

Berendsen JLM¹, el Allati I¹, Sylva LH¹, Blijdorp PA², Van Damme PhA³, Meijer GJ⁴

¹ Mondzorgkunde Hogeschool Utrecht, Oral Hygiene Practice C.M.M. Berendsen-Wolters, Venlo, The Netherlands

² Department of Oral & Maxillofacial Surgery, Rijnstate Hospital Arnhem, The Netherlands

³ Department of Oral & Maxillofacial Surgery, Maas Hospital Pantein Boxmeer, The Netherlands

⁴ Departments of Periodontology & Biomaterials and Oral & Maxillofacial Surgery, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Ardox-X[®] adjunctive topical active oxygen application in periodontitis and peri-implantitis – a pilot study (not published)

Abstract

Aims: The aim of the study was to gain insight into the healing effects of Ardox-X[®] in periodontitis and peri-implantitis. Healing is induced through the release of active oxygen in the peri-dental and peri-implant area. The results were to be compared with the generally accepted – ‘gold standard’ - treatment strategies for these disease entities. As reported in the literature, in addition to mechanical/instrumental treatment, antimicrobials such as chlorhexidine digluconate (CHX) and hydrogen peroxide (H₂O₂) are often prescribed and used in these situations, as well as in many other different oral and dental disorders. These medications are known to have advantageous effects, but they also have their limitations, disadvantages and adverse effects. This pilot study is meant to suggest that Ardox-X[®] might be a better alternative.

Material and methods: A case control study, in which 33 patients were included, has been carried out to examine the effects of adjunctive treatment with Ardox-X[®] in periodontitis situations. Full mouth dental pocket depth recordings have been made before and within 3 months after treatment with Ardox-X[®]. In the peri-implantitis study 34 patients were included, with a total of 40 dental implants. They were all treated according to a standardized Ardox-X[®] peri-implantitis protocol and were both clinically and radiographically re-examined after 3, 6 weeks and after 3, 6 months, respectively.

Results: In the periodontitis study, after 3 months treatment with Ardox-X[®], the average total pocket depth decrease was 56%. Different values were scored for male and female patients, 66 and 49%, respectively. Improvement was perceptible in all age categories. The age category of 40-44 years showed the greatest improvement (71%) and the category of 65-69 years the least (36%). There were no remarkable differences in relation to cigarette smoking habits: the average pocket depth decrease in smokers was 56%, in patients who had smoked in the past 55%, and in non-smokers 56%.

In the peri-implantitis study, the affected tissue had clinically noticeably recovered after 3 and 6 weeks in all cases. After 3 months, 75% of the peri-implantitis situations had been cured (with radiographically definite re-osseointegration in 15% of the implants), 9 peri-implantitis cases had not been cured yet and 1 implant was lost. After 6 months, radiographical examination showed re-osseointegration of 3 mm in 15% of cases, of 2 mm in 60%, and no signs of re-osseointegration in 4 cases.

Conclusions: From the case control periodontitis study results could be concluded that adjunctive Ardox-X[®] yielded better average total pocket depth reduction percentages than generally reported in the literature for other treatment strategies. From the Ardox-X[®] protocol peri-implantitis study results could be concluded that the clinical situation around implants improved markedly within 3 to 6 weeks in all cases. After 3 months, 75% of cases were clinically cured. Radiographically evidenced re-osseointegration of 2 mm could be noted in 60% and of 3 mm in 15% of cases after 6 months. These figures are indicative for faster and better pocket and peri-implantitis healing than reported in the literature for the generally accepted – ‘gold standard’ – adjunctive treatment regimens. A prospective double masked placebo controlled split mouth model adjunctive periodontitis treatment study with Ardox-X[®] is in its final preparation phase.

Key words: periodontal disease, implantology, treatment, re-osseointegration, clinical, radiographic

Introduction

Infections around teeth (periodontitis) and around endosseous dental implants (peri-implantitis) frequently occur in the elderly adult population. The estimated prevalence is approximately 50% (19.2 – 62.7%) for periodontitis and 1.0% - 19.0% for peri-implantitis, respectively (Bourgeois et al. 2007, Kaptein et al. 1999, Leeuwangh et al. 2006, Roos-Jansåker 2007). Untreated they cause symptoms of disease and ultimately loss of teeth and/or dental implants. Healthy life style, balanced, i.e. varied fresh food intake and routine oral hygiene measurements (tooth brushing, interdental cleaning [dental floss, brushes], mouth rinsing, et cetera) are meant to prevent these diseases to occur. In the healthy situation there is a so-called gingival sulcus or crevice, on probing not deeper than 3 mm around natural teeth (Fig. 1), with underneath the gingival soft tissues a firm fibrous tooth-bone attachment – the periodontal ligament.

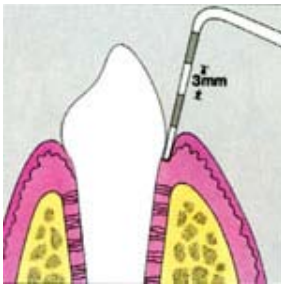


Fig. 1. Healthy gingival sulcus or crevice, on probing not deeper than 3 mm around the tooth.

In the healthy dental implant situation, underneath the soft tissue barrier there is direct implant-bone contact without any interface, so-called osseointegration (Fig. 2). Probing depths till 5 mm are interpreted as physiological.

