

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

HealOzone for the treatment of tooth decay

(occlusal pit and fissure caries and root caries)

1 Guidance

- 1.1 HealOzone is not recommended for the treatment of tooth decay (occlusal pit and fissure caries and root caries), except in well-designed randomised controlled trials.

2 Clinical need and practice

- 2.1 Tooth decay (dental caries) is a chronic disease that can result in the localised and progressive demineralisation (loss of mineral content) of the hard surfaces of the tooth. It is a multistage process initiated by the local accumulation of cariogenic bacteria on the hard surfaces of the tooth. Cariogenic bacteria metabolise dietary carbohydrates to produce plaque acids, which cause demineralisation of the tooth enamel (non-cavitated dental caries). Without successful treatment, the demineralisation can extend into the dentine and eventually into the pulp (cavitated dental caries). Common symptoms of untreated cavitated dental caries are significant pain and discomfort, which can lead to disturbances in eating and loss of sleep.
- 2.2 The progression of dental caries is a slow process in most people; at current levels of consumption of fermentable carbohydrates and fluoride exposure, most enamel lesions take more than 2 years to cavitate. A number of variables can affect progression time and the progression of dental caries may be more rapid in deciduous teeth because they are less well mineralised.

- 2.3 The type of dental caries can be classified by its location: pit and fissure caries occurs in the pits (small depressions) and fissures (small grooves) of the occlusal (biting) surface of teeth, the palatal surfaces of the upper molars and the vestibular surface of the lower molars. Caries can also occur between the surfaces of adjoining contact areas of adjacent teeth. Root caries occurs in the area between the tooth and the receding gum. Primary dental caries is decay on a previously sound natural tooth. Secondary dental caries is decay at the margin of a restoration (filling); this often necessitates replacement of the filling (re-restoration).
- 2.4 Carious lesions are first identified on the basis of clinical visual examination. Various techniques are used to diagnose and monitor progression or reversal of dental caries, although none have been well validated. In addition to visual examination and probing, X-rays and digital radiography can be used to estimate the depth of lesions or to identify lesions that are 'hidden' on visual examination. Lesions can be classed as soft, leathery or hard. Lesions that are progressing are classified as 'active' and those that have stopped progressing are described as 'arrested'. This distinction is clinically important because arrested lesions do not require any further preventive interventions.
- 2.5 Adults in the UK have an average of 1.5 decayed or unsound teeth, and 55 per cent have one or more decayed or unsound teeth (Adult Dental Survey 1998). Despite a reduction in the mean number of decayed, missing and filled teeth over the past 25 years, there are still many people with significant dental caries, which is often linked to socioeconomic factors. Forty three percent of 5-year-olds and 57% of 8-year-olds have obvious tooth decay in deciduous teeth, and between 52% and 77% of children aged 8 to 15 years have obvious tooth decay in permanent teeth (Dental Health Survey of Children 2003). Root caries usually begins between the ages of 30 and 40 years and is most prevalent in elderly people.
- 2.6 The treatment of dental caries depends on the severity of the lesion at presentation (whether or not it is cavitated) and on its location. People

undergoing dental treatment routinely should receive instructions on good oral hygiene and dietary advice to reduce the consumption of fermentable carbohydrates. After treatment, the activity status of dental caries lesions is assessed at follow-up visits to determine whether further preventive treatment is necessary.

- 2.7 Water fluoridation and topical fluoride delivery – in the form of toothpastes, mouth rinses, gels and varnishes – are the mainstay in the management of dental caries. The effectiveness of fluoride has been established by randomised controlled trials and summarised recently in a series of systematic reviews produced by members of the Cochrane Collaboration.
- 2.8 Non-cavitated pit and fissure caries is currently managed by removing plaque and treating with topical fluorides (for example, toothpaste and mouth rinse) and pit and fissure sealants where appropriate.
- 2.9 Cavitated pit and fissure caries is currently managed by removing plaque and tooth decay (using drills or air abrasion) and restorative treatment with a composite resin, glass-ionomer cement or amalgam. Amalgam is commonly used for filling posterior permanent teeth. The average lifetime of a restoration is about 8 years, although it varies with the size of the restorations.
- 2.10 Non-cavitated root caries is currently managed by removing plaque and treating with topical fluorides (for example, toothpaste and mouth rinse), which may be sufficient to prevent progression where the tooth is accessible to cleaning.
- 2.11 The management of cavitated root caries involves removing plaque and treating with fluoride. Restorative treatment with glass ionomer cements or resin-based fillings may be required.

