Next generation Er:YAG fractional ablative laser

A. Heinrich*, A. Vizhanyo, P. Krammer, S. Summer, S. Gross, T. Bragagna, C. Böhler
Pantec Biosolutions AG, Industriering 21, LI-9491 Ruggell/Liechtenstein

ABSTRACT

Pantec Biosolutions AG presents a portable fractional ablative laser system based on a miniaturized diode pumped Er:YAG laser. The system can operate at repetition rates up to 500 Hz and has an incorporated beam deflection unit. It is smaller, lighter and cost efficient compared to systems based on lamp pumped Er:YAG lasers and incorporates a skin layer detection to guarantee precise control of the microporation process. The pulse parameters enable a variety of applications in dermatology and in general medicine, as demonstrated by first results on transdermal drug delivery of FSH (follicle stimulating hormone).

Keywords: laser diode, diode pumped Er:YAG, fractional, dermatology

1. INTRODUCTION

For decades lasers have successfully been employed to reduce chronological and sun-induced skin aging. Full ablative skin resurfacing techniques using CO\textsubscript{2} or Er:YAG lasers, for example, results in strong improvements\textsuperscript{1,2}. However the procedure and recovery period are both quite painful, the healing process takes weeks, and the risk of infection lurks constantly\textsuperscript{3,4}. For many patients these side effects are unacceptable and therefore the development of less ablative or non-ablative laser skin rejuvenation therapies is rapidly increasing. Although the cosmetic outcome is not nearly as remarkable, treatment is much easier to tolerate, the risk of infection is low or non-existent, and downtime is drastically reduced in both length and severity. Fractional skin resurfacing emerged as a new concept for tissue remodeling and instead of a homogeneous treatment these lasers produce microscopic treatment zones or micropores that are surrounded by untreated tissue. Thus a rapid wound healing can be achieved and this concept combines a treatment with low side effects with a considerable impulse for wound healing due to deep coagulation. Fractional skin resurfacing has been investigated initially with the Er:Glass laser and in particular with the Fraxel laser (Reliant Technologies, Palo Alto, CA). The wavelength of 1540 nm has significant absorption in water leading to columns of coagulation up to several hundred microns depth. As reports show, epidermal and dermal necrotic tissue is eliminated through the epidermis and wounds are repaired by perilesional immigrating keratinocytes. For the Fraxel laser 3-6 sessions according to the indication are necessary to achieve a satisfactory result, although there are no systematic investigations about the correlation of treatment numbers and intervals\textsuperscript{5,6}. The concept of fractional skin treatment was further developed to ablative lasers such as the Er:YAG laser\textsuperscript{7-9} and the CO\textsubscript{2} laser\textsuperscript{10-12}. These lasers generate micropores surrounded by untreated and intact tissue. Since there is only few necrotic tissue that has to be removed before wound repair, the healing is fast and not comparable with full ablative skin resurfacing. Most of the commercial ablative fractional laser systems are CO\textsubscript{2} lasers, because the thermal impact in the skin is higher and therefore the activation of the collagen is stronger than with the Er:YAG with its cold ablation. Even though the rejuvenation of the skin treated with CO\textsubscript{2} is better the procedure is painful and anesthesia is commonly used in contrast to Er:YAG where no pain medication is needed. An ideal fractional ablative laser system should open the skin by cold ablation like the Er:YAG, have the thermal impact of the CO\textsubscript{2} in the dermis to activate the collagen and generate minimal pain. We believe that with our diode pumped Er:YAG laser system with its high repetition rate of several hundred Hz, the development of an ideal fractional laser system is within reach. It combines the painless generation of the micropores with a high thermal impact, which can be easily adjusted by varying the pulse parameters and increase the heat stacking of the laser pulses.

*arne.heinrich@pantec-biosolutions.com; phone +423 3777803; fax +423 3777899; www.pantec-biosolutions.com
The P.L.E.A.S.E.® Professional is a portable bench top fractional ablative laser system emitting at 2.94 µm (Er:YAG). The wavelength is on the main water absorption peak in the infrared and allows accurate and painless removal of skin layers. The new miniaturized diode pumped laser is a small, lightweight and cost efficient system that allows a fourfold reduction in volume and weight compared with standard lamp pumped lasers based systems (Fig. 1). The main applications are in conventional and aesthetic dermatology with or without a topical drug. The system allows precise skin microporation with depth control, fundamental requisite in transdermal drug delivery. The microporation process benefits from the high repetition rate of up to 500 Hz, which allows single micropore drilling and the incorporated beam deflection unit makes the system flexible in micropore density and generates a homogenous distribution. Furthermore, by changing of the laser parameters, respectively, heat stacking, the thermal impact in the skin layers can be increased to improve the rejuvenation effect.

