18 Multi-photonic Adjunctive Therapy for the Management of Periodontitis: Recent Advances and New Treatment Approach

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Abstract

The efficacy of photonic therapy adjunctive to conventional root cleansing procedures for the treatment of chronic periodontitis is matter of controversy. The meta-analyses of the clinical data available in the literature have failed to reach univocal conclusions because of broad variability among the applied photonic treatments, different in terms of light-emitting devices (laser or LED), wavelengths, irradiation power and modes, clinical indications, disease grading, follow-up times, and results assessment. Hovever, this complexity can also favour a different interpretation, which assigns a specific role to each photonic treatments in order to improve the outcome of the conventional treatments, in terms of reduction of periodontopathogenic bacteria and local inflammation, and increased regeneration of alveolar bone, periodontal ligament and gingiva. In this context, distinction should be made between high- and low-energy photonic therapies: the former can be used to achieve photoablation of the infected dental/periodontal tissues, while the latter can be used for anti-bacterial, anti-inflammatory and tissue biostimulation purposes. Recently, we and others have applied a multi-photonic protocol which combines laser photoablation of the infected epithelium, standard mechanical root cleansing and low-energy antiseptic phototherapy with a λ 405 nm LED in a first surgical session. Then, antisepsis is maintained by weekly sessions of photodynamic therapy with a solution of methylene blue photoactivated with a λ 635 nm low-energy laser to release bactericidal reactive oxygen species. The satisfactory objective results and patients' liking support the view that such multi-photonic treatments are a correct approach to supportive periodontal therapy.

Keywords

Photonic therapy · Laser · Periodontitis

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Abbreviations

BODIPY	boron dipyrromethene
iPAPD	improved PAPD
LED	light-emitting diode
LLLT	low-level laser therapy
PAPD	photo-ablative-photo-dynamic

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PBMT	photobiomodulation (or biostimulation) therapy
PDT	photodynamic therapy
PT	phototherapy
ROS	reactive oxygen species
SRP	scaling and planing of dental roots

Highlights

- In patients with chronic periodontitis, besides conventional root cleansing, various photonic treatments have been used, although their actual advantages are controversial.
- High-energy (laser) and low-energy (laser and LED) photonic tretaments have different indications: the former can be used to achieve photoablation of the infected periodontal tissues, the latter can be used for anti-bacterial, anti-inflammatory and biostimulation purposes.
- A new treatment protocol combining laser photoablation, ultrasonic scaling and root planing and bactericidal LED phototherapy followed by repeated applications of antiseptic photodynamic therapy has been shown to yield better results than conventional periodontal therapy.

Considerations for Practice

- In periodontal disease, there is a demand for adjunctive therapies capable of improving the outcome of the conventional dental root cleansing treatments in terms of reduction of persistent infection, local inflammation and periodontal tissue resorption and, possibly, preservation or even regeneration of alveolar bone, periodontal ligament and gingiva.
- Diverse high-energy (laser) and low-energy (laser and LED) photonic treatments at different wavelenghts can address such demand because of their anti-bacterial and tissue biostimulating properties, provided they are correctly performed.
- To better exploit their effects, high- and low-energy photonic treatments can be combined together: such adjunctive protocols to conventional periodontal therapy have provided satisfactory clinical results.

Patient Summary

Periodontitis is a chronic infectious disease of the tooth-supporting tissues which can cause teeth loss and overall health worsening. The standard treatment consists in mechanical removal of bacteria attached to the affected teeth but, due to bacterial regrowth, relapses are frequent. Antibiotics and antiseptics are not a solution because periodontal bacteria have become resistant. An alternative approach is to associate the conventional dental cleansing treatments with light-based – or photonic – supportive therapies, performed with laser and LED instruments. Light has many diverse effects depending on its wavelength, energy, tissue absorption, etc. Hence, satisfactory periodontal healing can be achieved by a combination of different photonic treatments exploiting the synergism of their curative effects.

