Laser Assisted Drug Delivery: A Review of An Evolving Technology

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Background: Topically applied drugs have a relatively low cutaneous bioavailability.

Objective: This article reviews the existing applications of laser assisted drug delivery, a means by which the permeation of topically applied agents can be enhanced into the skin.

Results: The existing literature suggests that lasers are a safe and effective means of enhancing the delivery of topically applied agents through the skin. The types of lasers most commonly studied in regards to drug delivery are the carbon dioxide (CO_2) and erbium:yttrium-aluminum-garnet (Er:YAG) lasers. Both conventional ablative and fractional ablative modalities have been utilized and are summarized herein.

Limitations: The majority of the existing studies on laser assisted drug delivery have been performed on animal models and additional human studies are needed.

Conclusions: Laser assisted drug delivery is an evolving technology with potentially broad clinical applications. Multiple studies demonstrate that laser pretreatment of the skin can increase the permeability and depth of penetration of topically applied drug molecules for both local cutaneous and systemic applications. Lasers Surg. Med. 46:249–262, 2014. © 2014 Wiley Periodicals, Inc.

Key words: microthermal zone; fractionated; fractional photothermolysis

INTRODUCTION

Topical drug delivery is essential to dermatological therapy. However, the cutaneous bioavailability of most topically applied drugs is relatively low with only 1–5% being absorbed into the skin [1]. In addition, some drugs that are absorbed do not penetrate deeply enough to reach the desired target in the tissue [2,3]. For a topical agent to be active, it must first traverse the rate-limiting outermost barrier of the skin: the stratum corneum. Many medications are too large to penetrate this barrier and require either an injectable or systemic delivery. Laser assisted drug delivery is an evolving modality which may allow for a greater depth of penetration by existing topical medications, more efficient transcutaneous delivery of large drug molecules, and even systemic drug administration via a transcutaneous route. Herein we review the existing applications of laser assisted drug delivery.

BACKGROUND INFORMATION

The outermost layer of the skin, the stratum corneum, is the most significant barrier to percutaneous drug absorption [1]. Several modalities have been developed to enhance the absorption of topically applied medications. Laser therapy is a unique ablative modality that has the ability to destroy the stratum corneum, epidermal, and dermal layers of the skin in a predictable and controlled manner, resulting in the potential for increased penetration of topically applied molecules.

The erbium:yttrim-aluminum-garnet (Er:YAG) laser and the carbon dioxide (CO_2) laser are the two types of laser devices most commonly studied in regards to laser assisted drug delivery. The Er:YAG laser has a wavelength of 2,940 nm and is strongly absorbed by water in the epidermis [4]. It exerts its ablation effect with minimal penetration depth and minimal heat generation and therefore minimal thermal damage [5–7]. The CO_2 laser

Abbreviations: Er:YAG, erbium:yttrium-aluminum-garnet; CO_2, carbon dioxide; PDT, photodynamic therapy; AK, actinic keratosis; BCC, basal cell carcinoma; ALA, 5-aminolevulinic acid; MAL, methylaminolevulinate; 5FU, 5-fluorouracil; MTZ, microthermal zone

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Conflict of Interest Disclosures: Dr. Ozog now has a provisional patent on laser delivery of botulinum toxin A.

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ablation, this thermal effect may also result in increased stratum corneum permeability [5].

Traditionally, the conventional Er:YAG and CO_2 lasers were used to ablate the epidermis in a continuous fashion. Fractional lasers are a relatively recent modality, with the concept of fractional photothermolysis first described in 2004 [8]. Similar to conventional lasers, fractional lasers ablate the skin, however as their name suggests, they do so in fractions, splitting the laser beam into microbeams [9]. These microbeams create microscopic vertical channels of ablation in the skin surrounded by thin layers of coagulated tissue referred to as the microthermal zone (MTZ) [6]. The MTZ is surrounded by relatively spared, healthy tissue, although some degree of adjacent tissue damage occurs as a collateral effect. The creation of these channels theoretically provides access pathways for topically applied drug molecules that would otherwise be too large to traverse the epidermal layer, while minimizing the healing time that is necessary after continuous laser ablation (Fig. 1). The location, diameter, depth, and other characteristics of these channels can be precisely controlled to the stratum corneum and epidermis (Fig. 2) or result in deeper ablation into the dermis. Both continuous ablation and fractional ablation have been used in drug delivery studies (Table 1).

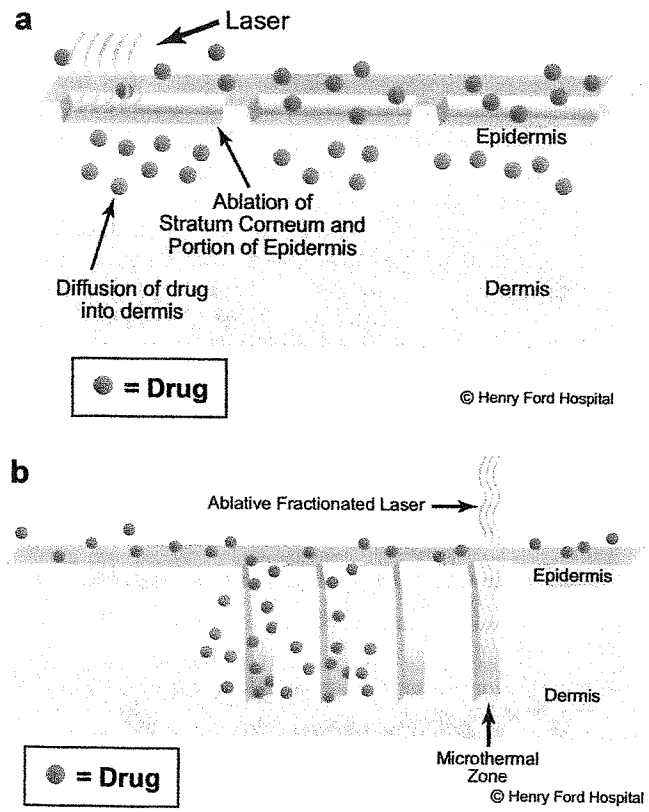

Fig. 1. Schematic of an ablative fractionated laser device allowing topical drug penetration by the creation of microthermal zones (MTZs). These MTZs serve as access channels, allowing the drug to penetrate the barrier of the stratum corneum. Modification of laser parameters can allow precise depth of ablation limited to the stratum corneum and dermis (**a**) or deeper ablation into the dermis (**b**).

