

Photodynamic therapies – Blue versus Green

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Introduction

After the successful introduction of antimicrobial photodynamic therapy based on methylene and toluidine blue, a green medical colouring agent which is activated at 810 nm has become available. The following article illustrates its indication, range of effects and therapy efficiency in comparison to the classical blue agents. Photodynamic therapy (PDT) as a minimally invasive oncological method performed with injected photosensitisers has been advanced to a non-invasive, surface-oriented therapy in dentistry. Its main indications are bacteria, which is why it has been marked "antibacterial": antimicrobial photodynamic therapy (aPDT). aPDT entails a light-induced inactivation of cells, microorganisms or molecules without destroying the tissue. Therefore, aPDT or PDT in periodontology, endodontology, professional tooth cleaning, as well as periimplantitis and mucosa treatment must be differentiated from invasive therapies such as hard-tissue treatments in enamel, dentine and bone, surgery, periodontal treatment, endodontology and invasive periimplantitis therapy.

In aPDT, two effects are brought together: the low-level, highly pervasive laser energy with the photodynamic effect resulting in high tissue efficiency and the colouring agent activation resulting in a bactericidal effect via singlet and triplet oxygen, which harms the unsaturated fatty acids in the colour-marked membranes and their organelles. In addition, they initiate the disintegration of the bacterial membranes and therefore cause the bacteria to die. These two effects are linked inseparably in aPDT. Parallely to reducing bacteria, laser light which has not been absorbed promotes healing. Even the application of laser light alone will reduce dental plaque¹, thus leading to a reduced healing time. In previous years, aPDT has been associated with a multitude of synonyms: PACT—photoactivated chemotherapy, PDD—photodynamic disinfection, LAD—light-activated disinfection, PAD—photoactivated disinfection, among others. These terms signify a principle rather than actually contributing to an enhanced insight into the concept. They can therefore be seen as marketing-oriented neologisms.

Laser-, LED- und colouring agent systems have become available in larger quantities and can be integrated to other therapies. Possible combinations are:

- LED 630 nm—toluidine blue O—Fotosan/Fotosan 630
- Laser 635—toluidine blue O—PACT system, R+J, Two in one, MDL 10, among others
- Laser 670 nm—methylene blue, HELBO system, Periowave, among others
- Laser 810 nm—methylene blue derivative—Photolase system
- Laser 810 nm—indocyanine green—EmunDo, PerioGreen

aPDT/PDT application in dentistry

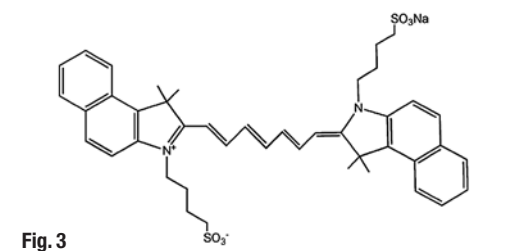
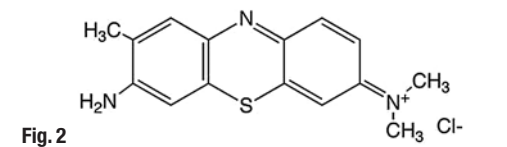
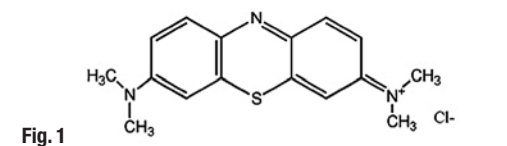
Periodontology

Periodontology is the most prominent field of application for aPDT/PDT in dentistry to date. aPDT can be applied specifically to target infected and contaminated tissues or organic structures (periodontitis, periimplan-

Fig. 1 Structural formula of methylene blue (MB).

Fig. 2 Structural formula of toluidine blue (TBO).

Fig. 3 Structural formula of indocyanine green (ICG).





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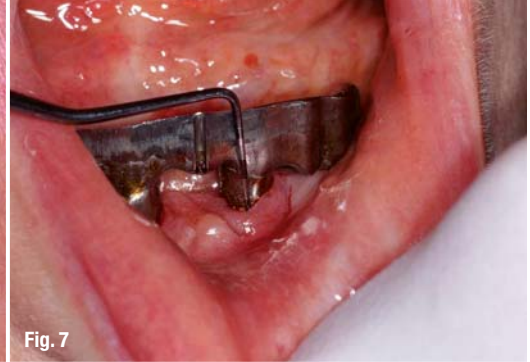
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Fig. 4 Intensity differences between methylene blue (Blue Sensitizer, HELBO, on the left) and toluidine blue O (PACT, Cumdente, on the right).



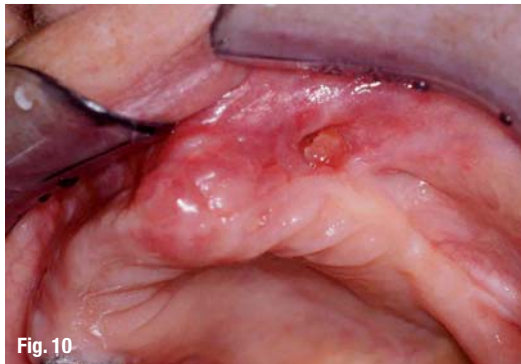
Case 1
Fig. 5 Blue Sensitizer (HELBO) applied to the sulcus.
Fig. 6 Laser light application to the sulcus.



Case 2
Fig. 7 Measuring of progressing bone resorption.
Fig. 8 Selective laser application according to protocol.
Fig. 9 Inflammation-free condition after 30 days.



