Review

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Principles and clinical applications of transcutaneous laser-assisted drug delivery: A narrative review

Baoyi Liu[1], Rajiv Sood[2], Fuyang Wang[1], Feng Zhang[2], Lu Sun[1], Xing Qiu[1], Dewei Zhao[1] and William Charles Lineaweaver[2]

Abstract

Introduction: Transcutaneous laser-assisted drug delivery (LADD) is recognized as a developing therapy for skin disorders.

Method: Current literature was reviewed to summarize current applications for LADD.

Discussion: 12 clinical applications for this therapy are currently reported.

Conclusion: LADD has potential for wide application in skin disorder treatment.

Keywords

Transdermal drug delivery, laser-assisted drug delivery, transdermal absorption of macromolecules, dot array laser, traditional laser, drug transdermal absorption

Lay Summary

Laser assisted drug delivery improves drug bioavailability for treatment of skin disorders. This technique is being assessed clinically in disorders ranging from skin cancers to alopecia.

Introduction

Transdermal penetration of locally applied compounds can be enhanced by external chemical or physical sources. Research on laser-assisted drug delivery (LADD) is increasing and is geared towards enhancing transdermal drug delivery (TDD).[1,2] Other techniques that enhance TDD include curetting, dermabrasion, ion electrophoresis, pressure waves, vacuum, and Radio frequency (RF).[3] Using these modes, many drugs have been successfully delivered through the skin, including triamcinolone acetonide, 5-aminolevulinic acid (5-ALA), 5-fluorouracil (5-FU), and methotrexate.[4–7] LADD is an emerging field of dermatology.

[1]Department of Orthopedics, Affiliated Zhongshan Hospital of Dalian University, Dalian, Liaoning, China
[2]Burn and Reconstruction Centers of America Augusta, Augusta, GA, USA

Corresponding authors:
Dewei Zhao, Department of Orthopedics, Affiliated Zhongshan Hospital of Dalian University, No.6 Jiefang Street, Dalian, Liaoning, China.
Email: zhaodewei2016@163.com
William Charles Lineaweaver, Burn and Reconstruction Centers of America Augusta, 3647 J Dewey Gray Cir, Augusta, GA 30909, USA.
Email: wmcl321@aol.com

In general, LADD bypasses the cuticle and many other barrier mechanisms, thereby enhancing the penetration and intradermal diffusion of locally applied substances.[8] Transdermal administration is when a drug passes through the skin barrier to the bloodstream or its target compartment. External physical or chemical sources can be used to enhance TDD. Laser-assisted administration is an increasingly widely used method that uses ablative or non-ablative lasers to remove or weaken cuticle and epidermal areas in order to access the subdermis.[9] In 1991, Nelson et al.[10] used the mid-infrared erbium-yttrium-scandium gallium garnet laser to promote the transdermal delivery of hydrocortisone and interferon gamma. They applied an energy density of 1 J/cm2 on isolated pig skin and observed the tissue sections to find a linear relationship between laser penetration depth and pulse number. In vitro the Franz cell box was used to measure cumulative drug penetration. The laser exfoliated 12.6% of the cuticle region and increased the penetration of hydrocortisone and interferon gamma by 2.8 and 2.1 times.[10] The results of this study have inspired subsequent research.

LADD involves controlled, selective epidermal and dermal disruption to allow penetration and absorption of topical drugs and macromolecular drugs.[9] In dermatological clinics, LADD has been used to treat a variety of conditions, including light damage, scarring, tumors, vitiligo and other numerous indications.[11,12] However, most studies on LADD have come from animal or in vitro models. There is still much to learn about the applicability of LADD in humans, and practitioners may face new safety concerns associated with this form of treatment. Challenges in predicting efficacy and safety of LADD include the unpredictability of drug dose and possible systemic toxicity, variability in absorption, induction of local and systemic hypersensitivity reactions, and inconsistencies in treatment regimen.[13]

The main mechanism of lattice LADD is the focal photothermal effect: laser is used to punch vertical channels deep into the dermal layer of the skin to promote drug transdermal absorption.[9] This characteristic can be used to treat many skin diseases with unsatisfactory effect of single external drugs. Not only can it be used to assist the transmission of some immunosuppressants and reduce adverse reactions brought by systemic absorption, but the degree of laser-assisted drug transport can also be controlled by adjusting energy and density. According to the absorption of moisture to laser wavelength and whether the skin tissue undergoes vaporization or stripping., the laser can be divided into ablative fractional laser (AFL) and non-ablative fractional laser (NAFL).[14,15] This characteristic can be used to treat many skin diseases that have had unsatisfactory results with single external drugs.