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is an effective treatment for superficial nonmelanoma skin cancers, actinic keratosis (AKs), and acne. Thicker lesions have shown to be more resistant to PDT due to the inadequate depth of penetration by topical photosensitizers [2,3]. A study using *in vivo* human skin revealed that 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) often fail to permeate to tissue depths >1 mm, in part due to the polar, hydrophilic nature of these compounds [2].

Laser pretreatment of the skin has been shown to increase the penetration of these photosensitizers. In an *ex vivo* porcine skin model, both continuous and fractional ablative Er:YAG lasers increased the penetration of topically applied ALA by 13.8- and 7.3-fold, respectively [9]. This study found the optimal parameters for maximizing ALA penetration while minimizing tissue injury to be 1 and 4 J/cm^2 for continuous and fractional ablation, respectively, which corresponded to a pore depth of 12.5 ± 7.8 μm localized to the stratum corneum. Another *in vitro* study showed that skin pretreatment with the fractional Er:YAG laser increased the flux of ALA 27- to 124-fold in nude mouse skin and 3- to 260-fold in porcine skin, which was independent of number of passes [10]. The skin received one to six passes (169 pores per pass) at a fluence of 2 or 3 J/cm^2 which corresponded to penetration depths of 8 and 12 μm, respectively. These investigators suggested that laser pretreatment of the skin could potentially reduce the required dose of topically applied ALA by 20% which may decrease side effects such as paresthesias, and dyspigmentation [10].

The fractional CO_2 laser has also been shown to enhance the delivery of photosensitizing agents used in PDT. Fractional CO_2 laser pretreatment of *in vivo* porcine skin significantly enhanced the penetration of topically applied MAL, along with the subsequent PDT response throughout the superficial and deep layers of the skin at a total energy of 366.4 mJ and power of 30.5 W (which consisted of four pulses of 3 milliseconds duration per pulse at 91.6 mJ per pulse) and laser-ablated channels of approximately 1,850 μm deep [11,12].

The ability of laser pretreatment to enhance the efficacy of PDT has also been demonstrated in clinical trials. In a split face study conducted by Togsverd-Bo et al. [13], ablative fractional CO_2 laser treatment prior to MAL application proved to be more effective in the treatment of AKs than conventional PDT alone. After 3 months of follow-up, clearance rates for grade I AKs were 100% in the laser pretreated side compared to 80% with PDT alone. Thicker AKs (grade II and III lesions) responded by 59% after PDT alone versus 88% with laser pretreatment, a

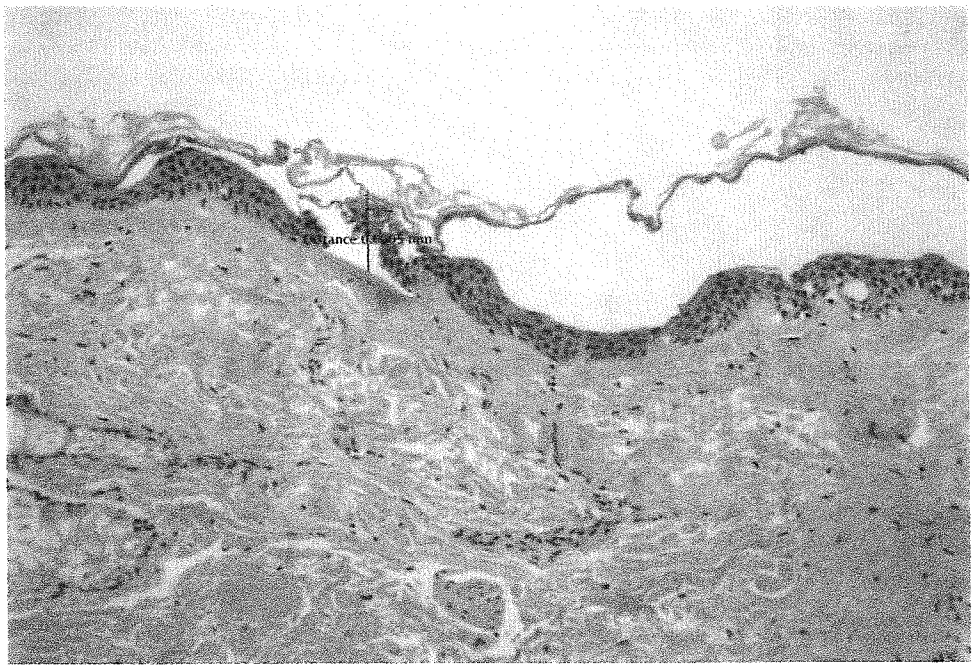

Fig. 2. Histologic section of a superficially ablated MTZ limited to the stratum corneum and epidermis using a fractional CO_2 laser (depth of ablation = 0.0316 mm).

finding that could bear clinical importance in the treatment of hyperkeratotic AKs which are often more recalictrant to treatment. The development of new AKs was also slowed by laser pretreatment and laser pretreatment also led to a greater improvement in photoaging compared to PDT alone. However, the latter finding is confounded by the ability of fractional laser treatment alone to treat photoaging, as a control group accounting for this was not employed. Yet, laser pretreatment also led to greater side effects, including increased pain, erythema, crusting, and dyspigmentation.

In a separate study, Helsing et al. [14] compared fractional CO_2 laser alone versus laser assisted PDT in the treatment of acral AKs in organ transplant recipients. MAL–PDT combined with laser pretreatment led to 73% improvement compared to laser alone. However, this study did not include an additional control arm investigating the clearance rates of MAL–PDT without laser pretreatment. In another study, investigators used ALA–PDT in combination with fractional CO_2 laser pretreatment to successfully treat recalcitrant periungual warts, suggesting another potentially important clinical application [15].

Kim et al. [16] demonstrated that laser pretreatment with a fractional CO_2 laser reduced the necessary incubation time without compromising treatment efficacy in the treatment of Bowen's disease. The investigators pretreated Bowen's lesions on 10 patients with a CO_2 fractional laser prior to the application of MAL and found that an incubation time of only 70 minutes yielded complete resolution in 90% of the lesions. A much longer incubation time of 3–4 hours is typically required to reach the same level of treatment efficacy when PDT is used alone in the treatment of Bowen's disease.