Case 3
Fig. 10 Entrance to the inflamed bone cavity after pus removal.
Fig. 11 Application of Blue Sensitizer to the cavity.
Fig. 12 TeraLite laser application.
Fig. 13 Removal of a bone sequestrum from a bone cavity which is almost completely epithelialised.



titis, infected mucosa or other areas of the patient's skin).²⁻⁴ De Olivera et al.⁵ have reached comparable clinical results in their split-mouth investigations of aPDT in comparison to scaling and root planing (SRP). Wilson et al.^{6,7} have introduced the basics of low-level laser application with photosensitive substances in bacteria.

PDT treatment can be applied in dentition damaged by periodontitis:

1. As an immediate measure in acute gingivitis or periodontitis.
2. As a consecutive conventional periodontitis therapy in intervals of three days up to two weeks.
3. In unspecific prophylactic bacterial reduction in extended professional tooth cleaning in intervals of one to two years.^{3,8}

aPDT applications have provided good results and a significant reduction of the microbial load.⁹ In periodontitis caused by *Porphyromonas gingivalis*, a reduced bone resorption in comparison to the control group was observed in animal studies after colouring agent-activated laser treatment with toluidine blue.¹⁰ Comparing different laser systems with regard to their adjuvant application, Brink and Romanos^{11,12} showed that mechanical cleansing combined with aPDT resulted in the highest possible reduction of microbes in the dental pockets. The highest reduction was verified after three months. *Actinobacillus actinomycetemcomitans*, now named *Aggregatibacter actinomycetemcomitans*, was eliminated after treatment with one of the systems (aPDT, 1,064 nm laser, 980 nm laser). Investigations in patients of an open dental practice showed a microbial reduction of 80,11 % after four weeks and 91,37 % after twelve weeks compared to the initial findings of aPDT in comparison to the above-mentioned laser systems. Sulcus bleeding index, pocket depths and mobility of the teeth were significantly reduced after treatment. In cases of minimal pocket depths of three to four millimetres, aPDT can be the sole therapy. A fast recolonisation of the periodontic tissue was minimised by PDT after two days.¹³ They showed in their study that roughly 95 % of *A. actinomycetemcomitans* and *F. nucleatum* and 99–100 % of the black-pigmented bacteria, such as *P. gingivalis* and *P. intermedium* and *S. sanguis* were eliminated. Rühling et al.¹⁴ did not note any advantages in PDT with regard to conventional treatment, but they admit that it can be an alternative. The initial treatment of periodontitis with amoxicillin and metronidazole (Winckelhoff cocktail) is favoured by Griffiths et al.¹⁵ over an invasive treatment. An initial administration of antibiotics achieved better results than did subsequent treatment. A critical discussion on the administration of metronidazole was conducted only reluctantly. Procedures which are specifically tropical (aPDT) and of a high selectivity are more favourable in the aftercare of periodontally dam-

aged patients than broad-spectrum antibiotic treatments, which have various side effects and are often accompanied with a limited compliance of the patients.¹⁶ Hägi & Sculean¹⁷ do not consider aPDT which is free from side effects and bactericidal a significant improvement over antibiotic therapies, with the exception of severe and aggressive periodontitis.

The importance of pulpal temperature rise in periodontal treatments is described by El Yazami et al.¹⁸ with an average temperature rise of roughly 0,5°C at 5,46 J/cm² for 60 s with a diode laser of 660 nm (output: 20 mW). Another advantage of aPDT is that it can be performed by a trained assistant if the patient has been treated accordingly before. This kind of laser treatment (class 3B) is a physical, non-invasive therapy¹⁹ which can be delegated. Whereas the doctor is in charge of supervision, control and overall responsibility of delegated tasks with respect to a commission with single allocation defined in concrete terms, he does not have to execute the delegated tasks. Treatment is free of pain and non-destructive on the tissues. However, its application in the bleeding dental pocket would neutralise its effect almost completely. Therefore, a time-shift is recommended in this treatment. The activation of epithelia and bone growth, vascularisation and an increase in phosphorylation are important for the production of ATP in the healing phase and their effects on mitochondria and enzymes of the respiratory chain have long been assumed.^{20,21} Bosatra²² showed that low-energy laser light induces the synthesis of fibres in the tissue in 1984. Tocco et al.²³ and Boulton et al.²⁴ proved an increase in fibroblast growth by HeNe (630 nm) and IR laser application.

Implantology

In implantology, aPDT is applied in mucositis or manifested periimplantitis as a closed therapy or as an open therapy in combination with surgical measures. An important advantage of athermal laser applications is the lack of superficial changes of the titan and of ruptures.

Oral and maxillofacial surgery

In oral and maxillofacial surgery, photodynamic disinfection of bone or soft tissue defects during the final surgical phase is an additional means of prevention. Local or systemic toxicity of the photosensitiser as well as damage by the source of light can be excluded because of the low energy level. Lingohr et al.²⁵ have described advantages with regard to apicoectomies. Neugebauer et al.²⁶ have observed positive effects on the prevention of alveolar ostitis and the dolor post extractionem and Conrad²⁷ on the augmentation of infected alveoli. Nagayoshi et al.²⁸ have proved a complete sterilisation of the bone cavity via ICG with radiation for more than 60 seconds at 810 nm in the periapical defect model. PDT can be an alternative to lengthy and highly-dosed antibiotic therapies in the treatment and post treatment



Fig. 14



Fig. 15



Fig. 16



Fig. 17



Fig. 18



Fig. 19



Fig. 20



Fig. 21

Case 4

Fig. 14_Injection of a surplus of TBO (Fotosan) in the periodontal pockets.

Fig. 15_High transillumination in palatal laser application.

