised, controlled trial	75	0	<u>Mental health summary score</u> Baseline: 49 12 months: 53 Within group: p < 0.01 Between groups: nonsign. <u>Physical health summary score:</u> Baseline: 30 12 months: 32 Within group: nonsign Between groups: nonsign.	<u>Mental health summary score</u> Baseline: 47 12 months: 48 <u>Physical health summary score:</u> Baseline: 29 12 months: 34	Scores derived from Figure 2.	High
Abidia, 2003	UK	Randomised, controlled trial	18	2	<u>SF-36 General Health Domain</u> Between groups: nonsign. <u>SF-36 Vitality Domain</u> Between groups: nonsign. <u>Hospital Anxiety and Depression Scale</u> Between groups: nonsign.			Moderate

Appendix 1:5

Outcome variable: Reduction of rectal bleeding in patients with post-radiation proctitis treated with hyperbaric oxygen therapy (HBOT) or conventional treatment.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					HBOT n (%)	Conventional treatment n (%)		
Clarke, 2008	USA	Randomised, controlled trial	120	1	6 weeks: 5/63 (8 %) p < 0.01	6 weeks: 0/56 (0 %)		Low

Appendix 1:6

Outcome variable: Hyperbaric oxygen treatment and Quality of life in patients with post-radiation proctitis treated with hyperbaric oxygen treatment (HBOT) or conventional treatment.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					HBOT score	Conventional treatment score		

Clarke, 2008	USA	Randomised, controlled trial	120	1	<u>Bowel Bother QoL scoreⁱ:</u> Baseline: 45.0 6 weeks:59.7 Within group: p < 0.001 <u>Bowel Function QoL scoreⁱⁱ:</u> Baseline: 60.3 6 weeks:69.8 Within group: non-sign.	<u>Bowel Bother QoL score:</u> Baseline: 52.9 6 weeks:59.6 Within group: non-sign. <u>Bowel Function QoL score:</u> Baseline: 60.8 6 weeks:68.3 Within group: non-sign.		Moderate
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Footnotes: i. Bowel Bother QoL scale ranges from 0 to 100. The higher score the less problems.
 i. Bowel Function QoL scale ranges from 0 to 100. The higher score the less problems.

Appendix 1:7

Outcome variable: Bleeding from the urinary bladder (macrohematuria) in patients with post-radiation cystitis treated with hyperbaric oxygen therapy (HBOT) or conventional treatment.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					HBOT n	Conventional treatment n		
Mohamad, 2010	Austria	Non-randomised, controlled study	14	0	Time of FU not reported: 2/10	Time of FU not reported: 2/4		Low

Footnote: FU = follow-up

Appendix 2

Excluded studies of the literature search for hyperbaric oxygen treatment for diabetic foot ulcer, radiation proctitis or radiation cystitis.

Study (author, publication year)	Reason for exclusion
Baroni 1987	Incomplete treatment in intervention group (i.e. less than 20 HBO treatment sessions in many patients)
Chen 2010	Incomplete treatment in intervention group (i.e. less than 20 HBO treatment sessions in most patients)
Doctor 1992	Incomplete treatment in intervention group (i.e. less than 20 HBO treatment sessions in most patients)
Faglia 1996	Wrong patient population (many received neo-vascularistaion)
Feldmeier 2022	Systemic review of case series – no controlled trials with regard to P1, P2 or P3
Fife 2002	Duplication – same patients as report in Fife et al. 2007
Hjelm 2009	Wrong outcome (patient perception)
Sidik 2007	Wrong intervention regimen (HBO administered in direct association with radiation therapy)
Sun 2006	Wrong outcome (cardiac neural regulation)
Wang 2009	Wrong comparison (extracorporeal shockwave therapy)
Wang 2011	Wrong comparison (extracorporeal shockwave therapy)
Lin 2011	Incomplete treatment in intervention group (i.e. less than 20 HBO treatment sessions in most patients)

Appendix 3, Search strategy, study selection and references

Question(s) at issue:

Is hyperbaric oxygen therapy effective in healing diabetic foot ulcers and treating radiation induced cystitis and proctitis?