Lesions thicker than 2 mm such as nodular BCC (nBCC) are generally percieved as a contraindication to PDT due to inadequate penetration depth. However, it has recently been shown that the combination of fractional CO_2 laser and PDT may significantly increase the clinical effectiveness in the treatment of these thick lesions [17]. Lippert et al. used a diode laser to ablate 56 nBCCs. One week later, the investigators pretreated half of each tumor with a fractional CO_2 laser and the other half with curettage alone prior to ALA–PDT. Fluorescence examination was performed before the start of PDT. Two weeks later, the laser pretreated side was treated with the fractional laser once more before the entire lesion underwent another ALA–PDT treatment. For 94.6% of the lesions, higher fluorescence in the portion of the tumor pretreated with the laser was observed. In addition, the final clearance rates were 92.9% for the treatment group and 80.4% for the control group. These findings suggest that laser pretreatment prior to the application of PDT may be an effective treatment of nBCCs thicker than 2 mm [17]. However, as photosensitizers are able to easily spread through tissue, the split-lesion study design is at high risk of introducing confounding errors. Also, the authors admit that the border of each tumor separating the two treatment areas was ill-defined, possibly decreasing the validity of the split

TABLE 1. Summary of Existing Studies Utilizing Laser Assisted Drug Delivery

Study	Topical drug	Laser	Study model	Findings	Referer
Forster et al.	ALA	Fractional Er: YAG	Porcine skin	Penetration enhanced 13.8-fold	[9]
Forster et al.	ALA	Conventional Er:YAG	Porcine skin	Penetration enhanced 7.3-fold	[9]
Lee et al.	ALA	Fractional Er: YAG	Porcine skin	Increased flux 3- to 260-fold	[10]
Lee et al.	ALA	Fractional Er: YAG	Nude mouse skin	Increased flux 27- to 124-fold	[10]
Haedersdal et al.	MAL	Fractional CO_2	Porcine skin	Significantly enhanced penetration as well as PDT response throughout superficial and deep layers of skin	[11,12
Togsverd-Bo et al.	MAL	Fractional CO_2	Human skin (15 patients with a total of 212 AKs, severity grade I–III)	At 3-month follow-up, complete lesion response was 100% and 88% for grade I and grades II–III, respectively (compared to 80% and 59% after PDT alone, respectively)	[13]
Helsing et al.	MAL	Fractional CO_2	Human skin (10 organ transplant recipients with a total of 680 AKs, severity grade I–III, and 409 wart-like lesions on the dorsal hands)	At 4-month follow-up, AK clearance rate was 73% and 82% of AKs were improved to lower lesion grades (compared to 31% and 52% for laser treatment without PDT). The clearance rate for wart-like lesions was 37% (compared to 14% for laser treatment without PDT)	[14]
Yoo et al.	MAL	Fractional CO_2	Human skin (12 Korean patients with a total of 40 periungual warts)	After 2.2 treatments, a mean clearance of 100% was achieved in 90% of the warts	[15]

Kim et al.	MAL	Fractional CO_2	Human skin (10 patients with Bowen's disease)	50% and 90% clearance rates were noted after 3 and 4 treatment sessions, respectively, suggesting that laser-PDT has similar treatment efficacy and requires a shorter photosensitizer incubation time compared PDT alone	[16]
Lippert et al.	ALA	Fractional CO_2	Human skin	52 of 56 nBCCs in the fractional laser treatment group responded to ALA–PDT, compared with only 45 of 56 in the control group (curettage alone)	[17]
Haak et al.	MAL	Fractional CO_2	Porcine skin	Laser pretreatment decreased required MAL incubation time and drug delivery was equivalent at ablations of various depths	[18]
Baron et al.	Lidocaine	Conventional Er:YAG	Human skin (320 patients)	Decreased needle-prick pain by 61% within 5 minutes	[4]
Singer et al.	Lidocaine	Conventional Er:YAG	Human skin (61 patients)	Significant pain reduction to IV cannulation within 5 minutes	[21]
Oni et al.	Lidocaine	Fractional Er: YAG	Porcine skin	Depth of ablation impacted the level of absorption: peak lidocaine levels were highest at an ablation depth of 250 μm compared to greater depths of 500 μm and more shallow depths of 50 and 25 μm	[23]
Koh et al.	Lidocaine	Fractional Er: YAG	Human skin (30 patients)	Energies of 2.0 and 3.5 J/cm^2 were equally effective in facilitating topical anesthesia and yielded similar adverse events	[22]
Bachhav et al	Lidocaine	Fractional Er: YAG	Porcine skin	Less absorption occurred with 150 pores, but there was no difference in absorption between 300, 450, and 900 pores. Increasing depths of ablation did not impact the absorption	[19]

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TABLE 1. (*Continued*)

Study	Topical drug	Laser	Study model	Findings	Refere
Yun et al.	Lidocaine	Conventional Er:YAG	Human skin (12 patients)	Laser pretreatment significantly decreased pain in full facial resurfacing however 42% of subjects were unable to undergo second pass	[24]
Bachhav et al.	Diclofenac	Fractional Er: YAG	Human and porcine skin	Transport of diclofenac increased up to 13-fold	[26]
Lee et al.	Opioids	Conventional Er:YAG	Porcine skin	10- to 35-fold enhancement of transdermal delivery of morphine, nalbuphine, and buprenorphine	[27]
Lee et al.	5FU	Q-switched ruby (594 nm)	Nude mouse skin	5- to 10-fold increased flux	[28]
Lee et al.	5FU	Conventional Er:YAG	Nude mouse skin	53- to 133-fold increase flux	[28]
Lee et al.	5FU	Conventional CO_2	Nude mouse skin	36- to 41-fold increase flux	[28]
Gomez et al.	5FU	Q-switched Nd: YAG (1,064 nm)	Rabbit ear	Significantly enhanced transdermal flux	[30]
Waibel et al.	5FU versus triamcinolone acetonide	Fractional CO_2	Human patients with hypertrophic scars	Both 5FU and triamcinolone decreased scar height and length. More adverse effects with triamcinolone	Unpublish
Lee et al.	MTX	Conventional Er:YAG	Nude mouse skin	3- to 80-fold enhanced permeation	[32]
Yu et al.	Prednisone	Fractional Er: YAG	Porcine skin	Significantly increased prednisone delivery, found to be dependent on pore depth and pore number	[33]
Waibel et al.	Triamcinolone acetonide	Fractional CO_2	Human skin (15 patients with hypertrophic scars)	Average clinical improvement of 2.73/3.0	[31]
Issa et al.	Triamcinolone acetonide	Fractional laser + acoustic pressure ultrasound	Human skin (four patients with hypertrophic scars)	Complete resolution was seen after one session in scars on the nose and mandibular area. A scar on the neck showed complete resolution after four sessions. A scar on the knee showed marked improvement after four sessions	[34]