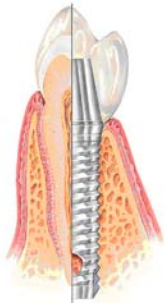


Fig. 2. Tooth and implant comparison, with direct implant-bone contact without any interface.

The chronic presence of dental plaque biofilm, dental calculus, with inherent oral microflora are the causative mechanisms in the etiology and pathogenesis of these two parallel presentations of the same disease entity, pockets and intrabony defects (Fig. 3).

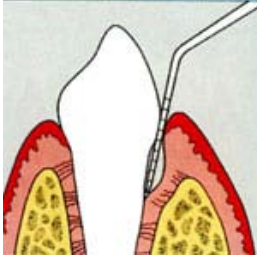


Fig. 3. Disease, on probing pocket deeper than 3 mm

Anaerobic gram negative micro-organisms induce a chronic inflammation and all inflammatory reactions are present (redness [rubor], bleeding, pain [dolor], swelling [tumor], loosening and hypermobility of teeth, suppuration, bad breath [*foetor ex ore* or halitosis]). Smokers and patients with a history of periodontal disease are at higher risk to develop peri-implantitis (Roos-Jansåker 2007). The indicated mechanical treatment of periodontitis and peri-implantitis lesions is rather invasive, painful (need for local anaesthesia and analgesics), intensive, time consuming, expensive and difficult (Greenstein 2005, Hanes & Purvis 2003). Additionally and alternatively chlorhexidine digluconate (CHX), hydrogen peroxide (H₂O₂)-solutions, triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol), povidone-iodine, other locally delivered antimicrobials (LDAs) and (systemic) antibiotics are often prescribed and used in different dental disciplines (De Araújo Nobre 2006, Hanes & Purvis 2003). These remedies are known to have advantageous effects, but they have limitations, disadvantages and negative side effects as well (Ribeiro et al. 2004). CHX has been reported to be highly cytotoxic in vitro and to exert toxic effects on periodontal tissues (Giannelli et al. 2007). Hydrogen peroxide has been associated with DNA-damage and carcinogenesis (Naik et al. 2006, Ribeiro et al. 2006). The administration of local and systemic antibiotics has been criticized for reasons of creating (multi)resistant micro-organisms, allergic reactions, hypersensitivity, and other adverse reactions in patients (Bidault et al. 2007).

Ardox-X[®] is a Hydro-Carbon-Oxo-Borate complex which is capable of releasing active oxygen, without freeing oxygen radicals as in hydrogen peroxide (H₂O₂)-solutions, and without inducing damage to the DNA of oral mucosal cells, or carcinogenesis (European Commission Health & Consumer Protection Directorate-General 2005, Li et al. 1998 a,b, Li & Ramaekers 2003, Ribeiro et al. 2004). Ardox-X[®] complex was originally discovered by a Dutch dentist and has been patented in 1996 (Van den Bosch 1997). The patented Ardox-X[®] technology made it possible to stabilize the active oxygen within the complex rendering a gradual active anionic oxygen release in a non-radical form. In-vitro studies have demonstrated that Ardox-X[®] obstructed the growth and development of harmful bacteria and fungi. These micro-organisms were not resistant to the high oxygen concentrations, as existing in the application of the oxygen complex in special care products (Kreis et al. 2004, Li et al. 1998 a).

There is a choice of 10 concentrations of Ardox-X[®] solutions, of which the highest concentration (10 eq) is used for the successful treatment of chronic nail infections (onychomycosis) and the lowest concentration (1 eq) is used for the treatment of gingivitis. The effects of Ardox-X[®] tooth gel on bacteria involved in periodontitis have been studied by Camp (2002). There is limited literature data about other indications and applications of Ardox-X[®], but it has been successfully used in halitosis, onychomycosis,

tinea pedis, psoriasis, eczema, burn lesions and chronic wounds as in diabetes patients (Enoch & Harding 2003, Kreis et al. 2004, Meinardi et al. 2004).

This study aimed at investigating the healing effects of Ardox-X[®] on the periodontal ligament and peri-implant mucosa, thereby introducing Ardox-X[®] as an alternative for the above mentioned remedies in periodontitis and peri-implantitis. The results will be compared with the generally accepted – ‘gold standard’ – treatment strategies for these diseases, as described in the literature (Greenstein 2005).

Materials and Methods

Periodontitis study

A case control study was performed to analyze the effects of treatment with Ardox-X[®] in 33 (20 female and 13 male) patients with periodontitis (Table 1). The inclusion criteria were: clinical diagnosis of manifest periodontitis, pocket depth measuring with the Goldman–Fox/- Williams probe (Fig. 4) and recording before the start of the treatment with Ardox-X[®] according to the protocol (concentration 5eq and 2eq for gel and mouth wash, respectively) and after maximally 3 months therapy.

Table 1.