PICO: (Patient, Intervention, Comparison, Outcome)

PICO1

P = Patients with diabetic foot ulcers of at least 4 weeks duration, who have received optimal conventional treatment, and in whom revascularisation intervention is not possible.

I = Hyperbaric oxygen therapy (HBOT) in addition to conventional treatment

C = Conventional treatment or placebo

O = Ulcer healing, ulcer size, amputation rate, quality of life, complications

PICO2

P = Patients with symptomatic proctitis as a delayed or persistent injury due to radiation therapy.

I = Hyperbaric oxygen therapy (HBOT) in addition to conventional treatment

C = No treatment, other conventional treatment or placebo.

O = Mucosal healing, quality of life, complications

PICO3

P = Patients with symptomatic cystitis as a delayed or persistent injury due to radiation therapy.

I = Hyperbaric oxygen therapy (HBOT) in addition to conventional treatment

C = No treatment, other conventional treatment or placebo.

O = Haemorrhage (macrohematuria), quality of life, complication

Search strategy

PubMed 2011-04-05

proctitis OR cystitis

AND

radiation OR radiation injuries[Mesh] OR diabetic foot OR diabetic angiopathies OR diabetes OR diabetic

AND

ulcer OR ulcers

AND

hyperbaric OR hyperbaric oxygenation[Mesh] OR HBO[tiab] OR HBOT[tiab]

Limits: English, German, Danish, Norwegian, Swedish, Publication Date from 1970

272 results

EMBASE (OVID SP) 2011-04-05

proctitis.mp. OR exp PROCTITIS/ OR cystitis.mp. or exp CYSTITIS/ OR (proctitis OR cystitis).ti,ab

AND

radiation injury.mp. OR exp radiation injury/ OR radiation.ti,ab. OR diabetic foot.mp. OR exp foot ulcer/ OR exp diabetic foot/ OR diabetic angiopathies.mp. OR exp diabetic angiopathy/ OR (diabetes or diabetic).ti,ab.

AND

(ulcer OR ulcers).ti,ab.

AND

exp hyperbaric oxygen/ OR (hyperbaric or HBO or HBOT).ti,ab.

Limit: Publication Date from 1970 to 2011/04/05, English, German, Danish, Norwegian, Swedish, Human

370 results

The Cochrane Library 2011-04-05

(diabetes OR diabetic) **in** Title, Abstract or Keywords **AND**

(foot OR ulcer OR ulcers OR angiopathies Or angiopathy) **in** Title, Abstract or Keywords

OR (proctitis OR cystitis) **in** Title, Abstract or Keywords **AND** (radiation) **in** Title, Abstract or Keywords **AND** hyperbaric **in** Title, Abstract or Keywords

50 results

Cochrane reviews 3

Other reviews 2

Technology Assessments 5

Economic evaluations 9

Clinical trials 31

CRD 2010-10-21

proctitis OR cystitis OR diabetic OR diabetes
AND
 hyperbaric OR HBO OR HBOT

14 results**CINAHL (ESCO) 2011-04-05**

S14	S3 and S13	137
S13	S9 or S12	6854
S12	S10 or S11	685
S11	TI (proctitis OR cystitis) or AB (proctitis OR cystitis)	476
S10	(MH "Cystitis+")	527
S9	S4 or S5 or S8	6170
S8	S6 and S7	1518
S7	TI (ulcer OR ulcers) or AB (ulcer OR ulcers)	9784
S6	TI (diabetic OR diabetes) or AB (diabetic OR diabetes)	49014
S5	(MH "Diabetic Angiopathies+")	5763
S4	(MH "Diabetic Foot")	3521
S3	S1 or S2	1158
S2	TI (hyperbaric OR HBO OR HBOT) or AB (hyperbaric OR HBO OR HBOT)	757
S1	(MH "Hyperbaric Oxygenation")	966

137 results**SBU, Kunnskapssenteret, Sundhedsstyrelsen 2011-04-05**

Nothing new was identified.

Reference lists:

A comprehensive review of reference lists brought 1 new reference.