The P.L.E.A.S.E. Professional has been used to deliver large molecular weight biopharmaceuticals through the skin barrier. With FSH (follicle stimulating hormone) a protein of 32 kDa size entered stably and reproducibly across the skin from a patch in the blood circulation and has shown excellent bioavailability, safety and tolerability in phase I clinical trials. For controlled drug release into the systemic circulation the laser system has to create defined micropores in the stratum corneum and therefore it incorporates a skin layer detection, which guarantees that the micropores reach the desired layers.

Figure 1. The P.L.E.A.S.E. Professional fractional ablative Er:YAG laser and in the inset the homogeneous distribution of micropores generated on thermal paper. The grid results from a disposable, which keeps the skin in the focus over the whole treatment area.

The paper is structured as follows, chapter two points out the characteristics for fractional ablation, in chapter three the transdermal drug delivery is described and finally in chapter four conclusions are drawn.

2. FRACTIONAL ABLATIVE LASER TREATMENT

The P.L.E.A.S.E. Professional incorporates a diode pumped Er:YAG laser with 1 W average power at repetition rates ranging from 100 up to 500 Hz and pulse energies up to 10 mJ. The generated laser pulses have pulse durations varying
between 30 and 250 µs and can be easily focused to less than 300 µm spots, enabling cold ablation with high energy pulses and high thermal impact with low energy pulses.

Traditional fractional Er:YAG systems generate micropores in a matrix of e.g. 13 x 13 by splitting the laser beam with a multi lens array into 169 laser beams, which leads to a fixed density of micropores of about 5% on skin. In order to increase the density to about 15%, the procedure has to be repeated three times and the applicator manually rotated resulting in inhomogeneous distribution of micropores. Furthermore the energy and the focus size of each of the beams are not identical, which further increase the inhomogeneity and results in non-optimal rejuvenation. The diode pumped Er:YAG in the P.L.E.A.S.E. Professional works different, since the high repetition rate of up to 500 Hz allows sequential drilling of each micropore. For this purpose scanner is incorporated to steer the laser beam over the skin. The density of micropores can be software set and homogeneous micropore distributions with densities up to 16% can be generated. Furthermore since the laser drills each micropore sequentially the focus and energy per micropore is identical resulting in a homogeneous distribution.

Figure 2. (left) Micropores generated with 100 ppp (in vivo), a slight coagulation, but no blood is visible. (right) Biopsy of porcine skin with 30 ppp (in vitro) and approximately 500 microns depth.

The sequential drilling of the micropores has also a drastic effect on the thermal impact on the tissue, because the full average power of about 1 W is concentrated for a short time onto a single micropore and heats up the tissue. In comparison classical Er:YAG laser systems, which distribute their energy in 169 beams have an average power per micropore of about 0.04W, which is 25 times less and therefore the thermal impact is smaller on the same scale. The effect of the high average power, respectively, heating per micropore is visible in figure 2, where 100 pulses per micropore (ppp) with 250 µm focus size have been applied. The edges of the micropore show coagulation, but no blood is visible in contrast to classical Er:YAG systems, because the blood vessels are immediately sealed. Also a biopsy of a micropore in porcine skin with about 500 microns depth is shown, which were generated with 30 pulses of 1.2 mJ energy and 40 µs duration. With the diode pumped Er:YAG the thermal impact can be precisely controlled and the heat can be generated where it is needed. For example a few high energy pulses can open the skin, drill into the target skin layer and a series of low energy pulses can heat the tissue with minor ablation. This feature is easily done by modulation of the laser diode current on a scale of 30 to 250 µs in contrast to lamp pump systems which cannot be modulated on these time scales.