Periodontitis patients	n
Female	20
Male	13
Total	33

n = number of patients



Fig. 4. Goldman–Fox/- Williams probe

Protocol Ardox-X[®]

The periodontitis / peri-implantitis treatment protocol in short:

- Curettage of the pocket
- Syringe the pocket with Ardox-X[®] gel (concentration 5eq), remaining in situ for 5 minutes
- Washing the gel away with saline
- Syringe the pocket again with Ardox-X[®] gel (concentration 5eq), application remains
- Instruct the patient to rinse and/or brush three times a day with Ardox-X[®] oral washing (concentration 2eq)

The protocol included that the pockets were curetted mechanically and Ardox-X[®] gel (concentration 5eq) was applied by a syringe. This was kept in situ for 5 minutes, was

rinsed off with physiologic saline solution, and the same concentration 5eq gel was applied again and then remained. The patients were instructed to rinse and/or brush three times a day with Ardox-X[®] oral washing (concentration 2eq). After maximally three months, the patients returned for a final clinical check-up.

Based on the full mouth pocket depth probing values a so-called pocket status form was completed for each patient. The forms were numbered and the patients' pocket depths were added up per pocket status. The differences between these sums before and after treatment with Ardox-X[®] were calculated per patient and transformed into difference percentages with the help of SPSS computer programs. Mutual comparisons have been made, between men and women, smokers, and patients who had smoked in the past and non-smokers, and between the different age groups, respectively.

Peri-implantitis study

A case control study to analyse the effects of treatment with Ardox-X[®] in 34 patients (25 female, 9 male) with a total of 40 dental implants, with peri-implantitis (Table 2).

Table 2.

Peri-implantitis patients	n
Female	25
Male	9
Total patients	34
Total implants	40

n = number

The inclusion criteria were the following: clinical diagnosis of manifest peri-implantitis, a minimal pocket depth of 5 mm (pocket depth measuring and recording with the Goldman- Fox/Williams probe) (Figure 4), with swollen soft tissues around the implant and bleeding occurring rapidly on inspection and initial cleaning (Fig. 5). A general characterization of inflammation/infection was required. The suprastructure had to be constructed according to the state of art techniques, and the patient's general condition had to correspond to the present valid standards required for performing justified implantology.



Fig. 5. Manifest peri-implantitis, with swollen soft tissues around the implant

First of all, the pockets were curetted mechanically and Ardox-X[®] gel (concentration 5eq) was applied by a syringe. This was kept in situ for 5 minutes, was rinsed off with physiologic saline solution, and the same concentration 5eq gel was applied again and then remained. The patients were instructed to rinse and/or brush three times a day with Ardox-X[®] oral washing (concentration 2eq). After three weeks, the patients returned for a clinical check-up and after six weeks the patients returned for a second treatment, which was identical to the first treatment. After three months, again there was a clinical check-up. If there were still signs of infection, the patient went back to the six weeks' schedule. When there were no further complications, the dental hygienist would see the patient for a clinical check-up every 2 years. The patients continued rinsing/brushing with the Ardox-X[®] oral washing (concentration 2eq).

The radiographs taken postoperatively and at 3 and 6 months after therapy respectively, were evaluated with respect to potential re-osseointegration around the implants and diminishing of the intrabony pocket radiolucencies (Fig. 6).

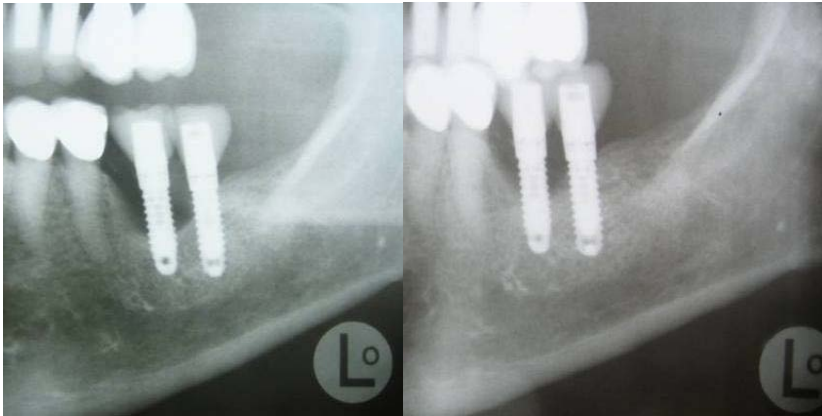


Fig. 6. Details of panoramic radiographs showing intrabony pocket radiolucencies around the implants; left side pre-treatment, right side 3 months post-treatment with Ardox-X[®]

Results

Periodontitis study

The average decrease of the pocket depth after treatment with Ardox-X[®] was 56%, meaning that after maximally 3 months treatment the total pocket depth decreased by more than half (Table 3).

Table 3.

Differences in pocket depth	n	average in %	SD
n	33	56	± 23

Average improvement of pocket depth in %

n = number of patients

SD = standard deviation

In the results a distinction could be made between men and women with regard to the average decrease of the pocket depth. The male patients had an average improvement of 66%, whereas the female patients had an average improvement of 49% (Table 4).

Table 4.

Sex differences	n	average in %	SD
Female	20	49	± 24
Male	13	66	± 17
Total	33	56	± 23

Average improvement of pocket depth in % with regard to sex

n = number of patients

SD = standard deviation

The improvement was perceptible in all age categories, but the age category of 40-44 years showed the greatest improvement (71%). The age category of 65-69 showed the slightest improvement (36%) (Table 5).

Table 5.