Fig. 16_Laser light application in the mandible.

Case 5

Fig. 17_PDT disinfection of the tissue surfaces after periodontal surgery.

Case 6

Fig. 18_Application of ICG solution.

Fig. 19_Transgingival laser application with bare fibre.

Fig. 20_Laser application of the periodontal pockets with bulb fibre.

Fig. 21_Removal of the inflamed pocket epithelium at 300 mW.

of bone defects induced by diphosphate. It can also be combined with surgery in the open operating site. A crucial side effect in laser therapy, however, is the stimulation of bone healing by photobiological effects of the laser radiation. Guzzardella et al.²⁹ have shown a significant effect on bone defect healing by laser light of a wavelength of 780 nm in their experiments. Laser irradiation resulted in bone growth twice or three times the amount as compared to conventional treatment. These findings have been confirmed by other studies³⁰, which have also been published on red wavelengths of HeNe lasers of low performance.^{31,32}

Endodontics

Various low-consistent sensitizers and long slim applicators are offered for the disinfection of the root canal. In addition to a possible discolouration of the root dentine, there is the danger of a lack in in-depth moistening of the dentinal tubuli, which would limit the effect on the prepared pulp cavity. The application of type-4 lasers must be considered with regard to safety as well as material and time saving.

Cariology (dentine hardening)

In cariology, PDT procedures for dentine hardening usually are time-dependent processes with blue colouring agents. Multiple applications are sensible and gen-

tle on the dentine, since carious dentine is disinfected and removed layer-by-layer. Disinfection of the occlusal fissures is another possibility. A pulpal increase in temperature in the photodynamic treatment of deep carious lesions results in a rise in temperature of 0,8 – 1°C after 30 seconds of irradiation.³³ While a blue colouring agent only permits a disinfection of the carious dentine, ICG can also result in dentine removal. ICG-based caries removal was examined by Rodrigues de Sant'anna et al.³⁴, who proved significant removal on the hard tissue. McNally et al.³⁵ also describe erosive processes without any ruptures in the substance, whereas the temperature rise in the pulpal area of extracted teeth depends on the ICG concentration as well as the laser performance. Caries removal via ICG is more invasive and has hardly been examined to date. However, it suffices with one single application. It remains to be seen whether it poses a real alternative to Er:YAG and Er,Cr:YSGG lasers.

Skin und mucosa infections

Infections of mucosa or skin are a common oral or periodontal phenomenon, resulting from bacterial or viral infections. Here, PDT can be performed by the dentist as well as the dermatologist and other specialists. Zolfaghari et al.³⁶ have proved a photodynamic effect on Staph. aureus by the combination of methylene blue and laser light. In recent years, mycoses of the oral cav-

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Fig. 22



Fig. 23



Fig. 24



Fig. 25



Fig. 26



Fig. 27



Fig. 28



Fig. 29

Case 7

- Fig. 22**_Transgingival laser application.
- Fig. 23**_Laser application in the dental pockets with bulb fibre.
- Fig. 24**_Application of the ICG solution in the periodontal pockets.
- Fig. 25**_Intrasulcular laser application in the mandible.
- Fig. 26**_PDT/PTT treatment.

- Fig. 27**_Condition free from inflammation and swelling after two weeks.

Case 8

- Fig. 28**_Insertion of the ICG colouring agent (EminDo, ARC).
- Fig. 29**_Laser application with bulb fibre.
- Fig. 30**_Healing of the acute episode after three weeks.



Fig. 30

ity have become a focal point of dental treatment. Here, photodynamic therapies are a new aspect in treating superficial mycotic infections. The target, which is the mycotic cell, as well as other microorganisms are eliminated, since the colouring agents are unspecific. In dermatology and mycotic therapy, activation via conventional or LED light systems have been favoured so far, since they are simple, reasonably priced and easy to apply on extensive surfaces. Malachite green, which is a triphenylmethan-based colouring agent activated at 810 nm, has been used against *Candida spp.*, whereas blue photosensitisers have been successfully applied in mycoses of mice in animal studies.³⁷ The colouring agent Green 2W, activated at 630 nm, has provided good results in an *in vitro* study on *Aspergillus fumigatus*.³⁸

Mucosa changes

The selective treatment of malign or semi-malign mucosa changes is often bound to special photosensitisers which are activated by differing wavelengths. Porphyrin and its derivatives are often used for PDT in cancer cells. 5-aminolaevulinic acid (5-ALA) is applied in fluorescence diagnostics in urology, gynaecology and dermatology as well as in the therapy of malign degenerations, such as urethral carcinomas in their initial stage. Methylene blue is applied as well, but its low insertion depth of less than 20 µm minimizes its effect.

Extended prophylaxis

PDT can prove an effective measure for an extensive prophylaxis to maintain healthy, but reduced gingiva which is unresponsive to further treatment after periodontitis.⁸ Generally speaking, low-level lasers are applied more and more by trained assistants, especially in the area of prophylaxis. If required, prophylaxis assistants can inform the patient on their own and perform the relevant tasks according to the therapy chosen by the dentist. In addition to an increase in treatment efficiency, delegating these tasks will result in a motivation boost for the assistant, who can now work more autonomously.

Photodynamic disinfection

Photodynamic disinfection auf prosthetics and impressions has been investigated in experiments. Vlahova et al.³⁹ have tested various Phthalocyanine photosensitisers, activated with an LED light at 635 nm, with regard to their performance in disinfection of MRSA, *Staph. aeruginosa* and *C. albicans*. The disinfection of silicones and composites by Ga-Phthalocyanine was 100% and 40% in Alginates. Therefore, Phthalocyanine can be seen as an alternative to other, specialised disinfection methods.

