Laser-assisted Drug Delivery: A novel use of lasers in dermatology

Dr Firas Al-Niaimi examines how lasers can penetrate the stratum corneum to aid treatment of aesthetic concerns

Abstract

Topical medicaments are the mainstay of the dermatologists' therapeutic arsenal. The stratum corneum in the upper layer of the epidermis is rather impermeable to water-soluble and large molecules. Traversing this layer is key to optimal drug delivery. Studies thus far suggest that laser pre-treatment improves transepidermal absorption of topical agents and allows for a much deeper penetration of drugs than is possible with topical medicaments alone. Laser-assisted drug delivery enhances the ability of topically applied medicaments to penetrate the skin, which may allow for more efficacious action of current treatments; such that conventional duration of treatment can be shortened or lower concentrations of active agents be used, potentially obviating side effects of treatment. In order to discuss how we eventually got to this stage, it is important to look at the animal model studies that have supported the concept of laser-assisted drug delivery. There has been a tremendous interest in the application of this modality across a range of dermatologic and aesthetic procedures. This article will, however, only focus on the aesthetic component; although this modality has been used in dermatologic conditions such as actinic keratosis, Bowen's Disease, basal cell carcinoma, vaccination, local anaesthesia, haemangioma, and burn scars. For further information on these applications the reader is advised to look up the recent published studies in this field.

Introduction

Topical therapies play an important role in dermatology, whether used for inflammatory dermatoses, (pre)malignant skin disease or aesthetic indications. For optimal therapeutic effect, delivery of the drug to the relevant compartment within the skin is required. In recent years, ablative laser devices have been employed to aid delivery of biological molecules throughout the various cutaneous compartments.[1-3] Whilst other physical mechanisms to enhance transdermal drug delivery have been investigated, including tape stripping, iontophoresis, radiofrequency, ultrasound and microneedling,[1] the focus of this article is to review the rationale underlying laser-assisted delivery of drugs and explore the future considerations of this modality. Non-laser methods of delivery will not be discussed here owing to the breadth of the subject.

Mechanisms of laser-assisted drug delivery

The stratum corneum is the outermost layer of the skin and is largely impregnable to compounds with molecular weights greater than 500 Daltons (Da).[4] Once the stratum corneum is traversed, the passage of molecules to the cutaneous compartments is comparatively unimpeded.[5] Laser technologies deploy a particular wavelength of light to selectively destroy the chromophore of interest. Ablative lasers in common use include the carbon dioxide (CO_2; wavelength peak 10,600 nm) and erbium-doped yttrium aluminium garnet (Er:YAG; wavelength peak 2940 nm) devices, both of which have wavelengths targeting water.[6] The water molecules are found both intra- and extra-cellularly. Laser devices have traditionally been used in continuous mode, in which the entirety of the water-containing epidermis being treated is ablated.[6] More recently, ablative fractional laser technologies (AFXL) have been developed. AFXL exploits fractional photothermolysis, in which multiple vertical columns of tissue are thermally destroyed to create unimpeded channels communicating with the outermost layer of the stratum corneum.[1-3] Each channel is surrounded by a cuff of dense thermally-coagulated tissue, collectively referred to as microscopic treatment zones (MTZs).[7] Only a fraction of the skin surface is treated, in which MTZs facilitate penetration of topical molecules from the surface to the layer of interest, whilst leaving most of the skin surface area untreated and intact.[7] The untreated skin serves as a reservoir of stem cells, growth factors and inflammatory cells that are able to rapidly migrate to the traumatised skin and facilitate faster healing with less scarring.[8] The depth of these ablated channels can be determined by the fluence used.