3 The technology

- 3.1 HealOzone is a medical device that is manufactured by KaVo and CE marked for the treatment of pit and fissure caries and root caries. The HealOzone treatment system comprises an ozone delivery device, a mineral reductant used by the dentist and a 'patient kit' (fluoride-containing toothpaste, mouthwash and mouth spray) for home use. The mineral reductant and patient kit are accessories to the ozone delivery device.
- 3.2 The HealOzone device delivers ozone at a concentration of 2100 parts per million to the site of dental caries on the tooth surface for between 10 and 120 seconds to destroy the cariogenic microorganisms. A mineral reductant is then applied to the tooth to neutralise residual bacterial acid, remove any residual ozone and provide minerals for the remineralisation process. The patient then uses the fluoride-containing patient kit for several weeks to remineralise the tooth before returning to the dentist for assessment. HealOzone treatment may be repeated at intervals of 3 and 6 months if the caries has not reversed, or restorative treatment may be carried out.
- 3.3 Lesions may also be treated with HealOzone before sealant placement (it is hypothesised that this improves sealant retention), and cavitated lesions may be treated before filling placement (it is hypothesised that this improves the longevity of restorations).
- 3.4 The capital cost of the HealOzone device is £11,950 (excluding VAT), with annual maintenance costs of between £220 and £450, depending on the service contract. The average estimated cost of adding HealOzone to conventional treatment (excluding capital and maintenance costs) ranges from £18 to £21 per tooth, depending on the type of dental caries. HealOzone is not currently available on the NHS.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 *Clinical effectiveness*

- 4.1.1 The clinical effectiveness of HealOzone treatment was compared with a control in a number of randomised controlled trials (RCTs), by comparing the number of dental caries lesions that reversed (for example, changing from leathery to hard) or progressed.
- 4.1.2 Ten RCTs of HealOzone treatment of primary dental caries were included in the systematic review conducted by the Assessment Group. Studies of less than 6 months duration were excluded from the review on the basis of clinical advice that follow-up periods of less than 6 months were inadequate to assess caries progression. Seven RCTs (two PhD theses, one pilot study [included in one of the theses] and four abstracts) evaluated the effect of HealOzone treatment on pit and fissure caries. Three RCTs (one published, one unpublished and one published in abstract only) evaluated the effect of HealOzone treatment on root caries. The studies were conducted in permanent teeth, with the exception of the study reported in one of the PhD theses. Two of the studies evaluated whether the addition of HealOzone treatment improved sealant retention: one in the treatment of pit and fissure caries, and another in the treatment of root caries.
- 4.1.3 The Assessment Group noted a number of factors in the studies that made it difficult to assess the effectiveness of HealOzone treatment alone and prevented a quantitative synthesis of the results. Several studies (particularly those published in abstract only) did not fully report the methodology used; for example, it was not always clear whether the assessors of treatment outcome were blinded to the treatment group. Also, the data analysis was not necessarily appropriate. For example, analysing the data by lesion without taking into account the fact that measurements derived from two or more

lesions in the same patient are not independent could introduce bias into the results. Study participants received repeat treatments at different timepoints in different studies and in some studies no repeat treatment was given.

Non-cavitated pit and fissure caries

4.1.4 The Assessment Group reported the results of five RCTs (one PhD thesis and four abstracts) that evaluated the effect of HealOzone treatment in adults with non-cavitated pit and fissure caries. The PhD thesis (n = 90; 258 lesions) reported that at 12 months in the HealOzone treatment group (ozone plus reductant) 7% of lesions had reversed, 57% remained stable and 36% had progressed, compared with 6% reversed, 49% stable and 46% progressed in the control group (reductant only). The mean change from baseline in clinical severity score at 12 months was not statistically significant ($p = 0.112$). There was no statistically significant difference in sealant retention between treatment groups at 12 months (33% had partial loss in the sealant margins in the HealOzone group compared with 30% in the control group).