Veterinary Medicine

In addition to human medicine and dentistry, veterinary medicine is another field in which photodynamic

therapies have proved to be successful treatment methods. Toth et al.⁴⁰ have given convincing results for the gentle treatment of infected extensive surface wounds, for instance eosinophil ulcerated dermatitis in horses.

Photosensitisers in dentistry

In dental procedures, four photosensitisers are currently applied. These are indocyanine green and three kinds of phenothiazines: methylene blue, toluidine blue, methylene blue derivatives. Whereas the effect of these colouring agents on bacteria can vary, their charge—anionic or cationic—seems to play a vital role in their binding to bacteria (gram positive or negative), as do preparatory medications or trypsinisation.⁴¹

1. Methylene blue

Methylene blue (MB), 3,7-bis(Dimethylamino)-phenothiazin-5-ium chloride (Fig. 1), was synthesised by chemist Henrich Caro (BASF, Germany) in 1876. Already in 1885 did Paul Ehrlich realise its advantages with regard to selective colouring in histology. Methylene blue can be applied as a vital colouring agent in the vital staining of live tissues. In the past, it was seen as an important antidote in nitrite or aniline poisoning. Its application as an antiseptic, for example in malaria, enteritis and pyelitis cases, has become obsolete. Methylene blue today is used as an antirheumatic and as a means of diagnosis. It has been considered a treatment option for Alzheimer's disease for some time and several investigations were conducted. Its low toxicity makes it an unproblematic substance in medicine, which can be seen from its MAC (maximum workplace concentration) value of 1,180 mg/kg (rat, perorally). If larger quantities (0.5 ml and above) of methylene blue are swallowed, urine will assume a green colour.⁴² Its absorption of max 661 nm makes this cationic colouring agent an ideal sensitiser for red laser applications.

2. Toluidine blue O

Toluidine blue O (TBO), also known as tolonium chloride (Fig. 2), is a blue colouring agent (3-amino-7-[dimethylamino]-2-methylphenothiazine) which is used for histological and intravital dyeing or as an antidote in methemoglobin generator poisonings. In dentistry and maxillofacial medicine, it is used as a test to differentiate between benign and malign precancerous leukoplakia. However, the specificity of this test is too low.

Similarly to methylene blue, toluidine blue has a low antiseptic effect. Its low toxicity renders it an unproblematic medical substance: its LD50 in rats when administered intraperitoneally is 215 mg kg⁻¹. If larger quantities of toluidine blue O are swallowed, urine will assume a green colour. An absorption of max 635 nm makes this colouring agent ideal for red lasers of this wavelength.⁴³

3. Methylene blue derivatives

Methylene blue derivatives are applied with wavelengths of 810 nm. There are only a few case descriptions in the literature. Balboaca et al.⁴⁴ have proved a shift in the activation wavelength to 810 nm in methylene blue derivatives. However, no exact description of the molecule applied in the Photolase system (Photolase Europe, Ltd., Hamburg), based on 810 nm lasers, was found. There was an attempt to explain the process by "changes in the colouring agent molecules based on phenothiazine causing a 'long-waved flank' which results in optical activation and irradiation of 810 nm". Since the necessary light dose can be achieved faster, treatment time is said to be shortened considerably. In addition, an increase in the output of reactive oxygen radicals (ROS) is said to result from the undiluted solution.⁴⁵ Other derivatives, such as New Methylene blue (NMB, 556416-1G; Sigma) can reduce the activation wavelength similarly to toluidine blue O.³⁷

4. Indocyanine green

Indocyanine green (ICG, Fig. 3), 1,7-Bis(1,1-dimethyl-3-[4-sulfobutyl]-1H-benz[e]indol-2-yl)heptamethinium-betain-Na, well-known in liver function tests, ophthalmology and oncology⁴⁶, is new in dentistry but seems promising for periodontology.

Indocyanine green is an anionic photosensitiser which is activated at 810 nm and leads to photo-oxidation. Here, the intra- and extracellular ICG concentration is vital and must comprise a temporal component.⁴⁷ Its absorption depends on the dissolving medium, bonds to the plasma proteins and its concentration.⁴⁸ The overall effect of indocyanine green consists of 20 per cent photodynamics (PDT) as well as fluorescence and, mainly, of its photothermal effect (PTT).⁴⁹ The thresholds in tissue coagulation are employed to make use of photothermal effects free from side effects in therapies of the ciliary body, which is a highly sensitive tissue.⁵⁰ For this, the dose-effect graph must be taken into account precisely. ICG in the form of sodium salt is combined with sodium iodide of up to 5% to improve solutions for medical treatment.⁵¹ In dentistry, the material used is free from iodide (EmunDo, ARC) or contains normal quantities of iodide (PerioGreen, ellexion). There are no findings on how far material containing iodide can trigger allergies or anaphylactic reactions in dentistry. Most of the medical treatments consider an injection of ICG and its concentration in the target cells.