18.1 Photonic Therapy in Periodontics: A Yet Unsolved Controversy

In developed Countries, chronic periodontitis is still regarded as a major health challenge for oral medicine: this disease not only represents the main cause of tooth loss but has also been associated with potentially severe systemic complications caused by enduring persistence of bacterial infection (Hajishengallis 2015). This is the reason why basic and clinical research are particularly intense in this field, aimed at improving the current therapeutic protocols. Recently, numerous meta-analyses and reviews have been dedicated to the most important advancements in periodontology, including the so-called photonic therapies. This term encompasses all those procedures exploiting the well-known biological effects of light in the visible and infra-red wavelength range, delivered by means of laser or light-emitting diode (LED) instruments, for curative purposes. With few exceptions, photonic therapies are performed in adjunct to the conventional treatments based on scaling and planing of the dental roots (SRP), which remain the essential therapeutic approach to periodontitis (Giannelli et al. 2019). Nowadays, photonic therapies are routinely applied for many medical purposes, in some instances as first-choice treatments, but this is not true for periodontics. In fact, most retrospective analyses of the results of the previous clinical studies have failed to provide convincing statistical data to demonstrate that adjunctive photonic therapy can result in better clinical outcomes than those achieved by conventional SRP (Schwarz et al. 2008; Mizutani et al. 2016; Cobb 2017; Mills et al. 2018). However, if considering the lack of well-defined and widely accepted therapeutic indications and protocols on the one hand and the many possible variables of photonic therapies on the other hand, this inconclusive result is not surprising. In fact, the efficacy of photonic therapy in periodontitis is influenced by many physical, biological, anatomical, and technical variables which render the results of previous primary clinical studies barely comparable by any meta-analysis. Photonic therapies have two main levels of variability: (i) a general level depending on differences in the irradiation characteristics, i.e. light wavelengths, illumination devices (laser or LED), light beam power (high-power or photoablative or low-power or non-surgical) irradiation modes (continuous or pulsed), and actual energy delivered to the target tissue; (ii) a specific level depending on clinical differences, i.e. periodontal disease grading, exact biological rationale and indications, light absorption characteristics of the targeted mucosa (inflammation, pigmentation), treatment protocols, follow-up times, and outcome assessment methods. This broad variability can easily explain the reason why the literature on the clinical effects of photonic therapies in periodontology is so controversial and difficult, if not impossible, to be interpreted (Cobb 2017). An unfortunate consequence of this confusion is that many dental practitioners are hesitant to include photonic treatments in their therapeutic repertoire against periodontal disease, either because they underestimate its actual potential or because they are worried by its complexity and lack of clear indications (Giannelli et al. 2019).

This article is not meant to compete with the numerous, excellent reviews written by renowned periodontologists (Schwarz et al. 2008; de Paula Eduardo et al. 2010; Javed and Romanos 2013; Aoki et al. 2015; Mizutani et al. 2016; Cobb 2017; Mills et al. 2018), which remain the main source for whoever wishes to delve into this complex matter. Rather, our intention is to focus on some new findings and concepts emerged from the most recent clinical studies on photonic therapy in periodontics, which can be helpful to identify its actual strenghts and limitations, as well as to design new effective treatment protocols.

18.2 How Photonic Therapies Can Work in Periodontal Disease

The purpose of any adjunctive therapy in periodontal disease is to improve the outcome of conventional SRP in terms of: (i) reduction of oral dysbiosis to a favourable ratio between normal bacterial flora and periodontopathogens, (ii) reduction of local inflammation, (iii) regeneration of alveolar bone, periodontal ligament and gingiva. For such goals, the photonic approaches can be definitely adequate.