Age	n	average in %	SD
35 – 39 years	3	66	± 7,5
40 - 44 years	5	71	± 31
45 - 49 years	3	54	± 16
50 - 54 years	2	53	± 35
55 - 59 years	7	66	± 18
60 - 64 years	6	51	± 21
65 - 69 years	7	36	± 19
Total	33	56	± 23

Average improvement of pocket depth in % with regard to age

n = number of patients

SD = standard deviation

In addition, the results of the Ardox-X[®] treatment had been related to cigarette smoking habits. For smokers, patients who had smoked in the past and non-smokers, the respective percentages were not much different (Table 6).

Table 6.

Smoking habits	Average improvement in %	n	SD
Non-smoking	19	56	± 20
Smoked in the past	3	55	± 23
Smoking	11	56	± 30
Total	33	56	± 23

Average improvement of pocket depth in % with regard to smoking habits

n = number of patients

SD = standard deviation

Peri-implantitis study

In general, already after three weeks of Ardox-X[®] protocol therapy, the peri-implant situation appeared clinically improved or even healthy in all cases (Fig. 7). After six weeks a decrease of the pocket depth was noticeable in all patients. In 30 cases, the soft tissue had settled more firmly and tight around the implants, which made it more difficult to probe. Additional curetting around these implants could and did not take place.



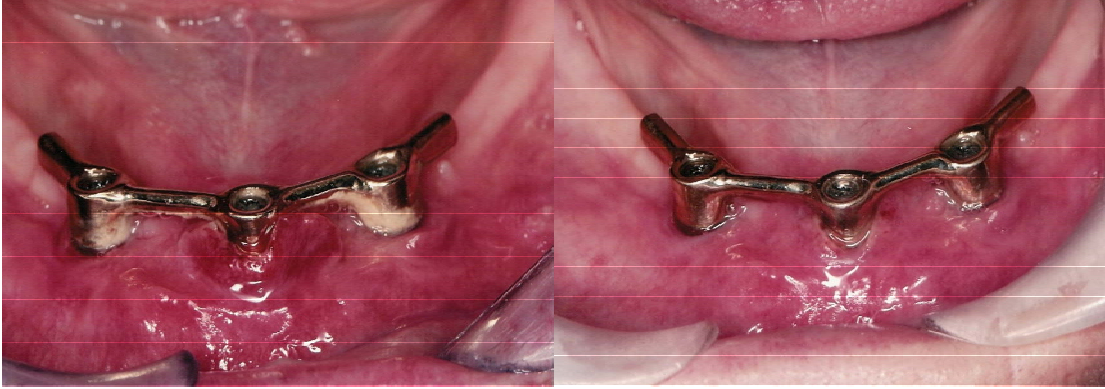


Fig. 7. Soft tissue recovery after peri-implantitis (Fig. 5), healthier situation after three months Ardox-X® protocol therapy

In order to avoid tissue damage, no mechanical cleaning was conducted, only the Ardox-X® gel (concentration 5eq) was syringed. In 4 cases repetition of the first treatment was indicated: curetting, syringing Ardox-X® gel (concentration 5eq) according to the protocol, washing the gel away and syringing the pocket again with Ardox-X® gel (concentration 5eq). Within three months, 30 implants (75%) could be cured clinically, 6 of which showed re-osseointegration on the radiographs all around the implants' deep pockets (15%). Nine other implants had not been cured yet and 1 implant was lost. After six months, 6 implants showed a re-osseointegration of 3 mm on the radiographs (15%). The other 24 cured implants showed a re-osseointegration of 2 mm (60%)(Table 7). In 4 cases there were no signs of re-osseointegration.

Table 7.

Peri-implantitis patients	n = 34
Implants	n = 40
After 3 weeks, in patients	- In 34 patients clinical improvement – healthy look
After 6 weeks, in patients - probing	- In 34 patients pocket depth reduction - In 30 patients soft tissue firmer/tighter around the implant(s) - In 4 patients indication for repeating treatment: irrigation pockets with Ardox-X® gel concentration 5eq, et cetera (see protocol)
After 3 months, in implants (clinically and radiographically)	- 1 implant lost - 9 implants not yet cured - 30 implants free of pathology (75%) - 6 implants re-osseointegration noticeable on the radiographs (15%)
After 6 months, in implants (radiographically)	- 6 implants re-osseointegration 3 mm (15%) - 24 implants re-osseointegration 2 mm (60%) - 4 implants no signs of re-osseointegration

n = number

Discussion

In the literature series of generally accepted – ‘gold standard’ - treatment strategies for periodontitis have been described.

The effect of dental plaque control and surgical pocket elimination on the establishment and maintenance of periodontal health was already described by Lindhe & Nyman in 1975. Their results demonstrated that it was possible to treat periodontal disease successfully, even in advanced stages, in patients willing to maintain a plaque-free dentition. In this way an improvement of the pocket depth with more than 47% was perceptible.

The therapy defined by the American Academy of Periodontology (2000, Greenstein 2005) is called initial therapy and consists of supra- and subgingival scaling and rootplaning, and potentially supplementary periodontal surgery, such as flap operations. At the same time dental hygienic guidance and correct instruction are essential. From the publication of the American Academy of Periodontology (2000) on the parameter of chronic periodontitis and the loss of supporting tissue, it could be inferred that the initial therapy will not be successful with all patients or in all cases. In specific places or with certain patients extra therapy may be necessary.