al.	Lysozyme vaccine (Hen egg lysozyme antigen)	Conventional Er:YAG	Nude mouse skin	3-fold increase in the production of serum antibodies	[36]
ɜt al.	Ovalbumin vaccine	Fractional CO_2	Nude mouse skin	8- to 15-fold increased delivery and augmented production of ovalbumin specific antibodies 28- to 538-fold compared to intact skin at 2 weeks	[37]
al.	Imiquimod	Fractional Er: YAG	Porcine and nude mouse skin	Revealed a decreased dose of 0.4% imiquimod with laser pretreatment approximated the delivery of nonpretreated application of 5% imiquimod	[38]
et al.	Vitamin C	Fractional and conventional CO_2	Porcine skin	Four or fewer passes with the fractional CO_2 laser achieved similar permeation with less epidermal destruction compared to an equivalent fluence using the conventional CO_2 laser	[40]
ɨl et al.	CE Ferulic formula	Fractional CO_2	Human patients	Split-face application of CE ferulic formula immediately after fractionated resurfacing achieved trends of faster healing times by 24–48 hours	[41]
s et al.	Cosmeceuticals	Fractional CO_2 ± acoustic pressure ultrasound	Human skin (14 patients)	At 6-month follow-up, a single treatment of laser alone and laser + ultrasound produced a 69% and 79% improvement in overall cosmetic outcome, respectively	[42]
ɜl et al.	Allogenic mesenchymal cutaneous stem cells	Fractional CO_2	Radiation induced immunosuppressed mice	At 3 weeks, 28.5% of bone marrow cells were from donor, indicating successful engraftment	[43]
ıoud et al.	Botulinum toxin	Fractional CO_2	Crows' feet	Statistically significant wrinkle reduction	Unpublished data

lesion design. Furthermore, the initial diode laser ablation may have debulked a substantial portion of the tumors, resulting in artificially high clearance rates attributed to PDT. Additional studies are needed to replicate these authors' conclusions.

Haak et al. [18] investigated the importance of depth of ablation and incubation time for fractional CO_2 laser assisted delivery of MAL in porcine skin. Three laser energies were used to create MTZs of various depths with the most shallow being in the superficial dermis (37 mJ/MTZ = 300 μm, 190 mJ/MTZ = 1,400 μm, and 380 mJ/MTZ = 2,100 μm). By means of histology and fluorescence photography, the investigators demonstrated that pretreatment with the laser significantly reduced incubation times required for a given accumulation of MAL from the skin surface to the deep dermis. After laser treatment and 60 min MAL incubation, surface fluorescence was 69.16 a.u. versus. 23.49 a.u. for nonlaser-treated skin exposed to 180 min MAL incubation. Through all skin layers (120–1,800 μm), after laser treatment and 120 minutes MAL incubation, fluorescence in hair follicles was 14.76 a.u. versus 6.69 a.u. and in the dermis was 6.98 a.u. versus 5.87 a.u. compared to that of nonlaser treated sites exposed to 180 min MAL incubation. Interestingly, the depth of ablation did not affect drug delivery, as similar fluorescence intensities were induced within the dermis for both shallow and deeper MTZs. This important finding suggests that once the barriers of the stratum corneum and epidermis are surpassed, MAL and other drugs may disperse readily within the dermis. Forster et al. also found that once the stratum corneum is disrupted, there may be no further benefit to creating deeper MTZs [9]. The investigators used an ablative Er:YAG laser at fluences from 4 to 24 J/cm^2 and energy levels from 4 to 8 J/cm^2 (which penetrated the stratum corneum) and 12 to 24 J/cm^2 (which penetrated to varying intraepidermal depths) prior to ALA application and revealed that energy levels >6 J/cm^2 yielded no further increase in ALA penetration. This may allow clinicians to ablate more superficially and therefore minimize patient recovery, while gaining equivalent efficacy for drug delivery.

TOPICAL ANESTHETICS

Several studies have revealed that conventional and fractional Er:YAG laser pretreatment of the skin may be beneficial in the transdermal delivery of topical lidocaine [4,19–23]. In human subjects, conventional Er:YAG laser pretreatment prior to the application of lidocaine cream has been shown to significantly decrease needle prick pain within 5 minutes of drug application [4,21]. This anesthetic response is a notable improvement compared to the hour it may take when lidocaine is applied to intact skin [4,19]. In the majority of these studies, adverse events (which include mild pain, moderate redness, and swelling) have only been assessed after needle insertion, hence, it cannot truly be determined whether these are the result of YAG laser at settings proven to effectively decrease pain of needle stick (fluence of 250 mJ/Pulse, a pulse width of 300 microseconds, and an estimated pore depth of less than 20 μm) [4,20]. This low energy causes little or no sensation when used to irradiate the skin [20]. In addition, Singer et al. [21] reported that the Er:YAG at a fluence of 3.5 J/cm^2 was painless in the majority of subjects and effectively reduced the pain of IV needle-stick. More studies comparing the pain of delivering laser for topical anesthesia versus that of a simple needle stick are required for this application to become clinically practical.

The clinical utility of this modality appears less promising for obtaining anesthesia in more invasive procedures such as full facial resurfacing. Yun et al. [24] pretreated 12 patients with low-fluence (1.3 J/cm^2) conventional Er:YAG to half of the face (reported to be painless), followed by 5% topical lidocaine application to the entire face. Subsequently, the subjects underwent full-facial resurfacing at which time at least two passes were performed at 20–25 J/cm^2 with 0 μm of coagulation for the first pass and 20–25 J/cm^2 with 50 μm of coagulation for the second pass. During resurfacing, patients had significantly less pain on the laser pretreated side, but only 58% of patients were able to tolerate a second pass, raising the concern for practical limitations. For now, clinical caution is also warranted given one case report of systemic lidocaine toxicity in a patient who underwent the application of 30% lidocaine gel preceding and following fractional resurfacing [25]. This patient was treated with two to eight passes of energy at 6–13 mJ consisting of 250 MTZs/cm^2 which penetrated 400–700 μm deep.