As a necessary premise, we must make a distinction between high- and low-energy phototherapies. High-energy irradiation requires laser instruments and is used to remove the infected dental/periodontal tissues: it is therefore defined as photoablative or photosurgical therapy. Its advantages over the conventional surgical methods are high selectivity (namely, laser wavelenght can be chosen to be specifically absorbed by molecules and chromophores in the target tissues), excellent bactericidal and hemostatic effects, minimal post-treatment inflammation and fast healing (Aoki et al. 2004; Schwarz et al. 2008; Ishikawa et al. 2009; Giannelli et al. 2019). On the other hand, due to high energy transfer to tissues, their damage threshold is close to the therapeutic range. Hence, a proper usage of laser photoablation requires specific training of dentists, who must be well aware of the pros and cons of the different laser instruments operating at different wavelengths: for instance, the lasers emitting in the far or intermediate infra-red spectrum, such as CO_2 (λ = 10,600 nm) and Erbium-doped garnet lasers, (Er:YAG, λ = 2940 nm; Er:YSGG, λ = 2780 nm), are chiefly absorbed by H_2O and apatite crystals of mineralized tissues and operate chiefly through vaporization, whereas those emitting in the near infra-red spectrum, such as Neodymium-doped garnet lasers (Nd:YAG, λ = 1064 nm) or the modern, versatile (and cheaper) diode lasers (λ = 655–980 nm) are absorbed by tissue pigments, such as melanin and hemoglobin, as well as bacterial cromophores, and operate chiefly through coagulation/carbonization (Aoki et al. 2004; Schwarz et al. 2008; Ishikawa et al. 2009; Giannelli et al. 2019). These different wavelengths also influence other parameters related to the target tissues, namely depth of penetration and adverse thermal effects due to light scattering, which render each laser type best suited for different, specific applications in the field of periodontology. For instance, CO_2 lasers, albeit capable to yield satisfactory long-term clinical results in expert hands (Crespi et al. 2011), nowadays are barely used in periodontics because of ease of target tissue over-heating and damage (Giannelli et al. 2012a). In general, Er-doped garnet lasers are preferred for removal/reshaping of mineralized tissues and calculus (Schwarz et al. 2003), whereas Nd-YAG and diode lasers are most suited for soft tissue and dental plaque photoablation and disinfection (Romanos 1994; Moritz et al. 1998; Gregg and McCarthy 2002; Schwarz et al. 2008; Kamma et al. 2009; Giannelli et al. 2012a; Mizutani et al. 2016).

Low-energy photonic therapy can be performed by both laser (in this instance, terms such as low-level laser therapy or LLLT, or soft laser therapy are currently used) and LED instruments. At variance with the high-energy laser treatments, all of which substantially cause tissue photoablation, in this case the mechanisms of action, methods of administration and biological effects can vary. Accordingly, low-energy photonic therapies can be subdivided in 3 distinct modalities: (i) photodynamic therapy (PDT); (ii) phototherapy (PT); (iii) photobiomodulation (or biostimulation) therapy (PBMT) (Giannelli et al. 2019).

(i) Photodynamic therapy (PDT) exploits the property of some organic compounds termed 'photosensitizers', e.g., cyclic tetrapyrroles, fullerenes, boron dipyrromethene (BODIPY) and phenotiazines (toluidine blue O, methylene blue) to release reactive oxygen species (ROS) when excited by light at wavelengths coinciding with their absorption peaks (Yin and Hamblin 2015). ROS are lethal for bacteria because they induce oxidative damage of plasma membranes and DNA. The short half-life (0.04 μs) and diffusion radius (~0.2 μm) of the generated ROS render PDT particularly effective for disinfection of periodontal tissues, since photosensitizers can bind to and concentrate in bacterial biofilms and dental plaque (Takasaki et al. 2009; Meimandi et al. 2017). A limitation of PDT is that its actual efficacy depends on the absorption spectra of the used photosensitizers, requiring strictly consistent excitation wavelengths (Giannelli and Bani 2018).

(ii) Phototherapy exploits the direct antimicrobial effects of specific light wavelengths due to the presence of photoactivable chromophores, e.g., porphyrins, in certain bacterial species, including several periodontal pathogens. Particularly effective is the light in the violet-blue spectrum (λ 405–520 nm), especially that in the narrow band of 405–

410 nm, which has shown excellent bactericidal effects against both Gram-positive and Gram-negative pathogens (Fukui et al. 2008; Barneck et al. 2016; Gillespie et al. 2017). The mechanisms of these effects, although not fully elucidated yet, are consistent with the endogenous generation of ROS in sensitive bacteria (Soukos et al. 2005). Interestingly, blue light (λ 405 nm) at bactericidal power has no effect on mammalian cells, which are protected from oxidative stress by multiple antioxidant metabolic pathways (Ramakrishnan et al. 2016). Moreover, blue light also induces the inactivation of lipopolysaccharide (LPS), a Gram-negative endotoxin responsible for the persistence of inflammation (Giannelli et al. 2017). These favourable characteristics account for substantial efficacy and safety of blue light for oral disinfection and restraint of septic inflammation and related periodontal tissue destruction. They also sustain the principle that phototherapy can be safely repeated in periodontitis patients until satisfactory clinical effects are achieved.