Locally delivered antimicrobials (LDAs) may be used in support of the initial therapy as adjuncts to mechanical therapy in treatment of recalcitrant deep (> or = 5mm), active, non-responding sites, providing the patient's oral hygiene is adequate (Hussein et al. 2007).

Recent interest in the local application of antimicrobial and anti-inflammatory agents has stimulated interest in the efficacy of various treatment regimens. The clinical and microbiological effects of subgingival and gingival marginal irrigation with chlorhexidine digluconate (CHX) have been studied (Jolkovsky et al. 1990, Giannelli et al. 2007). The findings suggested that it was possible to achieve beneficial effects from adjunctive single professional 0.12% CHX irrigation and home 0.04% CHX

subgingival irrigations in periodontal maintenance patients receiving supportive periodontal treatment. The average reductions in probing depth between the baseline and the three months' visit were 4.2%.

Along with good subgingival cleaning and an optimal dental hygiene, the microbiological compounding of the subgingival plaque, is one of the modifying factors. The use of a systemic periodontal antimicrobial therapy should always be based on detailed clinical examination and microbiological analysis. The micro-organisms involved are mainly: *Actinobacillus actinomycetemcomitans* (A.a.), *Porphyromonas gingivalis* (P.g.), *Tannerella forsythensis* (T.f.) (formerly *Bacteroides forsythus*), *Treponema denticola* (T.d.), *Prevotella intermedia* (P.i.), *Peptostreptococcus micros* (P.m.), *Fusobacterium nucleatum* (F.n.), *Campylobacter rectus* (C.r.), *Eubacterium nodatum* (E.n.), *Eikenella corrodens* (E.c.), *Capnocytophaga* species (C.s.) (Camp 2002, Leeuwangh et al. 2006).

In a study of Abbas & Van Winkelhoff (2004) the impact of antibiotics on the indication for periodontal surgery was described. Based on scientific literature about the clinical effects of antibiotics on the treatment of periodontitis with regard to plaque related disorders, it was concluded that application of antibiotics could be a valuable addition to conventional periodontal treatment. However, not all patients benefited from an antimicrobial therapy. Provided that it was used in the right way, particular systemic antibiotics (amoxicillin, metronidazole, or a combination of both) could reduce the indication for periodontal surgery significantly, especially around teeth with one root and in aesthetically sensitive areas. In mouths in which the infection was under control, the indication for successful regenerative periodontal surgery could increase. This also counted for plastic periodontal surgery, such as the covering of gingival recessions.

According to Renvert et al. (2006) the adjunctive use of minocycline microspheres resulted in improvements of probing depths and bleeding scores, whereas the adjunctive use of chlorhexidine only resulted in limited reduction of bleeding scores. For the deepest sites of the treated implants in the minocycline group, the mean probing depth was reduced from 5.0 to 4.4 mm (i.e. 12% reduction) at 12 months (Renvert et al. 2006).

The abovementioned treatment strategy of periodontitis has less effect on smokers than on non-smokers (American Academy of Periodontology 2000). In view of this information it could be stated that the adjunctive treatment of periodontitis with Ardox-X[®] seems to be a positive turn for smokers.

In respect of the effect of age on the treatment results it is worthwhile to note that in general the patient numbers in the higher age category are rising. Since the amounts in the different age categories in this pilot study are rather low, a realistic outcome as to the effects of Ardox-X[®] with regard to age cannot be determined. For this matter a more extended study would be needed, with a larger population and sufficient patient amounts in each age category.

A logical continuation of this case control pilot study into the effects of adjunctive Ardox-X[®] in periodontitis patients would be a prospective study in a preferably larger patient population, with defined protocols and explicit guidelines. Considering the group to be examined, a university periodontal practice would be a sophisticated choice for the place of action. In this way it should be possible to obtain a more realistic - evidence based - image of the effects of the adjunctive treatment of periodontitis with Ardox-X[®]

on probing depth, bleeding scores, gingival recession, and clinical attachment level (CAL).

Notwithstanding the fact that most implant systems have a 90% or higher success rate (O'Neal et al. 1992), one of the major causes of implant loss is peri-implantitis. More or less the same groups of micro-organisms seem to be involved in peri-implantitis as in periodontitis (Botero et al. 2005, Laine et al. 2005, Leeuwangh et al. 2006).

Generally accepted – ‘gold standard’ - treatment strategies for peri-implantitis have been described in the literature as well (De Araújo Nobre 2006). Peri-implant tissues are treated in more or less the same way as the periodontium of natural dental elements in case of periodontitis: an initial treatment with conservative measures as (ultrasonic) curetting, scaling, planing, and 0.1% chlorhexidine digluconate (CHX) irrigation, based on the principles of mechanical and chemical cleaning and disinfection (Wetzel et al. 1999). The titanium surface of the implants easily gets scratched and damaged by metal instruments. Because of that the surface-qualities of the implant are deteriorated and plaque-retention increases. In order to prevent this, it is deemed better to use specially designed implant instruments of a synthetic material, spray instruments or ultrasonic instruments, in combination with hydrogen peroxide-solution (3%) (Speelman & Collaert 1990, Strooker et al. 1998). If this treatment strategy is not successful it is advised that the patient will be placed on a 10 day systemic antibiotic combination course (e.g. amoxicillin and metronidazole). In case of lack of improvement, a flap operation, with or without gingivectomy and polishing of the implant surface can be performed and that open site could also be treated with an antimicrobial solution. If there is pain afterwards, analgesic medication in combination with a systemic antibiotic regimen is advised.