The photothermal effect of injected ICG has been applied in the therapy of telangiectatic leg veins in order to obliterate tissue changes subcutaneously in an elegant manner.⁵² Laser energies of 100 – 110 J/cm² are applied. Mathematical Modelling and comparison with the results of scientific experiments, ICG concentration and laser performance can be optimised with regard to the tissue. Thus, excessive heating of the tissue can be

prevented.⁵³ The lethal but selective effect of ICG on bacteria is a well-established fact. While *Staphylococcus aureus* and *Strep. pyogenes* are eliminated by the photodynamic effect, *P. aeruginosa* remains intact. The energy density applied was 411 J/cm². An effective concentration was reached already at 25 µg/ml.⁵⁴ ICG laser systems can advance acne treatments significantly in substituting or accompanying conventional therapies, since the agents applied did not show any serious side effects.⁵⁵

Szeimies et al.⁵⁶ observed excellent effects in the treatment of AIDS-associated Kaposi sarcomas on the outer skin, resulting in an almost complete remission of the sarcomas. Laser welding of wounds as described by Khosroshahi et al.⁵⁷ can be performed with a relatively low energy, avoiding in-depth tissues by topically applied ICG. The future will show if this technique can be involved in welding neural tissue. An effective impact of ICG on squamous cancer of the oral mucosa was proved by Lim & Oh.⁵⁸ The percentage of apoptotic cells increased to 84 % six hours after ICG-PDT with 20 µM ICG. The percentage of dead cells rose to 65 % in three hours of applying a solution of 200 µM ICG. Contrarily to other studies, they activated ICG via LED of a wavelength of 785 nm. This procedure can advance minimally invasive cancer therapy in the oral cavity significantly. Urbanska et al.⁵⁹ observed a high effectiveness of ICG in the pre-treatment of melanoma cells which was five to ten times higher than the effects of conventional laser treatment with diode lasers of a wavelength of 700 – 800 nm. Experts are currently working on the implementation of polyurethane composites in the production of intravenous catheters, since the antimicrobial activity against gram-positive bacteria results in a reduction of 2 log₁₀ units, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* after 15 minutes of exposure at an energy density of 31,83 J/cm². Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) showed only little reaction under the same conditions: they were reduced by 0.5 log₁₀-units.⁶⁰

ICG is not resorbed by the intestinal mucosa, which is why the danger of uncontrolled swallowing of the material is non-existent. The metabolism of indocyanine green occurs microsomal in the liver and is excreted only via liver and the pancreatic ducts.⁶¹ ICG is of a low toxicity. LD₅₀ values in animals were 60 mg/kg in mice and 87 mg/kg in rats.⁵¹ Restrictions of the visual field with regard to the visual sense after intraocular ICG application have further enhanced the discussion about the toxicity of the material. Engel et al.⁴⁹ proved in cellular experiments that the material which disintegrates during photo oxidation obtains a cell-inhibiting effect caused by its fission and decomposition products. ICG is suitable for liver function diagnostics because of its complete metabolism and excretion by the liver. In

addition, it can help differentiate between a normal, healthy liver, liver dysfunctions and drug- or medicine related liver anomalies because of its specific clearance rate.⁶² ICG which is administered intravenously has a half-life of three to four minutes, depending on the liver performance. During pregnancy, its administration is not risk-free. Only few allergic reactions on ICG containing iodine have been described in the literature.⁶³

Indocyanine green in dentistry

Only little published data is available on indocyanine green in dentistry, mostly *in vitro* studies, figures based on experience and case studies. Its application in periodontology has been postulated after successful *in vitro* tests with regard to periodontally pathogen germs by Boehm & Ciancio.⁶⁴ This however has not yet been proved by patient studies. More extensive studies are currently being conducted.

From the practitioner's point of view, the integration of PDT and ICG in aftercare and the long-term stabilisation of periodontitis/periimplantitis have proved of value.⁸ Combined with ICG photosensitisers, low laser performance has a good effect on various bacteria of the biofilm as well as the periodontal pockets. Therefore,

it can be used in support of conventional mechanical methods.

McNally et al.³⁵ evaluate the reduced hardware in colourant-based laser ablation of carious enamel and dentine as an advantage over Er:YAG lasers. In this regard, advantages postulated with respect to heat development, in-depth irradiation, pulpal damage, consumption of consumables and time must be discussed critically, even if the authors conclude that the dentine treated has no fissures and shows hardness similar to healthy material. With regard to the colouring agent, it can be argued that, in addition to various chemical properties, a differing quality and highly varying concentration of active substances are currently being offered. Figure 4 gives a split-mouth depiction of MB (Helbo) and TBO (Cumdente) photosensitisers. Some manufacturers do not declare the concentration of active substances in their colouring agents. The consistency of the solution has to match its application. Low consistencies are recommended for areas which are hard to moisten, such as root canals, while high viscosities are more appropriate for surface defects or areas of a long retention time such as the periodontal pockets. Each package is of a different user-friendliness and applicability. While blue dyes are provided in a dissolved form for direct application, the crystalline ICG has to be

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dissolved in a puncture vial first. The reason for this is its short shelf life of roughly four hours.⁴⁸

Since photosensitisers are designed for one application (ICG) or one patient and thus are of a short shelf life (blue colouring agents), the packing quantities are decisive. Packages of 0.5 to 1 ml are optimal, while quantities of more than 1 ml are too large and result in a high proportion of waste and high costs. In addition, prices differ significantly between the various providers and active ingredients.

Photoactivation

Light sources based on laser, LED or plasma lamps are appropriate for photoactivation. Conversely, the physical and therapeutical differences resulting from the variation in light sources are hardly known. Clinically, there are no differences in the results of identical procedures, wavelengths and powers of the light sources. There are no experiments with regard to the possible differences of the photobiological effects on healing and stimulation of the tissues in the various light sources (laser or LED). It seemed more important to find out about optical fibres and applicators appropriate to lead the light to its site of action effectively and without loss. For this, the material of the optical fibre as well as the quality of the optical coupling points play an important role, as they decide about power losses and, finally, the price. From a hygienic point of view, disposable applicators are preferable to permanent fibres.