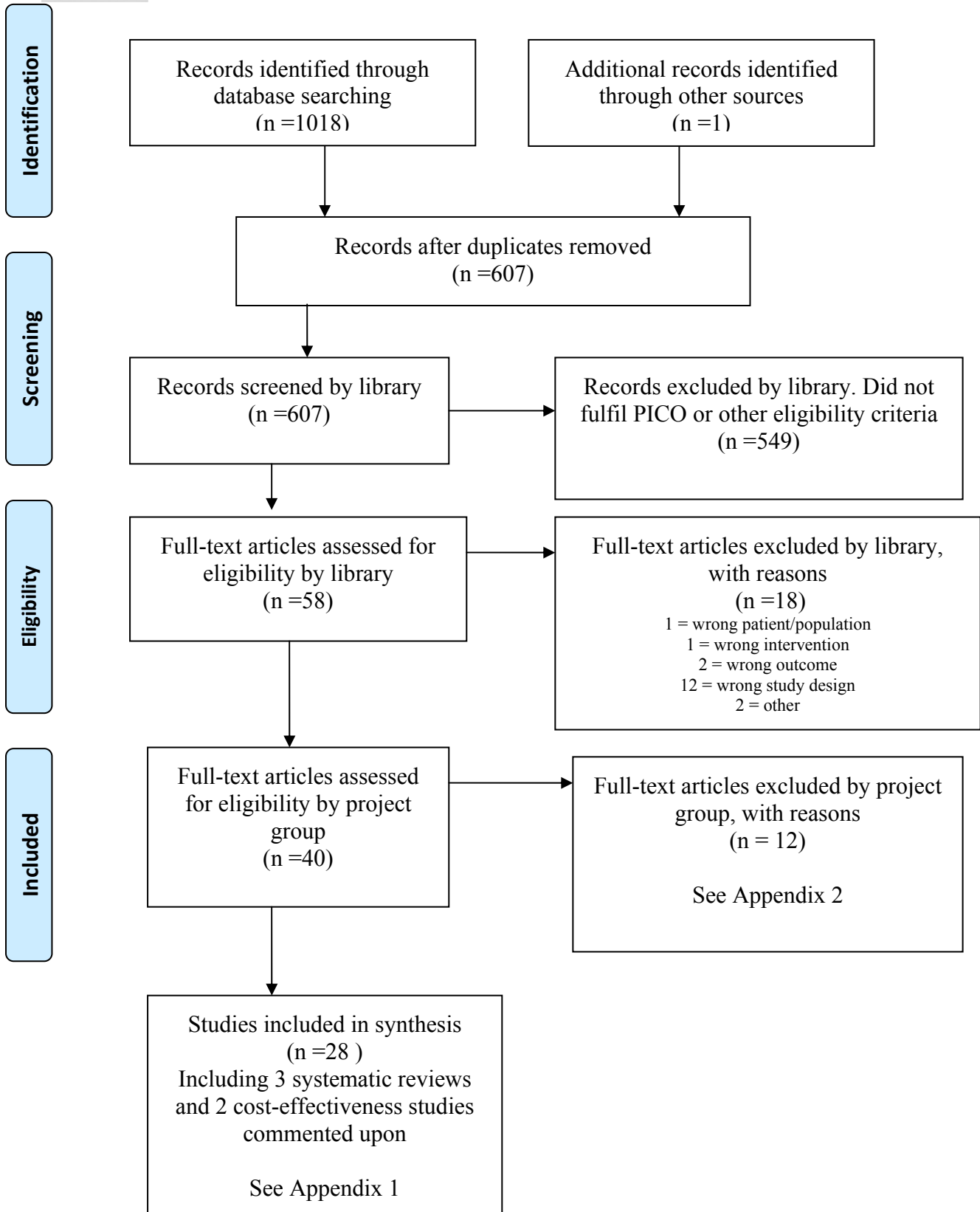
Eligibility criteria**Study design:**

- RCT and Cohort studies with control group
- Case series ≥ 20

Language: English, Danish, German, Norwegian, Swedish

Publication date: from 1970

Selection process – flow diagram



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Summary of Findings: Hyperbaric oxygen treatment in patients with chronic diabetic foot ulcer.