According to Wetzel, it appears that if peri-implantitis is to be ‘cured’ and re-osseointegration is to be achieved, an effective antibacterial therapy has to be applied (Wetzel et al. 1999). Even then, it remains difficult to achieve true re-osseointegration.

A published possible treatment modality of peri-implantitis to achieve bone formation around and re-osseointegration of dental implants is based on application of recombinant human bone morphogenetic protein type-2 (rhBMP-2) in peri-implantitis defects (Hanisch et al. 1997).

If all these measures have no noticeable effect and the patient remains in pain and discomfort, then removal of the implant would be the next step (Wiskott et al. 2004). Ultimately, approximately 10% of the implants fail.

Peri-implant problems could be looked upon as poorly healing chronic wounds (Blijdorp 2006). Generally, the vascularity, blood flow and oxygenation in the area surrounding chronic wounds are compromised, which hampers initiation and continuation of the healing process. Mainly due to the facts that tissue with a poor blood flow has a reduced resistance to infections and the process of self-healing is compromised, the role of adjunctive active oxygen is paramount (Blijdorp 2006).

With regard to the topical application of Ardox-X[®] active oxygen in peri-implantitis, in three weeks the clinical situation already looked healthy or at least healthier from the outside.

Similarly, parallel studies of Ardox-X[®] topical application in onychomycosis, burn lesions and chronic wounds, as in diabetes mellitus patients, showed overwhelming

results and the researchers noticed a recovery after only a few weeks, which generally could not have been obtained in several months with other methods (Kreis et al. 2004, Enoch & Harding 2003).

On the whole, dental implantology is successful, however, the longer the speciality exists (actually, more than 20 years now), the more patients there will be who can only retain their implants with difficulties, for general or local reasons. One of the reasons is the ongoing increase of higher age group patient numbers and the inherent progressive diminishing of motor and mental abilities. The patients' immune status also becomes weaker, and consequently dental implants, which are *corpora aliena* after all, may become more difficult to clean and to retain. Usually, after 8-10 years of presence, the lowest figures of implant loss are reached. Thereafter peri-implant problems tend to occur more frequently leading to higher implant losses. Up till now, the patients with peri-implantitis were treated by means of flap operations. The implants were partly uncovered, the surface of the implant would be polished and treated with disinfectants, etching gel and other (bio)materials (Strooker et al. 1998). The results of these treatment strategies were not always very encouraging. Chlorhexidine digluconate (CHX) was most frequently used in an attempt to eliminate the bacteria in the pocket. When intrabony problems underlie the soft tissue peri-implantitis, a surgical intervention with curetting might still be the right option. However, a surgical intervention alone is unlikely to reactivate the titanium surface or achieve wound recovery at both the soft tissue level and the bony structure level.

The adjunctive Ardox-X[®] topical active oxygen application is claimed to be a valuable contribution to 'diseased implant' salvage and implant survival (Blijdorp 2006). The Ardox-X[®] active oxygen not only has proven antibacterial and antifungal effects in-vitro, but it also has cleansing and purifying effects. The experience in general medicine with regard to chronic wound treatment is that Ardox-X[®] gel (concentration 5eq) cleans the wounds. One of the other in-vitro findings is that Ardox-X[®] is not mutagenic or cytotoxic, it does not cause cell death, neither of erythrocytes and leucocytes, nor oral mucosal cells and osteoblasts. It is thought to activate the release of wound-healing enzymes. There also are indications that it has pain and inflammation reducing effects. In comparison with hydrogen peroxide, which causes necrosis of erythrocytes and, in concentrations higher than 1%, stimulates radicals and therefore assumed to be carcinogenic, the Ardox-X[®] gel (concentration 5eq) stands out rather positively.

In fact, the exact working mechanism of Ardox-X[®] gel is not yet fully understood or known, i.e. why it activates wound healing so quickly and even brings about bone formation around infected implants. The clinical findings are promising. As mentioned above, more extensive clinical follow-up studies of Ardox-X[®] gel within the dental and medical field are indispensable (Blijdorp 2006). Some of the methods used in the actual pilot study have been proven to be adequate and detailed, specifically the technique of full mouth pocket probing with the Goldman-Fox/-Williams probe (Araujo et al. 2003, Buduneli et al. 2004, Grisi et al. 1998). In order to avoid traumatizing the healing tissue, the peri-implantitis patients should not be examined so early as after three weeks with a pocket probe. Other limiting factors are the radiographic representations of the buccal and lingual respectively palatal sides of the implants which are not perceptible. For that reason, in the future, 3-D cone beam CT-scanning would be an option

Conclusion

This paper hypothesizes that the adjunctive treatment of periodontitis and peri-implantitis, according to the Ardox-X[®] gel protocol shows a larger pocket reduction and faster wound healing compared to the generally accepted treatment strategies as described in the literature. Further and additional studies on (non-)prescription antimicrobial oral care products may lead to new regimens for decreasing the burden of periodontal and peri-implant diseases in the population. A prospective double masked placebo controlled split mouth model adjunctive periodontitis treatment study with Ardox-X[®] is in its final preparation phase to prove above mentioned hypothesis