(iii) Photobiomodulation therapy (PBMT) exploits light wavelengths in the red-IR range (λ 600–950 nm), characterized by deep tissue penetration and capability to induce biostimulatory effects. These are likely due to photochemical interaction with Fe^{2+}-heme chromoproteins, such as mitochondrial cytochromes, resulting in metabolic activation of cells (Hamblin 2018). The major effects of this activation consist in stimulation of cell proliferation, microvascular dilation and increased blood perfusion which, in turn, result in accelerated wound healing and bone formation as well as decreased inflammation, oedema and pain (Qadri et al. 2005; Aoki et al. 2015; de Paula Eduardo et al. 2010). Accordingly, PBMT has been used as adjuvant to the main periodontal therapies to reduce inflammation and pain in the immediate post-operative phase and to improve periodontal ligament and alveolar bone healing in the long term (de Paula Eduardo et al. 2010).

18.3 Multi-photonic Therapy in Periodontal Disease: 'United We Stand, Divided We Fall'

On the above grounds, it is becoming increasingly clear that each photonic therapy has specific indications and limitations, which must be known in order to correctly design effective treatment protocols adjunctive to conventional SRP. Knowledge of these essential points can also be helpful to re-analyze the results of the previous clinical studies in future meta-analyses to evaluate whether photonic therapies can provide significant advantages in the treatment of periodontitis, in order to exclude the misleading results of the studies biased by erroneous photonic treatments (Giannelli et al. 2019).

Another point clearly emerging from a better knowledge of the strenghts of the various photonic treatments is that they can be effectively and safely combined into a multi-photonic therapy to exploit their individual advantages or even the synergism between their different biological effects. In fact, periodontal disease shows a complex network of pathogenic events which can be specifically targeted (Kornman 2008). Its main clinical hallmark is progressive periodontal tissue destruction secondary to persistent infection and inflammation sustained by periodontopathogenic bacteria particularly adapted to this local microenvironment. These bacteria are capable of penetrating and persisting into the epithelial cells lining the periodontal pockets and outer gingiva, thereby escaping host immunity as well as conventional antiseptics and antibiotics (Tribble and Lamont 2010). There, they represent a hidden germ reservoire predisposing the patients to re-infection soon after SRP, and hence to disease relapses and chronicization (Mombelli et al. 2000; Johnson et al. 2008; Ardila et al. 2010). In recent years, we and others have collected convincing evidence that a multi-photonic therapy adjunctive to SRP can provide better clinical results than SRP alone, both in the short and long term. In a first pilot trial on 26 patients with chronic periodontitis, we first combined a photoablative treatment with PDT in a multi-photonic protocol termed PAPD (PhotoAblative-PhotoDynamic). This protocol consisted of 3 steps: (i) photoablation of the surface bacterial biofilm and infected sulcular and gingival epithelium with a λ 810 nm high-energy diode laser; (ii) SRP performed by ultrasonic scaler; (iii) repeated sessions of PDT with methylene blue photoactivated by a λ 635 nm low-energy diode laser, in order to hinder bacterial re-growth. The results of this study, performed as a split-mouth, have shown a statistically significant improvement of the main parameters used for periodontal disease assessment, namely probing depth, clinical attachment level and bleeding-on-probing, as well as of cytodiagnostic markers of infection and inflammation in periodontal exfoliative samples, in the PAPD-treated mouth quadrants as compared with the matching quadrants treated with SRP alone (Giannelli et al. 2012b). Of note, these improvements were maintained over 4-year follow-up of the same patients (n = 24), suggesting that the desired objective of our PAPD protocol, i.e. shifting the host-parasite balance in favour of the former in order to promote periodontal healing in the long term, had been achieved (Giannelli et al. 2015). More recently, to treat patients with severe periodontitis (n = 24), we have adopted an improved PAPD protocol (iPAPD) in which a single 5-min. application of antiseptic phototherapy with a λ 405 nm LED was performed after epithelial laser photoablation and SRP in the same clinical session (Table 18.1). Then, weekly PDT sessions were performed until normalization of the cytodiagnostic infection and inflammation markers, according to the original PAPD protocol. This iPAPD protocol has also yielded statistically significant improvements of the clinical and cytodiagnostic disease markers at 1-year follow-up (Table 18.2). In this study we also assessed the subjective satisfaction of the enrolled patients towards the received treatments: again, a significant majority of them preferred the iPAPD protocol over SRP alone because of reduced pain and discomfort, both during and after the operative phase and in the following days, and better aesthetic results due to restoration of the natural pale color of the vestibular gingiva (Giannelli et al. 2018). Representative images of the key iPAPD steps are shown in Figs. 18.1, 18.2, 18.3, 18.4, and 18.5.