4.1.5 In three abstracts, the proportion of lesions reported as clinically reversed at 6 to 12 months follow-up ranged from 87% to 99% in the HealOzone treatment group. All studies reported that no significant clinical changes were observed in the control group, but no data were provided. The fourth abstract (n = 38; 76 lesions) reported that all lesions were hard at 3 months (that is, all caries had reversed) in the HealOzone treatment group (air abrasion, ozone, mineral wash plus glass ionomer sealant); reversal rates were not reported in the control group (conventional drilling and filling). The Assessment Group noted that the results of these studies should be interpreted with caution because the lack of detail meant that their methodology could not be easily assessed.

Cavitated pit and fissure caries

4.1.6 A small pilot study reported in the PhD thesis described in Section 4.1.4 (n = 8; 17 lesions per group) evaluated the effect of HealOzone treatment on

cavitated pit and fissure caries. It reported statistically significant improvements in hardness and visual scores ($p < 0.05$) in the HealOzone group compared with the control group and no significant differences between groups in cavitation score, colour and perceived treatment need ($p > 0.05$).

Deciduous dentition

4.1.7 The study in the second PhD thesis ($n = 21$; 74 lesions) evaluated the effectiveness of HealOzone treatment in non-cavitated pit and fissure caries in deciduous teeth (children aged 7 to 9 years). Data were presented graphically; at the 12-month follow-up, there was a small reduction in the severity of dental caries in the HealOzone treatment group (ozone plus reductant), and an increase in severity scores in the control group (reductant only). There was a statistically significant change in clinical severity scores with treatment over time ($p < 0.01$).

Non-cavitated root caries

4.1.8 Three RCTs evaluated the effectiveness of HealOzone treatment for non-cavitated root caries; one published in full, one unpublished and one published only in abstract form. In the published study two lesions in each of 89 participants were randomised to treatment or control; 89 lesions per group. This study reported that 98% of lesions in the HealOzone treatment group (ozone application, reductant plus patient kit) became hard at 12 months compared with 1% in the control group (air treatment, reductant plus patient kit). The 21-month data from this study reported that 100% of lesions became hard with HealOzone treatment compared with 8% of lesions becoming hard, 80% remaining leathery and 12% becoming soft in the control group.

4.1.9 The abstract ($n = 260$ with two lesions each; 260 lesions per group) reported that 80% of soft lesions had reversed from clinical severity index 4 to 3 and that 94% of leathery lesions became hard and arrested in the HealOzone treatment group (ozone application) at 6 months. There were no statistically

significant changes in lesion severity for either type of lesion in the control group (no treatment).

4.1.10 The unpublished full-text study (n = 79; 220 lesions, the numbers in each group were not reported) investigated the effectiveness of HealOzone treatment (cleaning, ozone and reductant, with or without sealant) in cavitated and non-cavitated root caries at 12 months follow-up. The results for cavitated and non-cavitated lesions could not be disaggregated. Overall, HealOzone treatment was associated with a statistically significant reversal of dental caries compared with the control treatment (reductant, with or without sealant) ($p < 0.001$). In the treatment group 99% of lesions improved (47% lesions became hard, and 52% became less severe), compared with 12% (none became hard) in the control group. Sealant retention was also statistically significantly improved: 61% in the HealOzone group compared with 42% in the control group ($p < 0.05$).

Cavitated root caries

4.1.11 Although the unpublished study described in Section 4.1.10 did not present separate data for cavitated and non-cavitated root caries, it was reported that the percentage of cavitated lesions in the HealOzone group that became hard decreased from 9% at 1 month to 1% at 9 months follow-up. No results were reported for the control group.

Evidence from clinical and patient experts

4.1.12 The Committee heard from experts that, although HealOzone treatment sterilises the surface of the tooth, microorganisms will immediately start to recolonise the area and will be well-established about 2 weeks after HealOzone treatment.

4.1.13 The experts expressed concerns about the clinical trials that reported strongly favourable results. Their concerns included the unexpectedly poor

performance of the controls, problems in the accurate diagnosis of the severity of dental caries and the absence of objective outcome measures.