In general, additional studies are needed to determine the optimal laser parameters for laser assisted drug delivery but several studies involving lidocaine delivery have begun to delineate these parameters. Using human subjects, Koh et al. [22] demonstrated that greater Er:YAG pretreatment fluences did not result in greater anesthesia when comparing energies of 2.0 and 3.5 J/cm^2, but the lower fluence did not reduce side effects. There are conflicting data whether the depth of ablation has any impact on lidocaine absorption, and if there is a relationship, it does not appear to be linear. Using a fractional Er:YAG laser on a porcine skin model, Oni et al. [23] showed that an intermediate ablation depth of 250 μm resulted in greatest lidocaine absorption compared to the greater depth of 500 μm and more shallow depths of 50 and 25 μm. The investigators offered several possible explanations for these results: a vascular network in the skin at a depth of approximately 250 μm which would enhance absorption at this specific depth or increased bleeding, edema, exudate, and thickness of the coagulated lining of the MTZs induced by higher energy settings which may create a barrier to absorption. In contrast, Bachhav et al. found no significant association between treatment depth and lidocaine absorption for depths >30 μm. Using *ex vivo* porcine skin Bachhav investigated the effects of laser pretreatment with an Er:YAG fractional laser device on the absorption of

fluence (4.53 and 13.59 J/cm^2), intermediate fluence (22.65 J/cm^2), and high fluences (45.63, 90.6, 135.9 J/cm^2) to induce pore depths of 20 to 30 μm localized to the stratum corneum, 60 to 100 μm that penetrated the epidermis, and 150 to 200 μm that penetrated the dermis, respectively. Results revealed that the shallow pores were as effective as the deeper pores in delivering lidocaine. Data also revealed that lidocaine permeation increased as pore number increased from 0 to 150 but showed no further significant increase at 300, 450, or 900 pores. The investigators attributed this finding to the effect of drug depletion since more than 50% of the applied dose was delivered once the number of pores exceeded 150 [19].

NSAIDS

While the limiting factor of transdermal drug delivery is the stratum corneum, oral drug delivery is accompanied by a different set of limiting factors. For many orally ingested drugs, an extensive first pass metabolism results in a low systemic bioavailability. Therefore, to achieve desirable drug concentrations, a greater dose must be ingested. Diclofenac has a low systemic bioavailability and its use is limited by adverse effects on the mucosa of the gastrointestinal tract. Using porcine and human skin, Bachhav et al. demonstrated the ability of pretreatment with a fractional Er:YAG laser to enhance the transdermal transport of topically applied diclofenac [26]. They showed that at 24 hours post-treatment with a constant fluence of 22.65 J/cm^2 and pore depth of 50–80 μm, increasing pore number (150, 300, 450, and 900 pores) resulted in increased permeation of diclofenac across skin 3.7-, 7.5-, 9.2-, and 13-fold, respectively, compared to intact skin. They also found that at a constant pore number of 900, increasing fluence (22.65, 45.63, 90.6, 135.9 J/cm^2) significantly increased diclofenac permeation. Their study also demonstrated that the transport of the drug across the skin was increased by both laser fluence and pore number.

Potential clinical applications suggested by these authors included the use in arthritic conditions with the ability to avoid gastrointestinal adverse effects or to increase the efficacy of topical diclofenac in the treatment of actinic keratoses. In addition, they proposed that the medication could be manufactured as a once daily sustained release patch, a practical idea that could be generalized to other medications in regards to laser assisted drug delivery [26].

OPIOIDS

Opioids also have a low systemic bioavailability as a result of an extensive first pass metabolism and short half-life. Lee et al. [27] used the conventional Er:YAG laser to pretreat *in vitro* porcine skin to demonstrate a 10- to 35-fold enhancement of the transdermal delivery of morphine, nalbuphine, and buprenorphine. The investigators used a single pulse duration of 250 microseconds at an energy of 0.35–0.65 J to achieve fluences of 1.4–2.6 J/cm^2. Histologic gross changes of the epidermis or dermis were observed. The laser assisted transdermal delivery of narcotics could be useful clinically, potentially allowing for less frequent dosing, while allowing for more predictable drug levels.

CHEMOTHERAPEUTIC DRUGS

Topical formulations of 5-fluorouracil (5FU) are used in the treatment of skin lesions including actinic keratosis and basal cell carcinoma, but have the common side effects of dermatitis, crusting, and erosions. Using an *in vitro* nude mouse model, Lee et al. [28] demonstrated increased transdermal delivery of 5FU following pretreatment with the conventional Er:YAG (53- to 133-fold increase), conventional CO_2 (36- to 41-fold increase), and Q-switched ruby (594 nm) lasers (5- to 10-fold increase). The Er:YAG laser delivered a single pulse of 250 microseconds and delivered energies of 0.3, 0.35, 0.45, and 0.55 J/Pulse to achieve fluences of 0.8, 0.9, 1.2, and 1.4 J/cm^2, respectively. Histology revealed that different energies could achieve both partial and complete removal of the stratum corneum, with higher fluences generally inducing a deeper ablation. However, no significant difference in ablation was seen between 0.8 and 1.2 J/cm^2. The Q-switched ruby laser generates photomechanical waves that may transiently increase the permeability of the stratum corneum to facilitate the transport of macromolecules into the skin [29]. In another study using a rabbit ear model, Gomez et al. [30] showed that pretreatment with the Q-switched Nd:YAG laser at three different wavelengths (infrared: 1,064 nm, visible light: 532 nm, and ultraviolet: 355 nm) significantly increased the transdermal permeation of 5FU. The investigators found that the visible light radiation was the best to use due the wide range of fluences (3–8.4 J/cm^2 at 15 Hz) able to enhance drug delivery with no risk of skin lesions. Potential clinical applications could include the delivery of systemic doses of 5FU transdermally or the use of less concentrated topical doses to maximize treatment efficacy while minimizing cutaneous side effects.

