Biological Therapies in Dentistry

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Editor's Note: *This supplement of* Biological Therapies in Dentistry *was prepared to give dental clinicians an evidence-based report on the research related to the use of ozone therapy in dental practice. The only device available at the time* Biological Therapies in Dentistry *went to press was the HealOzone™ unit (KaVo Dental GmbH, Biberach, Germany).*

Ozone Treatment for Dental Caries: Clinical Studies

Recently, the HealOzone™ device (KaVo Dental GmbH, Biberach, Germany) became available as a therapeutic modality for the treatment of dental caries by the delivery of ozone to carious tooth surfaces. In some of the studies of this device, saliva served as the remineralizing solution, and in other studies, HealOzone was used in conjunction with a remineralizing kit containing a dentifrice, mouthrinse, and a spray containing fluoride, calcium, phosphorous, zinc, and xylitol. The kit is most effective when used in the first 4 weeks following the application of ozone since this is the time when lesions initially remineralize.

The mechanism of HealOzone's action is related to ozone's strong antimicrobial properties and its ability to oxidize proteins associated with the dental caries process.

The mechanism of HealOzone's action (Figure) is related to ozone's strong antimicrobial properties and its ability to oxidize proteins associated with the dental caries process. Ozone's oxidative reactions render it a powerful biocide that destroys bacteria by oxidizing bacterial cell walls and membranes; ozone may destroy these microorganisms by rupturing their membranes and blocking enzymatic pathways.[1] Ozone has the effect, through its oxidizing properties, of not only removing the protein protection and being bactericidal, but also oxidizing the biomolecules that allow the niche to survive and expand.[2–5] This has a severely disruptive effect on the bacterial population in the carious lesion and obliterates the cariogenic bacteria and their ecological niche, thereby swinging the equilibrium in favor of remineralization. No more acid can be produced within the lesion when the acid-producing bacteria are eliminated. For example, pyruvic acid, one of the strongest naturally occurring acids manufactured by bacteria and implicated in the progression of caries, is oxidized by ozone to acetate and carbon dioxide. Acetate is less acidic than pyruvic acid, and this decarboxylation reaction leads to mineral uptake because of the more alkaline conditions in the carious lesion. Following these actions, remineralization of the treated lesion occurs with saliva, and sometimes the remineralizing kit described above, serving as the remineralizing fluid.

Pit and Fissure Caries

A number of published studies have reported on the efficacy of ozone on pit and fissure caries.[6–15] Caries was treated in both permanent and deciduous teeth. The time between initial treatment and reassessment varied from 1 to 12 months, and some trials reviewed patients more than once. Treatment time with ozone varied between studies from 10 to 40 seconds. All patients received initial treatment with ozone, and in some circumstances, patients were re-treated at each review. Trial comparators were generally no treatment or placebo treatment with air applied through the HealOzone device. Representative studies and their findings are presented in the table.[6–15]

In reviewing all the studies published, *Biological Therapies in Dentistry* found that a significant reversal of caries by ozone therapy has been reported in over 2,000 patients in studies ranging from 1 to 12 months.[16–26]

From this table, it can be seen that clinical studies showed that caries reversal ranged from 80 to 99% with the post-treatment evaluation period ranging from 1 to 12 months. In reviewing all the studies published, *Biological Therapies in Dentistry* found that a significant reversal of caries by ozone therapy has been reported in over 2,000 patients in studies ranging from 1 to 12 months.[16–26] Also, the ozone application time ranged from 10

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Table. Treatment of Pit and Fissure Caries: Summary of Representative Studies

Author	No. of Patients	No. of Teeth	% Success*	Duration of Study (mo)
Megighian et al, 2003[6]	60	200	90	1
Holmes, 2003[7]	193	579	99	4
Abu-Naba'a et al, 2003[8]	90	258	88	12
Stinson et al, 2003[9]	98	279	99	12
Holmes, 2003[10]	376	2,364	99	12
Johnson et al, 2003[11]	105	114	81	1
Morrison and Lynch, 2003[12]	145	240	89	3
Morrison and Lynch, 2003[13]	108	186	81	3
Hamid, 2004[14]	184	184	87	3
Huth et al, 2005[15]	41	114	80	3

*Based on a statistically significant improvement in clinical measures at $p < 0.05$

to 40 seconds. Evaluation of caries reversal was based on clinical examinations and electronic caries monitor (ECM) and DIAGNOdent® (KaVo Dental GmbH) readings.