References

1. Abbas, F. & Winkelhoff A.J. van. (2004) Antibiotica beïnvloeden de indicatie voor parodontale chirurgie. [Impact of antibiotics on the indication for periodontal surgery]. *Ned Tijdschr Tandheelk* **111**, 425-429.
2. American Academy of Periodontology. (2000) Parameter on chronic periodontitis with advanced loss of periodontal support. *J Periodontol* **71**, 856-858.
3. Araujo, M.W.M., Hovey, K.M., Benedek, J.R., Grossi, S.G., Dorn, J., Wactawski-Wende, J., Genco, R.J. & Trevisan, M. (2003) Reproducibility of probing depth measurement using a constant-force electronic probe: Analysis of inter- and intraexaminer variability. *J Periodontol* **74**, 1736-1740.
4. Bidault, P., Chandad, F. & Grenier, D. (2007) Risk of bacterial resistance associated with systemic antibiotic therapy in periodontology. *J Can Dent Assoc* **73**, 721-725.
5. Blijdorp, P.A. (2006) Toepassing van actieve zuurstoftechnologie bij de behandeling van peri-implantaire wonden. [Application of active oxygen technology in the treatment of peri-implant wounds]. Rijnstate Hospital Arnhem, Arnhem, The Netherlands. (March 9).
6. Bosch, W.F. van den. (1997) Periodontitis associated bacteria test report OT9051 tooth gel, 4 to 9 months use in 6 patients. Diamond White Nederland BV, Explore BV, University of Nijmegen, The Netherlands.
7. Botero, J.E., González, A.M., Mercado, R.A., Olave, G. & Contreras, A. (2005) Subgingival microbiota in peri-implant mucosa lesions and adjacent teeth in partially edentulous patients. *J Periodontol* **76**, 1490-1495.
8. Bourgeois, D., Bouchard, P. & Mattout, C. (2007) Epidemiology of periodontal status in dentate adults in France, 2002-2003. *J Periodontal Res* **42**, 219-227.
9. Buduneli, E., Aksoy, O., Köse, T. & Atilla, G. (2004) Accuracy and reproducibility of two manual periodontal probes. An in vitro study. *J Clin Periodontol* **31**, 815-819.
10. Camp, P.J.M. (2002) Study number AOC-PARO-02-002. Advanced Dental Diagnostic BV, Malden, The Netherlands.
11. De Araújo Nobre, M., Capelas, C., Alves, A., Almeida, T., Carvalho, R., Antunes, E., Oliveira, D., Cardador, A. & Maló, P. (2006) Non-surgical treatment of peri-implant pathology. *Int J Dent Hyg* **4**, 84-90.

12. Enoch, S. & Harding, K. (2003) Wound bed preparation: the science behind the removal of barriers to healing. *Wounds* **15**, 213-229.
(<http://www.medscape.com/viewarticle/459733>).
13. European Commission Health & Consumer Protection Directorate-General (2005) SCCP/0844/04.
(http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_022.pdf).
14. Giannelli, M., Chellini, F., Margheri, M., Tonelli, P. & Tani, A. (2007) Effect of chlorhexidine digluconate on different cell types: A molecular and ultrastructural investigation. *Toxicol In Vitro* 2007 Nov 1 [Epub ahead of print].
15. Greenstein, G. (2005) Research, Science and Therapy Committee of the American Academy of Periodontology. Position paper: The role of supra- and subgingival irrigation in the treatment of periodontal diseases. *J Periodontol* **76**, 2015-2027.
16. Grisi, M.F., Novaes, A.B., Ito, I.Y. & Salvador, S.L. (1998) Relationship between clinical probing depth and reactivity to BANA test of samples of subgingival microbiota from patients with periodontitis. *Braz Dent J* **9**, 77-84.
17. Hanes, P.J. & Purvis, J.P. (2003) Local anti-infective therapy: pharmacological agents. A systematic review. *Ann Periodontol* **8**, 79-98.
18. Hanisch, O., Tatakis, D.N., Boskovic, M.M., Rohrer, M.D. & Wikesjö, U.M. (1997) Bone formation and reosseointegration in peri-implantitis defects following surgical implantation of rhBMP-2. *Int J Oral Maxillofac Implants* **12**, 604-610.
19. Hussein, I., Ranka, M., Gilbert, A. & Davey, K. (2007) Locally delivered antimicrobials in the management of periodontitis: a critical review of the evidence for their use in practice. *Dent Update* **34**, 494-496.
20. Jolkovsky, D.L., Waki, M.Y., Newman, M.G., Otomo-Corgel, J., Madison, M., Flemmig, T.F., Nachnani, S. & Nowzari, H. (1990) Clinical and microbiological effects of subgingival and gingival marginal irrigation with chlorhexidine gluconate. *J Periodontol* **61**, 663-669.
21. Kaptein, M.L., Lange, G.L. de & Blijdorp, P.A. (1999) Peri-implant tissue health in reconstructed atrophic maxillae - report of 88 patients and 470 implants. *J Oral Rehabil* **26**, 464-474.
22. Kreis, R.W., Bosch, W.F. van den & Changoer, L. (2004) Project chronic open wounds treatment. Rode Kruis Ziekenhuis Beverwijk and Ardoz Research Gouda. The Netherlands. Report May 2004.