Waibel et al. used pretreatment with a fractional CO_2 laser to deliver 5FU versus triamcinolone acetonide to synergistically create a therapeutic response when treating human hypertrophic scars (unpublished data). It has previously been reported that delivery of triamcinolone acetonide immediately after fractional laser therapy may take advantage of the ablative fractional channels to penetrate deep into dermal scars and synergistically decrease fibroblast proliferation (Fig. 3) [31]. However, corticosteroids have the potential to cause several adverse events including dermal atrophy, fat atrophy, hyperpigmentation, telangiectasias, and hypopigmentation. In addition, there is concern over systemic steroid absorption with laser assisted delivery of corticosteroids. Intralesional fluorouracil is a safe and effective means of controlling problem scars in terms of both recurrence and symptom control. This study evaluated using laser assisted delivery

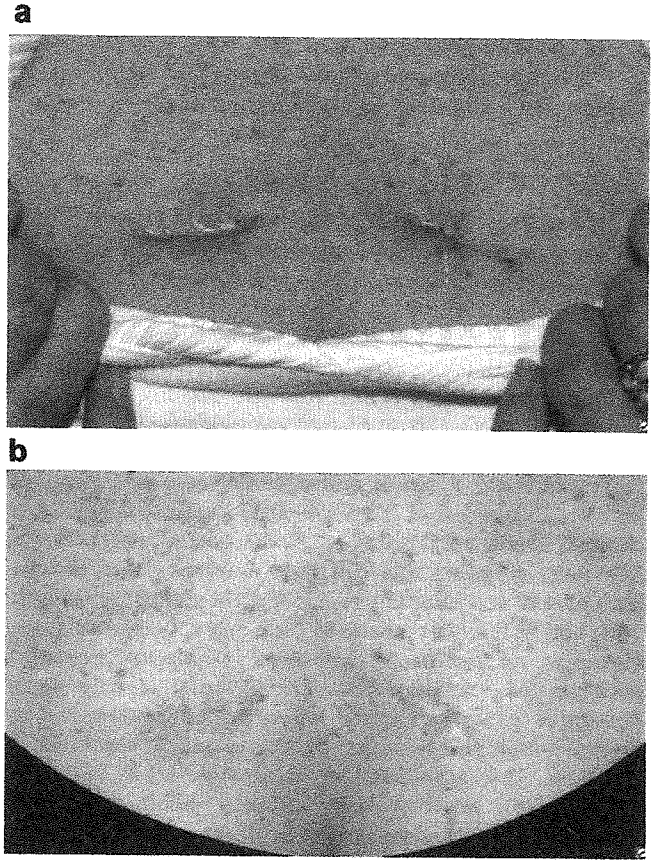

Fig. 3. Fractional CO_2 laser assisted topical delivery of triamcinolone acetonide (10 mg/ml) at baseline (**a**) and after three treatments (**b**).

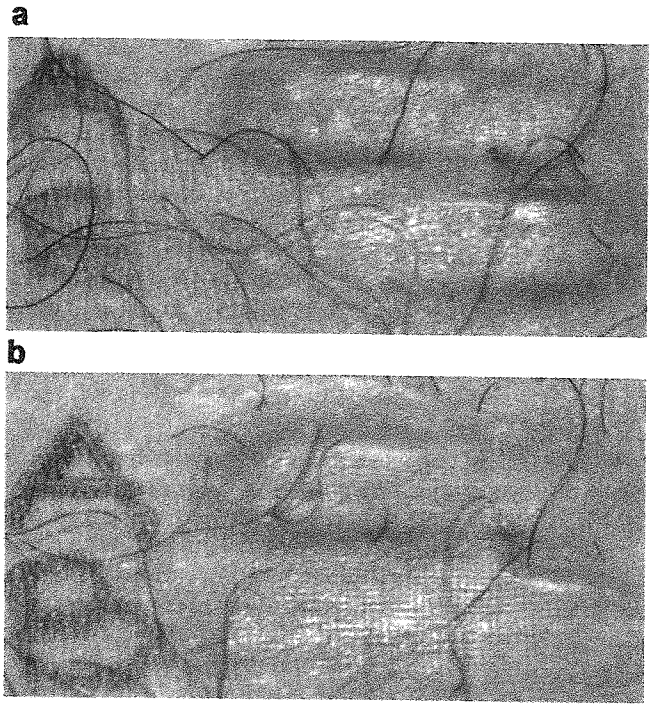

Fig. 4. Fractional CO_2 laser assisted topical delivery of 5FU and triamcinolone acetonide at pretreatment baseline (**a**) and demonstrating decreased height and length after three treatment sessions (**b**). A = 5FU; B = triamcinolone.

decrease hypertrophic and keloid scars. Waibel et al. found that both laser assisted delivery of triamcinolone acetonide and 5FU improved hypertrophic and keloid scars by decreasing their height and length (Fig. 4). However, triamcinolone acetonide had more adverse events including increased width in two scars and increased development of telangiectasias.

Methotrexate is another chemotherapeutic drug that is commonly administered via oral or via injectable routes to treat conditions including psoriasis and rheumatoid arthritis. Using a nude mouse skin model, Lee et al. [32] used a conventional Er:YAG laser with fluences of 1.4–3.7 J/cm^2 to increase the skin permeation of topically applied methotrexate by 3- to 80-fold in laser pretreated skin. Perhaps the systemic side effects (which include hepatotoxicity, bone marrow suppression, and gastrointestinal complaints) could be minimized with topical methotrexate applied directly on the skin following laser pretreatment.

CORTICOSTEROIDS

Prednisone is a corticosteroid used in the treatment of induce skin atrophy. Using a porcine model, Yu et al. [33] demonstrated that pretreatment with the fractional Er:YAG significantly enhanced the penetration of topically applied prednisone, which correlated with both greater pore depth and number. After demonstrating that fluence can control the pore depth (4.53 J/cm^2 selectively removed the stratum corneum, 22.65 J/cm^2 penetrated the epidermis, 135.9 J/cm^2 penetrated the dermal–epidermal junction and often penetrated the dermis), they examined prednisone delivery as a function of pore number (450, 900, and 1,800 pores) and fluence (22.65, 45.3, and 90.6 J/cm^2, at a constant pore number of 900). The results showed that delivery of prednisone was linearly related to pore number and showed a significant increase in relation to pore depth, however the investigators found that even relatively shallow pores may be sufficient to achieve the desired amount of drug transport.