Deciduous Teeth

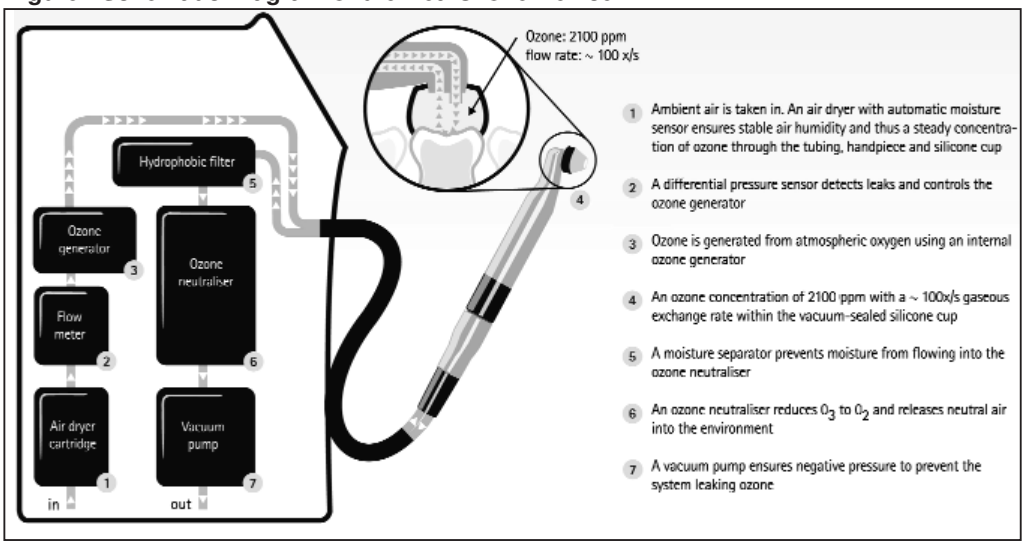
Ozone has been shown to reverse pit and fissures caries in deciduous teeth.[27–29] In a 6-month study in 50 teeth (17 subjects), ECM readings improved significantly ($p < 0.05$), as did DIAGNOdent readings ($p < 0.05$), compared with the baseline readings.[29] The carious lesions in the treatment group showed significant improvement in the texture and indices for perceived treatment needs.

In an interesting double-blind, controlled, and randomized clinical trial, Holmes showed that noncavitated occlusal fissure caries in deciduous teeth can be managed successfully using ozone.[30] This study examined primary occlusal fissure carious lesions over a 12-month period in 76 patients ages 2 to 12 years old in a general dental practice. Ozone was applied to each test lesion for 10, 20, 30, or 40 seconds depending on the clinical severity index and the DIAGNOdent assessment; the control lesions received only air and no ozone. If reversal did not occur, ozone treatment was repeated at a 3-month review. Patients were recalled at 12 months and were clinically reassessed. The results of this study showed a 98% reversal in the ozone-treated group. The control carious lesions, which had not received any ozone treatment, did not significantly change in the study period. The conclusion of this study was that ozone is an effective alternative to conventional "drilling and filling" for noncavitated deciduous carious lesions in general dental practice.[30]

> Ozone may be considered to be an effective alternative to conventional "drilling and filling" for noncavitated deciduous carious lesions in general dental practice.[30]

A more recent one-year study in 21 children by this investigator and colleagues reported on results of ozone treatment on 74 primary deciduous carious lesions (PDCLs) in the most severe category (judged to have almost exposed pulp owing to caries) compared with results of conventional treatment.[31] Each subject had one PDCL made caries free using conventional local analgesia, drilling, and filling with Optibond Solo Plus and Point 4 (KerrHawe, Bioggio, Switzerland) composite resin. The remaining PDCLs were treated with the atraumatic restorative technique (gentle hand instrumentation of caries) and ozone treatment for 20 seconds followed by filling with Optibond Solo Plus and Point 4. Up to 1 mm of leathery carious dentin was left overlying the pulpal floor prior to ozone treatment. The mean time required for the atraumatic restorative technique, ozone treatment, and placement of a restoration was 6 minutes; mean time for the conventional technique, including local analgesia, was 17 minutes ($p < 0.05$). After 18 months, 30% of the conventionally treated teeth had signs or symptoms suggesting pulpal necrosis compared with only 3% of the ozone treated teeth ($p < 0.01$).