In intrasulcular applications, the laser light reaches the colouring agent immediately and thus is applied directly to its site of action. A small percentage of the light is emitted to the depths where it can trigger photobiological effects. Mucosal thickness, blood circulation, mucosal pigmentation, absorption in the tissue, light parameters, remains of blood, secretions and colouring agents as well as absorption variations during treatment influence transgingival irradiation. It remains to be discussed whether the concentration of the sensitizer and exposure time are corresponding with the irradiation parameters and whether the graphs of the action time are extrapolated with regard to unfavourable anatomic cases. Light plays a vital role in the photobiological effect. Fotosan (LOSER & CO, Leverkusen, Germany) is a system which works exclusively transgingivally. Due to the many still unknown components, the current trend is directed towards intrasulcular light applications or combined intrasulcular transgingival applications.

Clinical cases

Therapies based on blue colouring agents are relatively simple. The sensitizer is applied to the periodontal pocket which must be free from bleeding after dis-

infection. It is then put to effect by diffusion for a consistent colouration of the aquatic space and is finally activated by laser. Most of these systems work with applicators which are injected in the periodontal pocket. Transgingival activation has become more and more prominent, in which case laser parameters must be in accordance with anatomical and physiological properties.

Case 1: Consecutive periodontitis therapy

In the following case, a 49-year-old female patient is treated by the PDT system HELBO (Bredent, Senden, Germany). During her regular dental cleaning, a new periodontal episode was noted after a successful laser periodontitis treatment four years earlier. The system used for this periodontal treatment included the TheraLite laser (660 nm, 100 mW), HELBO® 3-D pocket probe and the light absorbing colouring agents HELBO® Blue Photosensitizer (methylene blue). A time controller was used for an easy and controllable application of dye exposure and application times of the laser light on the treatment site. aPDT should succeed the professional dental cleansing after three to 14 days with respect to the degree of inflammation and latent bleeding tendency. A bleeding sulcus might have a reductive effect on the colouring agent penetration into the pockets and thus on the final treatment result. However, immediate treatment is still an option. Treatment starts with the application of the colouring agent solution (Fig. 5) circular around the teeth. The distribution of the intensely blue colouring agent can be well controlled. Exposure time is a minimum of three minutes, since this step is determined by diffusion and the molecules of the colouring agent penetrate into the biofilm, where they adsorb unspecifically and specifically to the bacteria via forces of attraction caused by electric charges. After the exposure, the colouring agent is sprayed off (Fig. 6) and the periodontal pockets are rinsed in order to avoid an unnecessary absorption loss of the laser light in the free colouring agents. All steps of the procedure which depend on time are paced by the time controller (Fig. 7). The tapered fibre applicator of the activated laser can be injected easily in the pockets and the activation energy (laser light) can be applied (Fig. 8). Depending on the individual tooth, four to six points of the pockets are irradiated. The treatment success was monitored after about three weeks, which showed a reduction in the depth of the periodontal pockets of a minimum of three millimetres (Fig. 9). In severe and therapy-resistant cases, treatment can be repeated on a weekly basis.

Case 2: Periimplantitis therapy in the acute phase

An acute periimplant inflammation can be a dramatic experience for the patient and a challenge for his dentist. Inflammation, bleeding, pain, pocket formation and loss of the periimplant attachment defined the clinical picture of the 56-year old female pa-



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tient (Fig. 10) who presented 10 years post-op with iliac crest bone which was applied via onlay procedure after resorption. Probing depth (Fig. 11) and radiological bone loss are decisive parameters of the diagnosis. In order to assess the severity of the damage and treatment options, the CIST system by Lang et al.⁶⁵ is an appropriate measure. The overall treatment procedure is conducted according to protocol: rinsing of the periodontal pockets, injection of the colouring agents (Fig. 12) and laser application according to the perimeters for single-rooted teeth for 20 seconds in all four sites (Fig. 13). Here, the applicator is placed on the base of the pockets. After laser treatment, the pockets are rinsed and then dried to instill the CHX gel (Fig. 14) and insert the prosthesis. This procedure is repeated weekly. Home care includes cleansing of the prosthesis and reciprocal instillation of CHX gel and Durimplant. After only a short amount of time, an inflammation-free result was reached (Fig. 15).

Case 3: Osteonecrosis treatment after bisphosphonate therapy

The dramatic event of multiple osteonecrosis of the maxilla occurred in a 86-year-old male patient after long-term bisphosphonate therapy. Bisphosphonates have been administered for more than 20 years in multiple myelomas (plasmacytoma), mammary carcinoma, kidney tumours, prostate carcinoma, osteoporosis and rheumatism. In this case, a multiple myeloma was diagnosed, but it was not confirmed later. The initial OPG of the patient (Fig. 16) showed a remaining dentition in the maxilla, teeth 17, 22, were situated in the devitalised bone and had to be removed. Markers of the devitalised bone are the lack in bleeding and hardly any resistance against extraction due to the destruction of the periodontium. A surgical revision of the maxilla was conducted INT with loss of the alveolar ridge and the maxillary sinus. After healing, the maxilla was fitted with a telescope obturator prosthesis (Fig. 17). Resulting from the following osteonecrosis episode, tooth 21 was lost and left an persisting ulcerating defect in regio 22/23 (Fig. 18). After deciding against another surgical therapy, a conservative long-term treatment via PDT was preferred over highly dosed antibiotics. Upon pus removal and rinsing, the entrance to an inflamed bone cavity with surrounding, highly reactive granulation became visible (Fig. 19). Blue Sensitiser (HELBO) was applied (Fig. 20) and left to take effect over a relatively long amount of time of roughly ten minutes. The remains of the colouring agent were rinsed (Fig. 21) and laser application (TeraLite laser, Fig. 22) followed. After several PDT applications during the following two weeks and the reduction of inflammatory complications, exposed bone became visible. This was removed as a bone sequestrum from an almost completely epithelialized bone cavity (Fig. 23). The defect was again lased via PDT (Fig. 24) and then healed autonomously

(Fig. 25). Even three years later, an irritation-free alveolar ridge without any signs of a relapse was diagnosed (Fig. 26).