A human study performed using laser assisted drug delivery of triamcinolone acetonide to improve scars was evaluated in a prospective, single arm, pilot study including 15 consecutive subjects with hypertrophic scars resulting from burns, surgical, or traumatic injuries (Fig. 3) [31]. Subjects were treated with three to five treatment sessions at 2- to 3-month intervals consisting of fractional ablative laser treatment and immediate postoperative topical application of triamcinolone acetonide suspension at a concentration of 10 mg/ml. The objective

ablative laser in the same treatment session as topical triamcinolone acetonide to synergistically improve complex scars. Combination same session laser therapy and immediate postoperative corticosteroid delivery resulted in an average overall improvement of 2.73/3.0. This study concluded that same-session therapy with ablative fractional laser assisted delivery of topical triamcinolone acetonide potentially offers an efficient, safe, and effective adjunctive treatment of challenging cutaneous hypertrophic scars.

In another study, Issa et al. [34] used ultrasound in addition to fractional laser to assist in the delivery of triamcinolone in the treatment of hypertrophic scars of four subjects. The skin was treated with fractional laser, followed by triamcinolone application, which was then followed by ultrasound treatment. Complete resolution was noted after a single treatment session in scars on the face (nose and mandibular area) while a scar on the neck required four treatment sessions. A scar on the knee showed significant improvement after four treatment sessions. Adverse effects included mild atrophy on the neck in one patient, which was observed 2 months after the last treatment.

VACCINATIONS

Transdermal vaccine delivery targets Langerhan and dendritic cells in the skin and for this reason has been proposed to generate a stronger immune response at lower doses than injections [35]. Using a nude mouse skin model, Lee et al. pretreated the skin with a single pulse of a conventional Er:YAG laser to enhance the permeability of a topical lysozyme vaccine through the skin 3- to 140-fold higher than that across intact skin. Additionally, antibody production in the serum was enhanced by threefold after pretreatment with this laser, which operated at an energy of 0.45–0.65 J with a beam spot diameter of 7 mm to achieve fluences of 1.2–1.7 J/cm [36]. In another study, Chen et al. [37] used a mouse model pretreated with the fractional CO_2 laser to increase the transcutaneous delivery of a model vaccine, ovalbumin, by 8- to 15-fold. This laser, which operated at a wavelength of 10.6 μm and an energy of 2.5 or 5.0 mJ, augmented the production of ovalbumin specific antibodies by 28- to 538-fold compared to intact skin at 2 weeks [37]. Histologic analysis revealed that an energy of 2.5 mJ treating 5% of skin coverage gave rise to the quickest onset of skin re-epithelialization, occurring at 1–2 days. The MTZs were 120 ± 5 μm in diameter and 113 ± 17 μm in depth. When the skin coverage was increased to 15%, the MTZs remained the same size but tissue recovery was delayed. Increasing the energy to 5.0 mJ, regardless of skin coverage, increased the size and depth of the MTZs and delayed skin healing [37]. With additional study, further applications for laser assisted topical delivery of vaccines may be developed.

IMIQUIMOD

genital warts, actinic keratoses, superficial basal cell carcinoma, and as an off-label treatment for Bowen's disease. Lee et al. [38] performed a study on porcine and nude mouse skin investigating the ability of a low-fluence fractional Er:YAG laser to increase the transdermal delivery of imiquimod. The investigators pretreated the skin with one to six pulses (169 pores per pulse) at a fluence of either 2 or 3 J/cm^2. They found that laser fluence and number of pulses plays an important role in the enhancement of imiquimod permeation. Exposure of one pulse at 2 and 3 J/cm^2 enhanced imiquimod flux 25- and 65-fold, respectively, and exposures of four pulses at these fluences enhanced the flux 46- and 127-fold, respectively, compared to that of intact skin. Six pulses at 3 J/cm^2 induced the greatest enhancement in flux. They demonstrated that a greatly decreased dose of 0.4% imiquimod with laser pretreatment approximated the delivery of nonpretreated application of 5% imiquimod. Histologic analysis showed that while laser ablated a small portion of the stratum corneum, with an average diameter of each MTZ being 250 μm, surrounding tissues remained unharmed [38]. Additional studies are needed to investigate the clinical implications for this finding.

TOPICAL ASCORBIC ACID (VITAMIN C)

Topical ascorbic acid has been used in the treatment of photoaging and as a lightening agent for cutaneous hyperpigmentation [39]. In a porcine skin model, Hsiao et al. [40] demonstrated that four or fewer passes with the fractional CO_2 laser achieved similar permeation of topical ascorbic acid with less epidermal destruction compared to an equivalent fluence using the conventional CO_2 laser. Although it appears that the fractional CO_2 laser can enhance transdermal delivery of ascorbic acid, additional studies are needed to further determine the clinical effects.

In a split face comparison, the effects of vitamin CE Ferulic acid formula (L'Oreal USA Creative, Inc., New York, NY) immediately after fractional ablative laser pretreatment to decrease postoperative recovery and increase neocollagenesis in fractional ablative laser resurfacing for photodamage was performed. Secondary objectives were to evaluate synergistic response of laser and topical application on the up regulation and formation of collagen through histological evaluation of mRNA and collagen I and III. Previous studies have shown that application of vitamin C, E, and ferulic acid improves wound healing and promotes the induction of collagen. Results from this study showed trends of decreasing downtime 24–48 hours with ability of patients to return to work and social life more quickly [41].

Investigation into other cosmeceuticals has recently been performed. Trelles et al. [42] designed a randomized double blinded split-face study in which half of the face was treated with fractional CO_2 laser while the other half of the face was treated with the same laser in addition to ultrasound for transepidermal delivery of a topical cosmeceutical formulation. Significant improvement was

however, the combined treatment yielded greater improvement scores at six months, with 79% improvement compared to 69% improvement for the laser treatment side alone.

ALLOGENIC MESENCHYMAL STEM CELLS

Waibel et al. [43] recently investigated the use of fractional laser pretreatment to deliver bone marrow stem cells through the skin of radiation-induced immunosuppressed mice. At 3 weeks post-treatment, the investigators observed bone marrow engraftment and functional recovery of the donor cells. This study is the first to suggest that laser technology may be useful in the delivery of stem cells to distant sites with chimerization of the delivered cells. Future studies are needed to determine the efficacy of delivering stem cells through the skin in the treatment of different diseases.