18.4 Conclusion and Perspectives

The multi-photonic supportive treatment to periodontal disease has been only recently developed based on new evidence on the actual efficacy, indications and possible synergisms of the various photonic therapies and is currently applied by few researchers worldwide (Giannelli et al. 2012b, 2018; de Angelis et al. 2018; Amaroli et al. 2020). For this reason, the overall number of patients studied is relatively small and insufficient to perform a reliable meta-analysis and draw definitive conclusions about the actual value of such methods to cure periodontal disease. What hinders a more widespread use of the multi-photonic therapies among dentists is that they require multiple light sources emitting at different wavelengths, whereas most of the dental lasers available on the market emit a single light wavelength, the only variable parameters being beam power and irradiation mode (pulsed or continuous). However, all low-energy phototherapies can be effectively performed by LED instruments, whose irradiation characteristics are similar to low-power lasers with the obvious advantage of being far cheaper and simpler. Ideally, dental practitioners wishing to perform modern photonic treatments could equip their surgeries with a photoablative diode laser and at least 2 LED instruments operating at λ 635 nm for PDT and λ 405 nm for antiseptic phototherapy.

We are of the opinion that a more detailed knowledge of the advantages and limitations of the photonic approach in periodontics will reduce

Table 18.1 Applied parameters for iPAPD multi-photonic therapy

	Near-IR GaAlAs diode laser	Violet-blue LED	Red diode laser
Irradiation modes and purposes			
	Photoablation mode	Phototherapy mode	Photodynamic mode
	Removal of infected sulcular and gingival epithelium	Antisepsis (phototoxic)	Antisepsis (oxidative)
Devices settings			
wavelength	810 ± 10 nm	405±5 nm	635±5nm Toluidine blue (1 μg/ml)
Wave emission mode	Continuous	Continuous	Continuous
Beam power	1 W	1 W	0.1 W
Light irradiation details			
Handpiece type	Polymide–coated silica fiber 0.6 mm	Focalized zoom handpiece	Light pipe glass 10 mm
Application mode	Contact	Non-contact	Non-contact
Distance from the target	0 mm	10 mm	30 mm
Light spot size	0.28 mm^2	95 mm^2	28.3 mm^2
Power density	353.4 W/cm^2	1.05 W/cm^2	0.35 W/cm^2
Fluence	66.7 J/cm^2	63 J/cm^2	21 J/cm^2
Tip movement speed	2.5 mm/s	Fixed beam	Fixed beam
Clinical protocol details			
Number of treatment	1	1	4–10 adjusted depending on healing markers[a]
Cooling system	Airflow	No	No

[a]Residual microbial contamination and inflammation performed on cytosmears of periodontal pocket exfoliative samples, as described (Giannelli et al. 2012b)

Table 18.2 Clinical periodontal parameters: conventional SRP vs. iPAPD+SRP

	Day 0	1 year	Statistical significance, 1 year vs. day 0
Probing depth (mm)			
SRP	4.9 ± 0.1	3.8 ± 0.3	
iPAPD+SRP	5.1 ± 0.2	1.2 ± 0.2	$p < 0.001$
Statistical significance	n.s.	$p < 0.001$	$p < 0.001$
Clinical attachment level (mm)			
SRP	5.3 ± 0.1	5.2 ± 0.1	
iPAPD+SRP	5.4 ± 0.1	3.1 ± 0.3	n.s.
Statistical significance	n.s.	$p < 0.001$	$p < 0.001$
Bleeding on probing (%)			
SRP	42 ± 4.6	23.2 ± 2.1	$p < 0.01$
iPAPD+SRP	36.7 ± 5.3	1.2 ± 0.6	$p < 0.001$
Statistical significance	n.s.	$p < 0.001$	
Periodontal index (%)			
SRP	26.5 ± 3.7	8.2 ± 1.5	$p < 0.001$
iPAPD+SRP	25.5 ± 3.6	7.4 ± 1.5	$p < 0.001$
Statistical significance	n.s.	n.s.	