4.2 Cost effectiveness

- 4.2.1 No published economic evaluations were identified on HealOzone treatment of dental caries. The manufacturer submitted an economic model. The Assessment Group developed a second model, but argued that, given the current state of the clinical effectiveness evidence, economic analysis is premature and the model should therefore be taken as illustrative only. The Assessment Group's model is therefore not described further here.
- 4.2.2 The submission from the manufacturer of the device assessed the cost effectiveness of adding HealOzone to conventional treatment that did not include preventive treatment. Effectiveness data for the addition of HealOzone treatment were based on average reversal rates of dental caries reported in the RCTs for non-cavitated (93.3%) and cavitated pit and fissure caries (79%), and for root caries (84.5%). The effectiveness of conventional treatment was based on the average annual progression rate of dental caries reported in clinical studies that were excluded from the Assessment Group's systematic review. The additional cost of HealOzone treatment per filling avoided was £9.58 in non-cavitated pit and fissure caries, £11.63 in cavitated pit and fissure caries and £5.18 in root caries.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of HealOzone treatment of tooth decay, having considered evidence on the nature of the condition and the value placed on the benefits of HealOzone by people with tooth decay, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the effective use of NHS resources.

- 4.3.2 The Committee considered the mode by which dental caries is reversed or arrested by HealOzone treatment. It accepted the evidence presented in the submission that ozone eliminated most microorganisms. However, given the testimony of clinical experts and lack of evidence to the contrary, the Committee concluded that it was logical that microorganisms would immediately start to recolonise the area and become well-established soon after HealOzone treatment. It considered the hypothesis that ozone could remove proteins in carious lesions by oxidation of amino acids, which could in turn enable remineralisation in the presence of the mineral reductant. However, the Committee noted a lack of evidence to support this theory.
- 4.3.3 The Committee considered the evidence in which patients in the intervention and control arm received fluoride treatment (mineral reductant and the patient kit). The Committee was aware that many of the measures used in the RCTs to monitor caries are not well validated and are unreliable. It discussed the validity of the evidence that reported little or no effect in the control group of the fluoride comparator treatment. The Committee noted that experts said they would have expected to see higher rates of caries reversal from fluoride treatment in the control arms. The Committee concluded that, in light of these concerns, the evidence could not be considered reliable.
- 4.3.4 The Committee accepted the Assessment Group's rationale for not examining the submitted trials of less than 6 months duration; the Committee agreed that shorter follow-up periods were inadequate to assess caries progress. Of the RCTs of HealOzone for non-cavitated pit and fissure caries that were of more than 6 months duration, the Committee took into consideration the fact that the non-significant results in the PhD thesis conflicted with the significant results of the abstracts. However, given the lower reliability of abstracts, the lack of information reported and the concerns over the robustness of the methodology used, it concluded that the benefits of HealOzone for non-cavitated pit and fissure caries had not been adequately demonstrated. Similarly, given the methodological concerns and the small sample size of the pilot studies in non-cavitated pit and fissure caries in deciduous teeth and

cavitated pit and fissure caries in permanent teeth, the Committee concluded there is insufficient evidence to recommend this technology in these subgroups and further research is required.

- 4.3.5 For the reasons expressed in 4.3.3, the Committee concluded that the evidence from RCTs of cavitated root caries was unreliable, and that HealOzone should not be recommended for the treatment of cavitated root caries.
- 4.3.6 In light of the Committee's conclusion that the evidence from the RCTs was unreliable, the Committee did not discuss the findings of the cost-effectiveness evaluations.
- 4.3.7 In summary, the Committee concluded that there was insufficient evidence on the effectiveness of HealOzone treatment for this technology to be recommended, except as part of well-designed RCTs.

5 Recommendations for further research

- 5.1 On the basis of the current evidence, the place of HealOzone in the treatment or management of dental caries is not proven. If this technology is to be considered for use within the NHS, further research is needed to provide evidence of its clinical and cost effectiveness compared with current best practice. Such research should include large-scale RCTs, use validated methods for the diagnosis and assessment of dental caries, and incorporate appropriate statistical methods for the analysis of dependent data within patients. It will also need to show evidence of effectiveness on patient-centred outcomes (for example, pain and numbers of fillings and tooth extractions) to assess both long-term benefits and effects on quality of life.

6 Implications for the NHS

- 6.1 HealOzone is not currently available on the NHS, so this guidance is not expected to lead to a change in NHS expenditure or have any impact on other NHS resources.