Figure. Schematic Diagram of the HealOzone Device



Another study evaluated the anxiety level of children (and their parents) treated with ozone and found that all children and parents reported significant anxiety prior to ozone treatment.[32] However, following the treatment, the children reported they would be pleased to return for future treatments. Also, 80% of the parents said they would be willing to pay more for this therapy compared with traditional drilling and filling.

Root Surface Caries

As the population ages, its members are at increased risk for root caries for a variety of reasons, with the foremost being recession and xerostomia. Xerostomia can be due to reduced salivary gland function associated with aging or to medications being taken by patients.

A study by Holmes addressed this problem in a geriatric population.[33] The objective of the study was to "assess the effect of an ozone delivery system, combined with the daily use of a remineralizing patient kit, on the clinical severity of non-cavitated leathery primary root carious lesions (PRCLs), in an older population group." The design involved the recruitment of a total of 89 subjects (age range 60–82 yr, mean ± SD 70.8 ± 6 yr), each with two leathery PRCLs. The two lesions in each subject were randomly assigned for treatment with ozone or air, in a double-blind design, in a general dental practice. Subjects were recalled at 3, 6, 12, and 18 months. Lesions were clinically recorded at each visit as soft, leathery, or hard and were scored with a valid root caries severity index.

> Leathery noncavitated primary root caries can be arrested nonoperatively with ozone and remineralizing products.

The results of the study showed that there were no observed adverse events. After 3 months, in the ozone-treated group, 61 PRCLs (69%) had become hard and none had deteriorated. In the control group, 4 PRCLs (4%) had become worse ($p < 0.01$). At the 6-month recall, in the ozone group, 7 PRCLs (8%) remained leathery and the remaining 82 (92%) PRCLs had become hard. In the control group, 10 PRCLs (11%) had become worse and one had become hard ($p < 0.01$). At 12 and 18 months, 87 subjects were available for reevaluation. In the ozone group at 12 months, 2 PRCLs remained leathery but 85 (98%) had hardened. In the control group, 21 (24%) of the PRCLs had progressed from leathery to soft (ie, had become worse), 65 PRCLs (75%) were still leathery, and 1 remained hard ($p < 0.01$). At 18 months, 87 (100%) of ozone-treated PRCLs had arrested. In the control group, 32 lesions (37%) of the PRCLs had worsened from leathery to soft ($p < 0.01$), 54 (62%) PRCLs remained leathery, and only 1 of the control PRCLs had reversed ($p < 0.01$). The authors concluded that leathery noncavitated primary root caries can be arrested nonoperatively with ozone and remineralizing products.

The findings of this study confirmed the findings of an earlier study by Baysan and Lynch.[34] In this 12-month study, 40 patients with primary root caries were treated with ozone for 10 seconds and a remineralizing solution for 5 seconds at baseline. After 1 month, the procedures applied at baseline were repeated without ozone application. After 3, 6, 9, and 12 months, the same procedures were performed. In addition, ozone was applied for a period of 10 seconds. Lesions were evaluated clinically and with ECM and DIAGNOdent. At baseline, all lesions were of a leathery consistency. At the 1-month recall, 26.5% of PRCLs had become hard in the ozone group, whereas all the lesions remained the same in the control group ($p < 0.001$). After 12 months, 47% of PRCLs had become hard in the ozone group and 9% of the lesions had become worse in the control group ($p < 0.001$). Also, ECM and DIAGNOdent evaluations showed a statistically significant improvement in ozone-treated teeth compared with controls.

Comment

The HealOzone unit has been shown to effectively deliver ozone to a variety of carious lesions in both permanent and deciduous occlusal surfaces as well as root surfaces of permanent teeth. Studies in over 2,000 patients have shown remineralization of treated surfaces and occlusal caries. This device is a new and painless way to treat early caries.