Case 4: Transgingival periodontitis treatment

A 68-year-old female patient presented with dentures in urgent need for restoration. Periodontal treatment was conducted in the form of PDT with TBO in the transgingival activation mode via the FotoSan system. The special feature of this device is the light source with a 15-Watts LED. Photosensitiser was inserted in the dental pockets after disinfection (Fig. 27) and left to take effect. The surplus of photosensitiser was removed before laser application. Since only a shortened row of teeth existed, including the second premolars, the photosensitiser was applied in one step at all teeth. The laminar applicator of the device is placed directly on the mucosa. The light is applied segmentally and tooth-by-tooth for activation. Figures 28 and 29 show the high transillumination of the tissue, which is why there is sufficient activation energy for the photosensitiser within the pockets. After irradiation, the remains of the sensitiser are sprayed off and CHX gel is placed in the pockets.

Case 5: Photodynamic Post treatment after periodontal surgery

In the days following a surgical periodontal procedure, oral hygiene is limited. Pain, swelling, tendency towards bleeding and the danger of damage to the soft tissue structures are significant restraints to mechanical cleansing. Some regenerative and augmentative procedures, such as the application of enamel matrix proteins (Emdogain, Straumann) requires only chemical cleaning via a disinfecting rinsing in the first few days after surgery. An efficient bactericidal method without any mechanical intervention is the application of PDT on the surfaces of mucosa, teeth and interdentially. Already in the year 2000 did Frentzen et al.⁶⁶ point out the possibility of a "laser tooth brush". This principle was applied successfully in the following case of a female patient with progressed aggressive periodontitis after surgical periodontal treatment via Emdogain. At the first follow-up two days after surgery, the postoperative condition corresponded with the healing process and a photodynamic cleaning of the teeth was conducted. Figure 30 depicts the activation of the blue colouring agent with a laser by R+J (Berlin, Germany) and a therapeutic approach which allows light application on the surface.

Case 6: Treatment of chronic periodontitis

A 46-year-old patient presented with chronic periodontitis caused by insufficient care. Bone loss and crater-like irruptions became visible in the OPG. After cleaning the tooth necks (SRP), a combined PDT and PTT treatment was conducted in a separate session. Superficial anaesthesia with Oraqix is sufficient for light cases of periodontitis. After rinsing the pockets with physio-

logical saline, an ICG solution (EmuDo, ARC) is applied and the first laser application is performed transgingivally with bare fibre (400 mW, 810 nm, Q 810, Henry Schein, Germany) for ten seconds per periodontal unit from vestibular to palatal/lingual. Alternatively to bare fibres, the therapy, transgingival or bleaching hand piece can be used. The second step consists of laser application at and in the dental pockets with bulb fibres and, depending on the condition of the mucosa, with 200 up to 300 mW. Depending on size and undercut, eight to twelve seconds of irradiation are estimated time frames. Constant movement is necessary since the photothermal effect is significant already in low powers and excessive burns must be avoided. The inflamed inner epithelium of the periodontal pocket can only be removed efficiently with a power of 300 mW. The same procedure is conducted via a palatal approach. Because of the therapeutic character of the minimally invasive approach, the same principles that are applied to operative laser-surgical procedures are adopted to PDT/PTT with extended hygienic demands. For example, protective glasses have to be worn in any applications of type-4 lasers of a wavelength of 810 nm. When the PDT/PTT treatment is finished, the sulcus is rinsed and the treatment result will show that a minimally invasive procedure was performed. After treating all five quadrants, and after the periodontium has finished healing, only slight discolourations by the CHX rinsing solution were visible after four weeks. The development of the clinical parameters and the pocket depths indicate good final results.

Case 7: Acute gingivitis/periodontitis treatment

Other than PDT with blue colouring agents, which can be applied without any tissue damage, ICG-based methods allow the selective removal of the inner epithelia of the periodontal pocket from the sulcus at 300 mW and via bulb fibre. This is usually the standard in photothermal therapy (PTT).

The 64-year-old female patient presented with an acute inflamed periodontitis episode and a massive mycotic infection by *Candida albicans* (CFU ++++) in the oral cavity and on the lips five years after restoration of the dentures. The mycosis was treated with a combination of Amphotericin B and Miconazol. The periodontal treatment was conducted after surface anaesthesia with Oraqix by successive mechanical cleansing followed by PDT/PTT. Laser application was conducted with the Q810 laser (Henry Schein) with universal fibre and disposable bare and bulb fibre attachments. After rinsing and application of the EmunDo photosensitizer, transgingival laser application with the bare fibre at 400 mW was performed. Afterwards, the periodontal pockets were lasered with bulb fibre at 300 mW according to protocol. A light de-epithelialisation of the marginal periodontium at 400 mW and rinsing ensued. Since only anterior dentures have remained, this case is

treated jaw-by-jaw and not quadrant-by-quadrant. After rising, the ICG solution is inserted in the periodontal pockets of the mandible. In addition, transgingival and intrasulcular laser application and de-epithelialisation are conducted. Finally, CHX gel is applied to the pockets and the cone prosthesis as a reservoir. Only shortly after PTT, the patient appears free from inflammation and swelling. The periodontal pockets depths showed convincing results and there are no periodontal inflammations when the prosthesis is worn. Bleeding cannot be provoked.