7 Implementation and audit

- 7.1 HealOzone is not currently available on the NHS, so there are no implementation or audit considerations.

8 Related guidance

- 8.1 Dental recall: recall interval between routine dental examinations. *NICE Clinical Guideline* No. 19 (issued October 2004).

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.
- 9.2 The guidance on this technology will be considered for review in August 2008. Consideration will be given to an earlier review if the Institute is made aware of important new evidence that may impact on this guidance before this date.

David Barnett
Chair, Appraisal Committee
February 2005

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The committee is split into three branches. In order to ensure consistency, the chair of each branch is also a member of a branch of which he is not chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences,
University of Manchester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley

Vice Chairman, InContact

Dr Mark Chakravarty

Head of Government Affairs and NHS Policy, Procter & Gamble Pharmaceuticals (UK) Ltd

Mr Richard Devereaux-Phillips

Public Affairs and Reimbursement Manager, Medtronic Ltd

Professor Jack Dowie

Health Economist, London School of Hygiene

Professor Gary A Ford

Professor of Pharmacology of Old Age and Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Miss Linda Hands

Clinical Reader in Surgery, University of Oxford

Professor Peter Jones

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

Professor Robert Kerwin

Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Ms Rachel Lewis

Staff Nurse (Nephrology), Hull Royal Infirmary

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology Assessment, University of Southampton

Dr Neil Milner

General Practitioner, Sheffield

Dr Rubin Minhas

General Practitioner with a Special Interest in Coronary Heart Disease, Primary Care
CHD Lead, Medway PCT and Swale PCT

Mr Miles Scott

Chief Executive, Harrogate Health Care NHS Trust

Professor Mark Sculpher

Professor of Health Economics, Centre for Health Economics, University of York

Dr Ken Stein

Senior Clinical Lecturer in Public Health, Peninsula Medical School, Exeter

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

B. NICE project team

Each appraisal of a technology is assigned to one or more Health Technology
Analysts and a Technology Appraisal Project Manager within the Institute.

Eleanor Donegan, Louise Longworth and Sarah Garner

Technical Leads, NICE project team

Emily Marschke

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Aberdeen Health Technology Assessment Group.

Brazzelli M, McKenzie L, Fielding S et al. *Systematic review of the effectiveness and cost-effectiveness of 'HealOzone' for the treatment of occlusal pit/fissure caries and root caries*, November 2004.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document. Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsor:

- KaVo Dental Limited UK

II Professional/specialist and patient/carer groups:

- Association of Consultants and Specialists in Restorative Dentistry
- Beyond Fear (dental phobia support group)
- British Association for Study of Community Dentistry
- British Association of Dental Nurses
- British Dental Association
- British Dental Health Foundation
- British Dental Hygienists' Association
- British Society for Disability and Oral Health
- British Society for Oral Medicine
- British Society of Paediatric Dentistry

- Faculty of General Dental Practitioners (UK), Royal College of Surgeons
- Gorlin Syndrome Group
- Lay Advisory Group, Faculty of General Dental Practitioners
- National Oral Health Promotion Group
- Royal College of Paediatrics and Child Health

Others:

- Association of British Healthcare Industries (ABHI)
- British Dental Trade Association
- Department of Health
- European Medical Technology Industry Association (EUCOMED)
- Harrow Primary Care Trust
- Torfaen Local Health Board
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Association of Welsh Community Health Councils
- British Medical Association
- National Collaborating Centre for Acute Care
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- British Society for Dental Research
- Centre for Evidence Based Dentistry
- Cochrane Oral Health Group
- Health Economics Research Unit and Health Services Research Unit, University of Aberdeen
- National Coordinating Centre for Health Technology Assessment

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on HealOzone treatment by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the Appraisal Consultation Document.

- Dr Paul Batchelor, Consultant and Senior Lecturer in Dental Public Health, University College London.
- Professor Liz Kay, Professor of Dental Health Services Research, The Turner Dental School
- Professor Edwina Kidd, Emeritus Professor of Cariology, Guy's, King's and St Thomas' Dental Institute, Division of Conservative Dentistry, London
- Mr Peter Sanders, Lay Advisory Group Chairman, Faculty of General Dental Practitioners
- Mr Andy Solecki, Chairperson, Beyond Fear