For statistical comparison, the patients' quadrants were assumed as test units. The reported values are means ±SEM of 2 sampled sites per quadrant. Values were checked for normal distribution and then compared by within-subject, repeated-measures ANOVA and Newman-Keuls multiple comparison test. n.s. not significant (adapted from Giannelli et al. 2018)

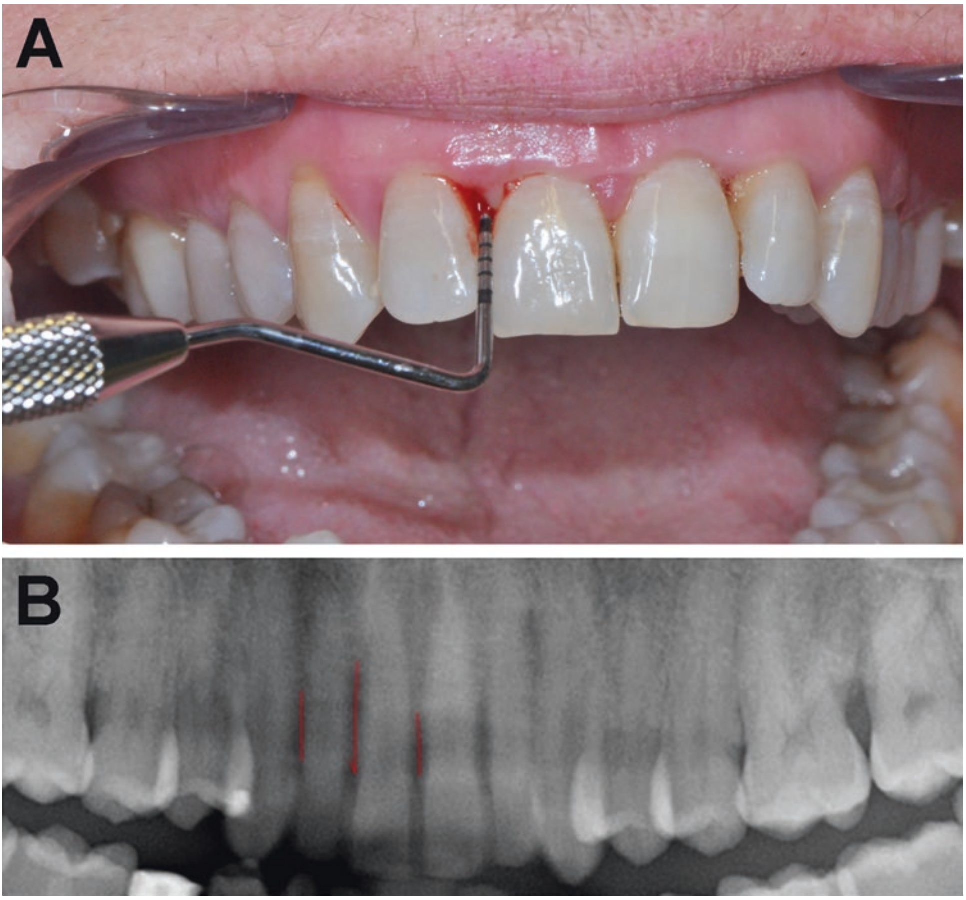

Fig. 18.1 Representative pictures of pre-treatment probing depth (**a**) and radiography (**b**) performed at patient's admission. In (**b**), the red lines indicate the extent of recession of the inter-alveolar bone ridges

Fig. 18.2 iPAPD, phase 1. The gingival mucosa underwent photoablation with a λ 810 nm high-energy diode laser in contact mode (i.e. with the optic fiber tip touching the gingiva) under airflow cooling to remove the junctional, sulcular, and outer gingival epithelium, ~5 mm from the gingival margin, all around the teeth. Fiber diameter: 0.6 mm; irradiaton mode: continuous emission; beam power: 1 W; optic fiber movement speed: 2.5 mm/s; power density: 353.4 W/cm^2; fluence: 66.7 J/cm^2. Under these operating conditions, pain and discomfort are minimal and anaesthesia is usually unnecessary