Increased penetration of drugs or molecules via MTZs can be understood using Fick's first law in physics, which in its simplest form states that the degree of flux of molecule (J) across a barrier is a product of the partition coefficient (Km, a reflection of the number of molecules available for diffusion across a membrane), the diffusion constant (Dm, a reflection of the inherent diffusibility of a molecule across the membrane) and concentration difference of that molecule on either side of that barrier (ΔC), divided by the path length (L):[9]

$$J = \frac{Km \times Dm \times \Delta C}{L}$$

Fick's first law in physics

Increased permeability of the stratum corneum via MTZs increases Km, therefore increasing the overall flux of the molecule. As the molecular size of the drug increases, there is greater frictional resistance to movement of the molecule and Dm decreases, hence decreasing overall flux.[9]

Pre-clinical studies: animal models

Work on animal models has informed the clinical use of AFXL. Photodynamic therapy (PDT) comprises the photodynamic reaction between a photosensitiser, light of a select wavelength (or band) and oxygen to generate reactive oxygen species that target microbes and malignant cells. PDT is most commonly used in dermatological practice to combat non-melanoma skin cancer (NMSC) and acne vulgaris.[10]

Haedersdal undertook CO_2-AFXL prior to treatment with MAL-PDT on porcine skin creating single MTZs, each 300 micron in diameter and 1850 micron in depth, surrounded by a 70 micron cuff of thermally coagulated tissue.[11] In skin treated with AFXL and MAL-PDT (AFXL-PDT), increased porphyrin fluorescence was observed in a uniform fashion up to 1.5 mm from the ablated channels. This suggested that for MAL, MTZs placed at 3 mm intervals, equating to less than 1% surface area, could be used to treat the entirety of the lesion. This finding is substantiated by an additional study that used an Er:YAG laser to create multiple MTZs, and suggested that there is no increase in lidocaine absorption if the number of pores is increased beyond a certain density.[12] Moreover, there was no increased absorption of lidocaine if progressively higher fluences were used to extend the MTZs beyond the stratum corneum into the epidermis or dermis.[12]

5-fluorouracil (5-FU) is a chemotherapeutic agent commonly used in dermatology for treatment of NMSCs, including actinic keratoses (AKs), Bowen's disease and superficial basal cell carcinomas (BCCs).[13] Imiquimod (5%) is a commercially available immunomodulatory agent that is similarly used to treat various NMSCs.[14] Work in murine skin has suggested that 5-FU penetration was enhanced 36-133 fold following pre-treatment with Ruby, CO_2 or Er:YAG lasers.[15] Similar work has demonstrated enhanced transdermal delivery of imiquimod in porcine and murine models following a low-fluence fractional Er:YAG laser,[16] with enhanced imiquimod delivery up to 65 fold after one pass and 127 fold after four passes. The authors further demonstrated that reduction in dose of imiquimod to 0.4% delivered equivalent concentrations of imiquimod as topically applied 5% imiquimod (commercially available), which may allow for the future use of lower concentrations of drugs leading to similar clinical efficacy.[16]

Together, these findings in porcine skin suggest that there is a critical density of MTZs, beyond which additional MTZs confer no benefit with respect to penetration of the drug. Photosensitisers can penetrate superficial and deep levels of skin and conventional settings for the LED illumination can be employed. Pre-treatment with AFXL permits greater penetrance of drug, in particular larger and more hydrophilic molecules, which may act in a shorter timeframe.[2,3] Furthermore, AFXL pre-treatment may improve efficacy of topically-applied medicaments and permit lower concentrations of active agents to be used with reduced frequency or duration of application.

Local anaesthetics

Many dermatological procedures are performed under local anaesthesia. Topical agents have a long latency before effect takes place and anaesthesia may be incomplete owing to poor penetration of the skin, whilst injections are associated with pain. Pre-treatment with the conventional Er:YAG laser prior to application of topical 4% lidocaine has been shown to reduce sensation to needle prick within five minutes compared to laser plus placebo (62% reduction) or lidocaine alone (61% reduction).[17] Similarly, a blinded randomised controlled trial (RCT) of 61 patients (adults and children) attending the emergency department who required cannulation showed that pain upon cannulation was significantly lower when pre-treated with the Er:YAG laser prior to application of 4% lidocaine.[18] There appears to be no diminution in the degree of analgesia at lower energy laser settings (2.0J/cm2), compared to the high energy (3.5J/cm2) settings used in the aforementioned studies, as inferred from an intra-individual study of 30 patients comparing both settings, with one used on each antecubital fossa.[19]

These proof of principle studies are supported by clinical applications. In a randomised, split-face clinical study of 12 patients, Yun and colleagues looked at the effect of pre-treating one side of the face with low fluence Er:YAG prior to application of 5% topical lidocaine and whole face resurfacing in two passes.[20] Subjective pain scores on the side of the face that had been pre-treated with ablative laser were significantly lower than the side not pre-treated with ablative laser. However, only 56% patients were able to tolerate the second pass of the resurfacing, forcing us to question its value in future work.