Case 8: Therapy of advanced periimplantitis

A 79-year-old patient presented with advanced periimplantitis. In agreement with the patient, conservative, non-invasive maintenance measures are taken, preferably without any antibiotics. Home care involves mechanical tooth cleaning, rinsing for disinfection, instillation of CHX gel in the periimplant sulcus and Durimplant application. Advanced bone loss became visible on the X-ray and was proved by the measured pocket depths. There was neither block nor infiltration anaesthesia, but an intrasulcular surface anaesthesia via Oraqix. After careful cleansing, the ICG photosensitizer (EmunDo, ARC) is inserted and activated transgingivally via bare fibre at 400 mW and 810 nm (Q810, Henry Schein) as well as bulb fibre at 300 mW. A single treatment already resulted in immediate remission of the inflammation. A stable condition was achieved after healing. However, this success should not blind us to the fact that this is only a symptomatic treatment which hardly contributes to the formation of new bone and must be evaluated clinically as a dormant state of periimplantitis.

_Economic aspects of PDT application

From an economic point of view, PDT methods are more costly than laser treatments exclusively with type-4 lasers, due to the fact the colouring agents (photosensitizers) and sometimes disposable applicators have to be used. Therefore, possible applications have to be examined with regard to more efficient methods which can be used instead of photodynamic caries hardening, which has to be repeated on consecutive treatment days. Periodontal treatment of singular teeth which is based solely on laser or selective caries removal via Er:YAG laser is one possible alternative.

_Conclusion

The integration of PDT has proved itself in the treatment and post-treatment with long-term stabilisation of periodontitis/periimplantitis.⁸ Low laser power combined with photosensitizers on various bacteria of the biofilm and in the periodontal pocket showed good results and can therefore be used in addition to conventional mechanical cleansing. Thus, PDT can already

be found in a compilation of evidence-based laser-supported treatment methods.⁶⁷

All light-activated procedures have been viewed as comparable to PDT treatment and were said to differ only in their colouring agents, their intrinsic effect and the wavelength used for activation. This assessment, however, cannot be supported when the real modes of action are taken in consideration. Because of the good adhesiveness of the colouring agents, depending on exposure time, photodynamic therapies with blue colouring agents encompass a photodynamic effect as well as solely disinfecting properties of the dyes along with an efficacy which exceeds the treatment. There is however no intrinsic disinfecting effect in photodynamic therapies based on indocyanine green. The therapeutical effect is limited to the treatment time, which is the amount of time in which the colouring agent is activated by laser. This effect consists of photodynamics (PDT) with a percentage of 20 %, fluorescence and, mainly, photothermal effects (PTT).⁴⁹ These components of the therapeutical effect explain the limited destruction of the pocket epithelium and minimised bleeding. Another sensible application of the wavelength of 810 nm was added when ICG was introduced. In both of the two applications, a strict protocol which includes the abidance to the exposure and activation times of the colouring agents as well as rinsing and drying procedures and the level of laser energy applied is vital. While an extension of the activation time does not result in tissue damages in PDT based on methylene or toluidine blue, the specified treatment time must not exceed in ICG. Moreover, the intrinsic effect of the photosensitiser seems to be a philosophical problem, since the treatment success does not depend on the question if the effect of the photosensitiser occurs when activated or without activation. Both PDT and combined PDT/PTT are gentle, yet efficient therapy methods for acute and chronic periodontal and periimplant defects. A separation between PDT und treatments with extensive bleeding are recommended, since the colouring agent could be rinsed or diluted in an invalid level by the bleeding. In addition, binding to plasma proteins or blood cells can also minimize the effect of the photosensitisers. PDT and PDT/PTT have increased the range of treatment modalities for bisphosphonate-reduced necrosis of the jaw and a multitude of infections. Economic aspects have to be taken into account in PDT or PDT/PTT application in single teeth, endodontics, caries hardening, and disinfection of the surgical site, among others. Because of the high efficiency of PTT when ICG is applied, a singular therapy per cycle will be sufficient, whereas phenothiazine-based colouring agents will necessitate the repetition of the treatment within short intervals. Both of the two procedures cannot necessarily substitute antibiotics, but they can contribute significantly to reduced antibiotic applications. The bacterial load in the periodontal pockets can be reduced consid-

erably, which is an advantage with regard to sluicing bacteria in immediately following periodontal surgeries. ICG is more efficient because of its proved in-depth effects which include PTT effects on microorganisms in bordering tissues. PTT is followed by healing of the defect in case of laser light applications beyond a threshold level causing tissue damages. This healing usually processes fast and does not cause retractions since the defect is limited in size.

PDT and combined PDT/PTT cannot be compared with or replace each other. Although both of the two procedures can be applied equally, the wishes of patient and dentist as well as therapy goals determine their usage. PDT alone cannot be applied in non-invasive delegation procedures, the treatment of tissue defects or pain-free conservational therapies. A maximum power of 0.2 Watts must not be exceeded in ICG-based therapies. Further investigations with regard to these treatment areas are necessary. If the treatment can be of an invasive character or more extensive, combined PDT/PTT treatment must be preferred. In most cases, this will be performed by the dentist. Combined PDT/PTT indocyanine-green based treatment constitutes a new instrument for the dentist, which offers laser treatment at low laser energy levels of 200 up to 400 mW as well as a low photodynamic component for the sterilisation of periodontal pockets via oxygen radicals and a photobiological component to support the healing process. Therefore, PTT can result in an improved performance in modified mechanisms of action in periodontal treatment when compared to blue-based PDT procedures.

Editorial note: A complete list of references is available from the publisher.

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