BOTULINUM TOXIN

Mahmoud et al. recently performed a prospective randomized controlled trial investigating the efficacy of laser assisted drug delivery of a topical botulinum toxin solution for crow's feet (unpublished data). Laser treatment was performed to the bilateral crows feet using a fractional carbon dioxide laser (pulse energy of 100 mJ with 100% density). One hundred units of abobotulinum toxin A were applied topically to the treatment side immediately after laser pretreatment, resulting in statistically significant wrinkle reduction. This study demonstrated that pretreatment with the fractional CO_2 laser allows for clinically effective drug delivery of botulinum toxin solution.

POTENTIAL COMPLICATIONS AND PRACTICAL LIMITATIONS OF LASER ASSISTED DRUG DELIVERY

The epidermal ablation induced by conventional and fractional Er:YAG and CO_2 lasers have the potential to cause skin irritation, erythema, a prolonged postoperative recovery period, papular swelling, and dyspigmentation [6,10,11,44]. In general, however, the frequency of adverse events with fractional laser is relatively low, as demonstrated by Graber et al. who reported a complication rate of 7.6% in a series of 961 treatments with the fractional Er:YAG laser. These complications included acneiform eruptions, herpes simplex virus exacerbations, erosions, postinflammatory hyperpigmentation, prolonged erythema, prolonged edema, and dermatitis. Bacterial infection appears to be a rare event, as only one case of impetigo was reported in that series [44].

The CO_2 laser has the added effect of causing increased thermal injury with the potential for greater collateral fibrosis and scarring compared to the Er:YAG laser. Clinically, hypertrophic scarring is a rare complication but has been reported to occur with both fractional and conventional ablative lasers [45,46]. The neck is more and treatment density as well as the avoidance of pulse stacking or performing multiple treatment passes [45,46].

Fractional lasers have been shown to offer the same advantages as conventional lasers (including increased flux, permeation, and depth of many topical agents) with the additional benefit of quicker healing time [9,10,46]. It has been suggested that the synergistic use of corticosteroids and laser treatment of the skin could further enhance tissue recovery [47].

As additional studies are conducted, special attention must be paid to the potential adverse effects of this technology. For topical medications, the increased permeability achieved by the laser may allow for lower topical dosages and therefore fewer cutaneous side effects without sacrificing efficacy. Alternatively, the increased permeability could allow for increased local accumulation of drug, resulting in increased side effects. The latter possibility may be particularly true for agents already known to commonly cause cutaneous side effects such as 5FU and imiquimod. There also remains the potential for inadvertent systemic absorption leading to systemic toxicity, as previously reported with lidocaine [25]. Similarly, when lasers are used to deliver systemic medications, excessive local accumulation in the skin could result in unexpected cutaneous side effects even in the face of expected serum levels.

The pain of the treatment itself must also be considered. Superficial ablation at low fluences is relatively painless [20]. For deeper ablation utilizing higher energies, some level of anesthesia is usually needed to increase tolerability. Local infiltration of an injected anesthetic or the application of a topical anesthetic is usually sufficient. Anesthesia by forced air-cooling can also significantly increase patient comfort and is often employed during treatment [48].

Another practical concern is the postoperative healing associated with ablative laser modalities. As discussed, fractionated lasers allow for relatively rapid tissue healing compared to conventional ablative lasers, however, there is still usually some degree of recovery downtime. Higher treatment fluences and densities which may be required for delivery of certain drug molecules can be expected to result in increased healing times. For conditions where multiple long-term treatments would be needed, it may be impractical to have significant wounding and abrasions of the skin on a continual basis. Further research will be needed to determine if a marked decrease in ablation density could be coupled with an increase in target drug concentration to yield identical results with less tissue destruction.

Lastly, cost will likely be a significant barrier to the widespread adoption of laser assisted drug delivery techniques. In general, the purchase of a laser device represents a significant financial investment for practitioners, which is a challenge particularly in the current environment of declining reimbursement. Likewise, the introduction of laser pretreatment is sure to increase costs

enhanced delivery. A cost–benefit analysis should be undertaken by physicians and their patients, but will surely vary depending on the drug used and the condition being treated.

CONCLUSION

Several animal and human studies indicate that certain lasers can augment transcutaneous drug delivery. Lasers have not only been proven to reduce the required topical dosage in the treatment of certain lesions, they have proven to allow deeper drug penetration with minimal tissue damage, which is especially true for fractional lasers. Additional human studies are needed to determine the optimal treatment parameters, especially in regards to the achieving the ideal balance of fluence, treatment density, and drug concentration. It will also be important to determine which drugs are compatible with this route of delivery and which vehicles are best for permeation. Studies have recently began to investigate the influence of different vehicles on laser assisted drug penetration [49]. The determination of these variables will be essential for its ultimate clinical applicability. Additional studies using placebo controls are also needed. For instance, the majority of the current studies do not analyze how much of the therapeutic effect is attributable to the laser alone, the therapeutic agent, or the combination of laser and therapeutic agent. The development of smaller, more portable, and more inexpensive laser units could also allow this technology to become more feasible in the average clinical setting.

In order to develop these applications, more studies are needed, especially in regards to clinical therapeutic outcomes as opposed to simply demonstrating enhanced delivery. Although several studies have been conducted on animal models with promising results, human studies are fewer in number.

As these studies are performed, the potential clinical applications are vast. The existing literature described above has several promising clinical applications, and one can imagine many other potential clinical uses. For example, compared to traditional intralesional injections, fractional lasers may allow for more optimal dispersion of drug molecules with less pain, so this technology could potentially be applied to common dermatologic treatments such as intralesional immunotherapy for warts. Other potential therapeutic applications could include the development of noninvasive treatments for nonmelanoma skin cancer. Rarer diseases such as follicular mycosis fungoides could also benefit by using laser pretreatment to allow topical medications access to deep follicular units. Likewise, wound healing agents, tissue tightening drugs, bio-identical hormones, and drugs that cause skin thickening or skin thinning are among topical drugs that could be used with lasers to enhance delivery into the deep dermis. The delivery of systemic medications by transcutaneous route also deserves additional investigation. As a impact the specialty of dermatology as well as other fields of medicine. Further studies are needed to develop and explore the many potential clinical applications.

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