> Larger trials with greater numbers within treatment and control arms are required for each of the proposed therapies to corroborate efficacies and side effects of therapy

Vitiligo

Vitiligo is an auto-immune condition in which depigmented patches occur on the skin. In a study involving 25 patients with stable, symmetrical vitiligo, recalcitrant to other therapies, a half-body comparative analysis, in which patches of vitiligo on one half of the body underwent CO_2-AFXL, followed by topical application of betametasone solution under occlusion followed by a course of narrowband-ultraviolet B (NB-UVB) phototherapy (treatment), whilst patches on the other side (control) received CO_2-AFXL and NB-UVB alone was performed.[21] Treatments with CO_2-AFXL were given at half monthly intervals, whilst NB-UVB was given two to three times weekly over six months. 44% of patients achieved more than 50% repigmentation on the treatment arm, which was significantly better than the control arm, owing to greater penetration of the topical corticosteroid. Whilst the results are of interest, the protracted course of treatment and associated expense may preclude this treatment in other healthcare systems, however the study provides further support of the application of this concept.

Hypertrophic and keloid scars

Improvement in the appearance of scars is often observed following AFXL treatment and is likely attributable to removal of a section of the fibrotic scar and a relative normalisation of collagen structure and composition.[22]

Waibel investigated 15 patients with hypertrophic scars resulting from trauma, injury or burns. Each patient received up to five treatments with CO_2-AFXL (10-15% density using the UltraPulse Lumenis machine) followed by topical triamcinolone application (10mg/ml or 20mg/ml).[23] Blinded observers noted improvements in texture, degree of hypertrophy and dyschromia at six months following the final treatment session. The authors suggest that AFXL as a method of drug delivery may have benefit over triamcinolone injections owing to uniformity of depth and distribution of triamcinolone, as well as avoiding the pain associated with intralesional injections.

Another group reported the treatment of a total of 70 keloid scars in 23 patients with 2940nm AFXL (180J/cm^2, 5% coverage) every other week with concomitant betametasone cream twice daily under occlusion until either complete flattening of the scar was achieved or no further improvement was seen.[24] After a median of nine laser treatments, there was a median 50% improvement in scar appearance, gauged through photographic evaluation by two independent observers. Eight months after treatment, keloid recurrence was 22%; all recurrences were noted within two months of cessation of laser treatment.

Atrophic scars

Poly-L-lactic acid (PLLA; Sculptra) is commonly used as a subcutaneous filler for facial volume restoration, which is purported to stimulate fibroblast proliferation and collagen formation. 19 patients with atrophic scars from various causes, including acne, trauma and surgery, were treated with CO_2-AFXL followed by topical application of PLLA.[25] The treatments appeared to be tolerated with post-procedural mild pain, while erythema and swelling were the most commonly cited concerns. Each patient required an average of one single treatment. Four blinded observers reported improvements in scar contour, atrophy and colour three months after treatment.[26]

Despite the above being a non-controlled study, PLLA is a large molecule and will not be able to penetrate the impermeable stratum corneum.[27] The improvement observed suggests the enhanced penetration achieved through pre-treatment with AFXL. It is also possible that the AFXL effects on upregulating collagen synthesis may have had a synergistic effect with PLLA.

Botulinum toxin

Botulinum neurotoxin type A (BoNTA) is a neurotoxin secreted by *Clostridium botulinum*, an anaerobic, Gram-positive bacterium and is widely used to reduce the appearance of wrinkles and rejuvenate the skin. Recent work suggests that topical application of BoNTA (in its current form) may not penetrate the stratum corneum to elicit clinically discernible endpoints compared with injected toxin.[28] A split face study was conducted on 10 subjects involving CO_2-AFXL of the face with application of topical BoNTA on one side and normal saline on the other side as a control.[28] Compared with the control side, topical application of BoNTA resulted in significant reduction in the number of periorbital wrinkles at one week and one month following treatment. These results suggest that BoNTA delivery can be enhanced pre-treatment with AFXL. Comparison with injectable BoNTA and newer topical formulations of botulinum neurotoxin remain to be performed and will likely guide development of this novel method of delivery in the near future.[29]