Fig. 18.3 iPAPD, phase 2. Conventional SRP was performed using Gracey curettes (Hu-Friedy, Milan, Italy) and ultrasonic scaler (Mectron Dental, Loreto, Italy) with metal tip and set to 80% power at high frequency (36 kHz) under water cooling (28 ml\min) until the root surfaces were clean and smooth. Of note, preliminary photoablation of the inflamed, swollen epithelium of the periodontal pockets facilitates SRP, because it yields an accessible gap between the dental root and its periodontum, with excellent hemostasis

Fig. 18.4 iPAPD, phase 3. Phototherapy was then performed with a λ 405 nm LED for additional disinfection in the same surgical session. Handpiece: glass lightpipe; beam diameter: 10 mm; beam power: 1 W; non-contact mode ~10 mm from the target; spot area: 95 mm^2; power density: 1.05 W/cm^2; fluence: 63 J/cm^2. An additional property of λ 405 nm irradiation is that it induces a pale green autofluorescence of the coagulated keratins, allowing to visually check the photoablated epithelium

confusion and uncertainty on this matter and, consequently, promote confidence and use of such techniques among periodontologists. If this would occur, the demand for new user-friendly and effective photonic instruments specifically suited for odontostomatological use should also increase. In this context, while high-energy laser photoablation will remain a field for specifically trained, expert professionals, low-energy photonic treatments, which often need to be repeated until the desired therapeutic goals are achieved, could be administered at the patients' home under medical supervision by means of portable LED instruments, thereby maximizing their curative efficacy.

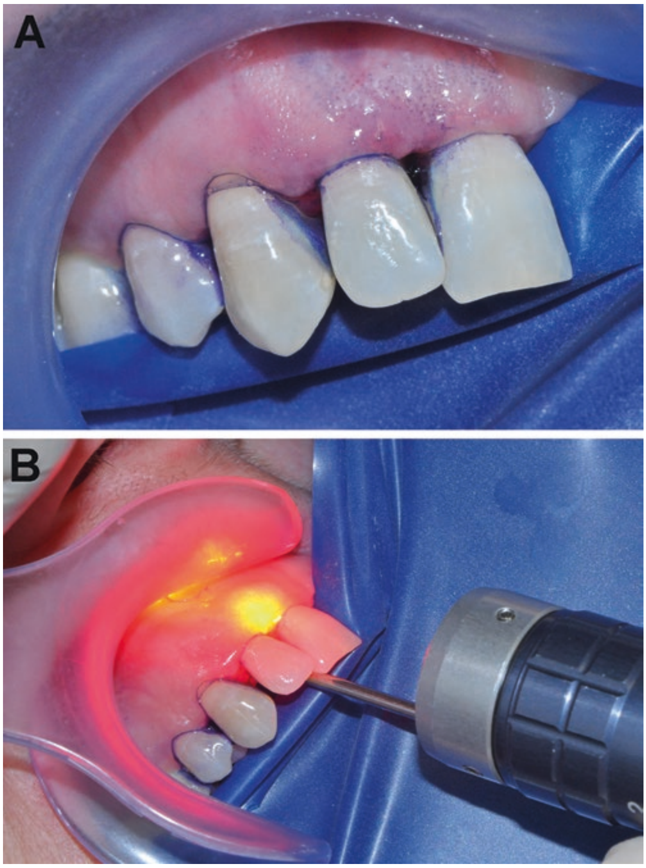

Fig. 18.5 iPAPD, phase 4. (**a**) Rinsing with the photosesitizer: 7 days after the previous treatments, the periodontal tissues, including the pocket, the surrounding mucosa and the dental root, were rinsed with the phenotiazinic dye toludine blue O (0.1% w/v in water) using a flexible needle. (**b**) PDT: 5 min. later, photoactivation of the photosensitizer was performed by irradiation with a λ 635 nm low-energy diode laser through a perpendicular zoom handpiece, slowly moving the focused light spot on the buccal and vestibular mucosa for 5 min. Handpiece: focused zoom; beam power: 100 mW; non-contact mode ~3 cm from the target; spot area: 28.3 mm^2; power density: 0.35 W/cm^2; fluence: 21 J/cm^2. PDT was repeated once weekly for up to 10 applications, until negativization of bacteria and inflammatory cells in gingival cytosmears occurred

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