3. TRANSDERMAL DRUG DELIVERY

The P.L.E.A.S.E. Professional’s main purpose is transdermal drug delivery. For this application the micropores should be generated with small thermal damage and ideally reach into the epidermis. The diode pumped Er:YAG laser with its low energy pulses allows precise skin removal and in figure 3 two biopsies with 1 and 5 ppp are shown. With 1 pulse just the stratum corneum is removed while 5 pulses drill deep into the epidermis but leaves the dermis intact.
For transdermal drug delivery the opening of the stratum corneum, the main diffusion barrier for large molecular weight drugs is essential and therefore must be guaranteed. The dermis comprises blood vessels and nerve ends, in order to prevent pain or bleeding the micropore should not enter too deep. It is crucial to notice that the stratum corneum thickness varies significantly among individuals. Furthermore the moisture of the stratum corneum or other tissue layers when exposed to air varies as function of seasonal environmental humidity changes. Therefore a reliable and preferably inexpensive measurement technique is needed, to detect in real time when the complete removal of the stratum corneum is achieved.

The human skin comprises layers of different water content, the stratum corneum having a water content of about 15 – 20%, the epidermis and dermis having water contents of about 60 – 80%. The back scattered light of the Er:YAG laser with a wavelength directly on a main absorption peak of water contains information about the water content of the ablated biological tissue, respectively, skin layer of the micropore generated in. As long as the stratum corneum is ablated by the laser beam, the sensor received back scattered light of relative high intensity, due to the low water content of the stratum corneum. As soon as the laser beam hits the epidermis, the intensity of the back scattered light decreases because the epidermis absorbs the laser beam stronger due to the high water content. The measurement of the back scattered light allows detecting the transition from the stratum corneum to the epidermis. With this measurement it is possible to reproducible generate micropores with minimal thermal damage suited for transdermal drug delivery (Fig. 4).

Figure 3. (left) Biopsy of porcine skin with 1 ppp and clearly visible removal of the stratum corneum and (right) with 5 ppp the micropore reaches into the epidermis.

Figure 4. (left) A micropore in the epidermis (in vivo) with no signs of coagulation and (right) the micropore after two days with clearly visible shrinkage of the skin.
FSH is a protein hormone found in humans and other animals and regulates the development, growth, pubertal maturation, reproductive processes of the body. FSH also stimulates the growth and recruitment of immature ovarian follicles in the ovary. During an in vitro fertilization (IVF) protocol FSH is self-administered by the patients for 10 - 12 days by subcutaneous or intramuscular injection stimulating follicle growth. The painless transdermal delivery would avoid daily injections improving ease of use and convenience.

The purpose of the study is to investigate the primary pharmacokinetic characteristics as well as the safety and tolerability of the newly developed FSH protein patch in healthy male volunteers. Due to its size and physicochemical properties FSH, a 32 KDa protein hormone, cannot passively permeate across intact skin. Therefore, prior to patch application, the skin was microporated. This pre-treatment facilitate FSH transport through the skin and accelerate its entry into the systemic circulation. The phase I clinical trial has given excellent results and for the first time a molecule as large as this protein has been successfully transdermally delivered. The serum profiles have demonstrated that the P.L.E.A.S.E. – FSH patch combination is able to achieve reproducible pharmacokinetics with negligible inter-individual variability. In figure 5 the blood level over a full day is shown and proves the constant FSH release of the patch, which is a strong benefit over injections.

4. CONCLUSION

The P.L.E.A.S.E. Professional is a portable bench top fractional ablative laser system emitting at 2.94 µm (Er:YAG) with the wavelength coinciding the main water absorption peak in the infrared. The new diode pumping scheme and consequently the new pulse parameters position the laser system between the classical Er:YAG and the CO₂ with the increased thermal impact compared to classical Er:YAG and reduced pain and carbonization compared to CO₂. The main applications are in conventional and aesthetic dermatology with or without a topical drug. The microporation process benefits of the high repetition rate of up to 500 Hz which allows single micropore drilling while the incorporated beam deflection unit makes the system flexible in micropore density. Furthermore, by during the process changing of the laser parameters it is possible to bring heat into the target skin layers to increase the rejuvenation effect. Also transdermal drug delivery has been demonstrated with FSH a large molecular weight biopharmaceuticals. With FSH a protein of 32 kDa size entered stably and reproducibly from a patch across the skin in the blood circulation.
REFERENCES