Non-ablative fractional laser

More recently, work has been undertaken using non-ablative fractional lasers (NFXL), in which a controlled zone of thermal injury is generated, rather than a fully ablated MTZ. Pre-treatment with the non-ablative 1550-nm erbium glass laser has been shown to enhance delivery of Amino-levulinic acid in human subjects, as gauged by cutaneous porphyrin fluorescence.[30] Advantages of non-ablative devices are increased patient tolerability and reduced post-procedural downtime.[31] Although there has been some use of this technology in combination with topical therapy (bimatoprost for hypopigmented scars for example),[32] use of such technology is yet to be used in larger clinical studies. In addition, it is unclear if the effect of pre-treatment with NFXL enhanced the penetration of the molecule, as the latter can penetrate easily through the stratum corneum.

Platelet rich plasma

Platelet-rich plasma (PRP) has gained a lot of popularity in recent years and has been used in dermatologic practice in cases of scarring, alopecia, wound healing, and rejuvenation.[33] PRP has been used post AFXL in a number of studies although primarily as an adjunctive to enhance synergistic effect of the AFXL and to reduce post AFXL erythema.[34] None of the published studies primarily looked at AFXL to enhance the delivery of PRP but it is plausible that the combination of both modalities has synergistic effects.[35] In clinical practice some practitioners routinely use the application of PRP post AFXL; primarily to speed up recovery and reduce post-procedural erythema.

Future considerations

Larger trials with greater numbers within treatment and control arms are required for each of the proposed therapies to

Pre-treatment with the conventional Er:YAG laser prior to application of topical 4% lidocaine has been shown to reduce sensation to needle prick within five minutes

Key points

1. The stratum corneum is the outermost layer of the epidermis and is impermeable to large and hydrophilic molecules
2. Ablative fractional lasers create channels of ablated tissue with islands of normal skin in between to hasten recovery
3. Laser-assisted drug delivery through the use of fractional ablative lasers has gathered increasing interest in recent years
4. Currently, most of the evidence with this modality is with the combination of photodynamic therapy and fractional lasers
5. Alternative methods of drug delivery include the use of ultrasound, radiofrequency, electroporation and iontophoresis

corroborate efficacies and side effects of therapy. Future cohorts will need to account for differing body sites, and efficacy of treatments in varying ages, genders and ethnicities. Optimal laser parameters, including fluence, density and scheduling of treatments, need to be determined to facilitate maximal drug penetration, whilst allowing rapid recuperation of the skin.

As well as selecting which drug within a category (such as corticosteroids) is likely to yield the best result, the optimal vehicle for topically applied medicaments, whether gels, patches, creams or ointments, together with duration and frequency of application and the necessity for occlusion is yet to be determined. Additional consideration needs to be afforded to potential toxicity from medicaments, as already has been demonstrated with lidocaine toxicity occurring following AFXL resurfacing.[28] Furthermore, these drugs or molecules were designed for topical application and their current concentrations may prove too high or toxic for direct dermal introduction.

Rigorous health economic analysis comparing the efficacies and cost-effectiveness of these new modalities of treatment compared to tested, longer-established treatments may ultimately determine the take-up of these new technologies, at least in clinical practice.

Conclusion

Work on animal models and preliminary initial studies have supported the use of AFXL technology as a future adjunct to topical therapies. Studies thus far suggest that AFXL improves transepidermal absorption of topical agents and allows for a much deeper penetration of drugs than is possible with topical medicaments alone. This may allow more efficacious action of current treatments, such that conventional duration of treatment can be shortened or lower concentrations of active agents be used, potentially obviating side-effects of treatment. The prospect of using AFXL to facilitate transdermal vaccination and as an adjunct for inflammatory dermatoses and cosmetic indications remain in its infancy. As larger trials are published, involving greater numbers of patients and utilising various laser and topical medicament parameters, we will enhance our understanding of this nascent modality of treatment delivery and better serve the patients.

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