Outcome variable	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE
Number of studies										
Complete healing										
6	3 RCT 3 non-randomised controlled studies	Some limitations (?)	Some inconsistency (-?)	Some indirectness (-?)	No imprecision	Unlikely	Not relevant	1.98* (1.21; 3.23)	Difference in healing rate: Δ = 28 – 66 % Median = + 38 %	+++ Moderate
Reduction of surface area of ulcer										
4	2 RCT 2 non-randomised controlled studies	Some limitations (?)	Some inconsistency (?)	Serious indirectness (-1)	Uncertain precision (?)	Unlikely	Not relevant		Difference in reduction of ulcer area: Δ = 5 – 30 % Median = - 15 %	++ Low
Amputation										
5	3 RCT 2 non-randomised controlled study	Some limitations (?)	Serious inconsistency (-1)	Some indirectness (-?)	Serious imprecision (-1)	Unlikely	Not relevant		Difference in frequency: Δ = 4 – 64 % Median = - 17 %	+ Very low
Quality of life										
1	1 RCT	Serious limitations (-1)	No inconsistency	Serious indirectness (-1)	No problem	Unlikely	Not relevant			+ Very low

* Footnote: The calculated estimate of the relative ratio is based only on the three RCTs.

Summary of Findings: Hyperbaric oxygen treatment in patients with radiation cystitis.

Outcome variable	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE
Number of studies										

Bleeding										
1	1 non-randomised, controlled study	Very serious limitations (-2)	No inconsistency	Very serious indirectness (-2)	Serious imprecision (-1)	Unlikely	-	-	-	+ Very low

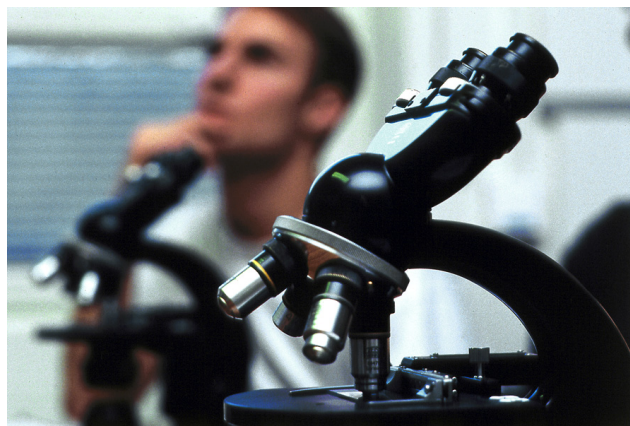
Summary of Findings: Hyperbaric oxygen treatment in patients with radiation proctitis.

Outcome variable	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE
Number of studies										

Mucosal healing										
1	1 RCT	No limitations	No inconsistency	Serious indirectness (-1)	Serious imprecision (-1)	Unlikely	-	-	Difference in healing rate: Δ = + 8 %	++ Low
Quality of life										
1	1 RCT	No limitations	No inconsistency	Very serious indirectness (-2)	Serious imprecision (-1)	Unlikely	-	-		+ Very low

Region Västra Götaland, HTA-centre

Health Technology Assessment
Regional activity-based HTA



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is

currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE ⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕○)
Low quality of evidence	= (GRADE ⊕⊕○○)
Very low quality of evidence	= (GRADE ⊕○○○)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

For diagnostic studies, the GRADE system should be applied for clinical outcomes and we have thus chosen not to use it for diagnostic accuracy studies. In the present report, we have evaluated the level of evidence for diagnostic accuracy according to the system previously used by SBU, (Swedish Council on Health Technology Assessment), briefly described below.

High level of evidence

At least two studies of high quality or a systematic review of good quality

Moderate level of evidence

One study of high quality and at least two studies of moderate quality

Low level of evidence

At least two studies of moderate quality

Very low level of evidence

Only studies of low quality

Christina Bergh, Professor, MD.
Head of HTA-centre