23. Laine, P., Salo, A., Kontio, R., Lijoki, Y., Lindqvist, C. & Suuronen, R. (2005) Failed dental implants – clinical, radiological and bacteriological findings in 17 patients. *J Cranio-Maxillofac Surg* **33**, 212-217.
24. Leeuwangh, M.J., Soehardi, A. & Damme, Ph.A. Van. (2006) Microbiële aspecten bij falende implantologie in (partieel) edentate patiënten - Een voorlopige rapportage. [Microbiological aspects of failing implants at (partially) edentulous patients. A preliminary report]. Master-Thesis, Radboud University Nijmegen, Nijmegen, The Netherlands.
25. Li, Y. & Ramaekers, F.C.S. (2003) Effect of various reactive oxygen donors on DNA damage. Loma Linda University, Loma Linda, Ca, USA, MUBio Products BV, University of Maastricht, Maastricht, The Netherlands.
26. Li, Y., Zhang, W., Xu, Y., Davis, J. & Klaunig, J. (1998a) Peroxide content and free radical generation by OT7051 tooth whitening gel, Ref: 98-004. Loma Linda University, Loma Linda, Ca, USA and Indiana University, Bloomington, In, USA.
27. Li, Y., Zhang, W. & Yang, J. (1998b) Cytotoxicity and mutagenicity of a non-peroxide based tooth whitening gel. Ref: 98-006. Loma Linda University, Loma Linda, Ca, USA.
28. Lindhe, J. & Nyman, S. (1975) The effect of plaque control and surgical pocket elimination on the establishment and maintenance of periodontal health. A longitudinal study of periodontal therapy in cases of advanced disease. *J Clin Periodontol* **2**, 67-79.
29. Meinardi, M.M. & Bos, J.D. (2004) Efficacy on 19 therapy resistant onychomycosis patients. Amsterdam Medical Centre, Amsterdam, The Netherlands.
30. Naik, S., Tredwin, C.J. & Scully, C. (2006) Hydrogen peroxide tooth-whitening (bleaching): review of safety in relation to possible carcinogenesis. *Oral Oncol* **42**, 668-674. [Epub 2006 Feb 20].
31. O'Neal, R.B., Sauk, J.J. & Somerman, M.J. (1992) Biological requirements for material integration. *J Oral Implantol* **18**, 243-255.
32. Renvert, S., Lessem, J., Dahlén, G., Lindahl, C. & Svensson, M. (2006) Topical minocycline microspheres versus topical chlorhexidine gel as an adjunct to mechanical debridement of incipient peri-implant infections: a randomized clinical trial. *J Clin Periodontol* **33**, 362-369.

33. Ribeiro, D.A., Bazo, A.P., da Silva Franchi, C.A., Marques, M.E. & Favero Salvadori, D.M. (2004) Chlorhexidine induces DNA damage in rat peripheral leukocytes and oral mucosal cells. *J Periodont Res* **39**, 358-361.
34. Ribeiro, D.A., Marques, M.E. & Favero Salvadori, D.M. (2006) Study of DNA damage induced by dental bleaching agents in vitro. *Braz Oral Res* **20**, 47-51. [Epub 2006 May 22].
35. Roos-Jansåker, A.M. (2007) Long time follow up of implant therapy and treatment of peri-implantitis. *Swed Dent J Suppl* **188**, 7-66.
36. Speelman, J.A. & Collaert, B. (1990) Het parodontium als peri-implantair weefsel. [The periodontium as peri-implant tissue; a review]. *Ned Tijdschr Tandheelkd* **97**, 327-331.
37. Strooker, H., Rohn, S. & Winkelhoff, A.J. van. (1998) Clinical and microbiologic effects of clinical versus mechanical cleansing in professional supportive implant therapy. *Int J Oral Maxillofac Implants* **13**, 845-850.
38. Wetzel, A.C., Vlassis, J., Caffesse, R.G., Hämmerle, C.H. & Lang, N.P. (1999) Attempts to obtain re-osseointegration following experimental peri-implantitis in dogs. *Clin Oral Implants Res* **10**, 111-119.
39. Wiskott, H.W., Dubrez, B., Scherrer, S.S. & Belser, U.C. (2004) Reversible and irreversible peri-implant lesions: report and etiopathogenic analysis of 7 cases. *J Oral Implantol* **30**, 255-266.

Acknowledgements

Ardox-X[®] was kindly supplied by Ardoz Research B.V. The Netherlands
P.O. Box 4017, 5203 GA 's-Hertogenbosch, The Netherlands
<http://www.ardoz.com> info@ardoz.com

Funding

The authors received no specific funding for this article.

Competing Interests

Ardoz Research B.V. The Netherlands had no role in the decision to submit this paper, or in its preparation. The authors declare that they have no financial or competing interests.

Address:

Dr. G.J. Meijer, DMD, PhD
Departments of Periodontology & Biomaterials and Oral & Maxillofacial Surgery, Radboud University
Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
E-mail: drgjmeijer@wanadoo.nl

Correspondence:

Dr. Ph.A. Van Damme
Department of Oral & Maxillofacial Surgery Maas Hospital Boxmeer, P.O. Box 55, 5830 AB
Boxmeer, The Netherlands
E-mail: philip.a.vandamme@gmail.com