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Safety of Ozone for Dental Therapy Established

Ozone has been used in dental therapy for over 3½ years by 4,000 dentists with no reports of side effects (E. Lynch, personal communication, May 2005). Also, in clinical studies in over 2,000 patients, no adverse effects have been reported. Ozone as a therapeutic agent is similar to many medicaments that are only effective if applied in the correct dose and for valid procedures.

The current literature addresses the potential of adverse events from ozone exposure beyond the levels recommended by the European Union (EU) and US Food and Drug Administration (FDA). The only device used for treating dental caries in the published research is HealOzone™ (KaVo Dental GmbH, Biberach, Germany). Other methods of ozone production have been used within controlled in vitro environments, but their implications of risk to operator and patient safety are considerable. At the time of this writing, HealOzone is the only approved device for intraoral applications. The main features that support its safety are as follows:

- The tight-fitting design of the delivery device made by the cup and tooth contains the ozone treatment at the diseased site.

Ozone has been used in dental therapy for over 3 years by 3,000 dentists with no reports of side effects. Also, in clinical studies in over 2,000 patients, no adverse effects have been reported.

- The device operates by suction only, the pathway for ozone being under negative pressure. Therefore, ozone will not leak out. In the event of a leak, air can leak in but no ozone can leak out owing to the design of the device.
- If the seal is incomplete or if a leak arises, a flow sensor shuts down the ozone generator.
- After the delivery of ozone, automatic suction remains on for an additional 10 seconds to purge away any remaining ozone.
- Ozone is stable for only a brief time. It decomposes to form oxygen and hence disappears rapidly.

None of the clinical studies included in this article reported any adverse events associated with ozone therapy. One study reported that the intraoral concentration of ozone around the application cup (1–2 mm) was below the FDA and EU permissible levels in air.[1] Shargawi and colleagues used ozone in a gas form produced with variable emitter distances, exposure times, and relative humidity and under aerobic and oxygen-free conditions.[2] When used in a nonventilated room, levels of ozone produced did not exceed recognized safety limits.

Other studies used ozone dissolved in water in different concentrations. The authors of one study found that ozonated water, not being isotonic, had no negative effect on the periodontal cells (cementoblasts and fibroblasts) remaining on a freshly extracted tooth surface after irrigation for 2 minutes.[3] In another study, mouse fibroblasts were also subjected to ozonated water, and their metabolic activity remained high when the cells were treated, in contrast to what was found when they were rinsed with a 2.5% NaOCl (sodium hypochlorite) solution.[4] In a third study, in implants treated with ozone, there was regeneration of periodontal cells similar to that around natural teeth.[5] These studies provide a good basis for claiming the safety of ozone applications on soft tissue, which has already been reported in earlier studies that treated gingivitis and periodontitis.[6]

It should be noted that ozone is a naturally occurring gas that is produced in the upper atmosphere. It is heavier than air and is thus affected by gravity. As ozone descends toward the earth, it binds to any pollutant in the atmosphere with which it comes in contact, thereby cleansing the air. When ozone binds the water molecules present in water vapor in the atmosphere, it forms hydrogen peroxide, a component of rain water. Rain water is cleaner than tap water; this is demonstrated by the fact that plants grow better when irrigated with rain water than with tap water.

The HealOzone device for delivery of ozone to tooth surfaces has been shown, over a period of over 3 years of clinical use, to not produce any adverse effects.

Ozone is created in nature in three ways: (1) by lightning, resulting in the wonderful fresh smell after a thunderstorm; (2) through waterfalls and waves crashing at the seashore, which accounts for the energetic feeling and calm experienced when near these sites; and (3) by photons from the sun that split nitrous oxide, a pollutant formed by the combustion of hydrocarbons in the internal combustion engine. Occupational exposure to ozone occurs through its production by office photocopying equipment, electric arc welding, mercury vapor lamps, laser printers, x-ray generators, and high-voltage electrical equipment.

Comment

The HealOzone device for delivery of ozone to tooth surfaces has been shown, over a period of over 3½ years of clinical use, to not produce any adverse effects. These clinical findings are not surprising since a number of studies have shown that the HealOzone device results in no significant release of ozone into the air of the oral cavity and has a flow sensor that shuts down the delivery of ozone if a leakage occurs.

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