Background information

Administering drugs through the dermal route is frequently challenging because of the skin's external barrier. This barrier consists of the cuticle and the tight junction.[16,17] In the 1990s, investigators demonstrated that the transdermal bioavailability of topical drugs was approximately 1–5% of the applied dose. Some drugs faced challenges penetrating the skin to reach deeper targets, limiting their effectiveness and leading to unsatisfactory therapeutic outcomes.[10,18] On the other hand, although systematic administration may be more easily utilized by the body, it comes with the drawback of potential side effects and the mentioned influence on the skin through dose factors. It is essential to carefully consider the balance between therapeutic benefits and potential adverse effects when choosing a method of medication administration. For a topical substance to penetrate the skin, there are three pathways: intercellular movement through intercellular space, intracellular movement and intracellular movement through cellular water pores, as well as infiltration through follicular and glandular structures.[13,19]

Enhancing drug delivery: Insights into common AFL

Laser activated drug penetration technology is divided into complete ablation technology and partial ablation technology. In addition to ablative mechanisms that promote drug absorption, non-ablative lasers also help improve skin drug delivery. Laser modes using surface skin ablation as a drug osmotic enhancement mechanism include excimer (193 nm), Nd: YAG (355,532,1064, or 1320 nm), Er: YAG (2940 nm), and CO2 laser (10,600 nm). YAG and CO^2 laser are the most popular laser drug delivery methods.[8] Common AFL mainly include Er: YAG laser (wavelength 2940 nm) and CO^2 laser (wavelength 10 600 nm), whose wavelength can be highly absorbed by water. Traditional exfoliating laser is used to exfoliate the epidermis in a continuous manner, but it is easy to cause postoperative scar, erythema and abnormal pigment.[5] AFL strips the epidermis in the form of a dot array. It divides a laser beam into tiny laser

beams (the size of the laser spot is measured in microns) that penetrate the cuticle of the epidermis and reach the dermis, instantly removing dead tissue and creating tiny vertical channels corresponding to the beam. Surrounding it are thin layers of thermally solidified tissue that form microscopic treatment zones (MTZs). The structure provides a channel for the transport of external drugs. MTZs are surrounded by healthy skin tissue, which greatly reduces the time (1–2 days) required for the skin to return to normal barrier function after dot laser treatment.[12] Hsiao et al.[20] used conventional CO^2 laser and lattice CO^2 laser, respectively, to assist the transdermal transmission of amino potassium cyclitic acid, and compared their transdermal permeability. It was found that the two laser treatments promoted the transdermal penetration of amino potassium to a similar degree.[20] However, under the same energy, dot matrix CO^2 laser has much less damage to skin than conventional CO^2 laser.[20] In laser-skin interactions, three mechanisms are involved in enhancing drug delivery: direct ablation, light-wave mechanism and photothermal effect.[21] Partial ablation breaks the skin barrier through the formation of micropores. The drug delivery molecule is then released from the carrier into the microchannel. These drugs mainly accumulate in microchannels, forming reservoirs for further diffusion. The formation of microchannels increases the diffusion area and makes the infiltration efficiency higher. The drug spreads vertically into the deeper layers of the skin. This delivery into deeper layers of the skin results in increased healing ability. In addition to vertical diffusion, drugs can also spread laterally to surrounding tissues. Light waves, which are unipolar compression waves, can be generated by various methods, not limited to lasers. The wave can penetrate the epidermis temporarily without stratum corneum (SC) ablation.[22] Photomechanical wave induced intracellular lipid destruction and lacunar dilation allow drugs to enter the deep layer of the skin. The intensity of the laser absorbed by water can be converted into heat. This phenomenon is especially important for carbon dioxide lasers.[23] The photothermal effect destroys the skin barrier performance, allowing the drug to easily permeate the skin.

Enhancing drug delivery: Insights into common NAFL

Common NAFL wavelengths include 1440 nm, 1550 nm and 1565 nm. NAFL can also provide channels for drug delivery by producing MTZs similar to AFL. The difference is that the water uptake of the laser wavelength is less, so the MTZs are not caused by vaporizing strips of cuticle, but by normal cascading corneous layer forming in the thermal damage of columns, producing the microscopic epidermal necrosis, dermal collagen degeneration and severely damaged skin barrier function.[14] Compared with AFL, NAFL significantly reduced patients' discomfort and shortened postoperative recovery time. Lim et al.[5] investigated the transdermal absorption of amino acid after pretreatment with a wavelength of 1550 nm erbium glass laser. The results showed that ALA penetration was significantly increased in NAFL-treated skin compared to untreated areas.

Factors affecting laser-assisted drug transdermal delivery

The density of the channel

It has been found that pore density plays an important role in laser-assisted drug transdermal absorption. Bachhav and colleagues[24] used Er: YAG laser to study the effect of channel density on the cumulative osmotic effect of lidocaine in pigs. Under a certain energy, the number of channels is set as 0, 150, 300, 450 and 900 per 3 cm_2 respectively. The results showed that increasing the number of channels did increase the cumulative penetration of lidocaine, but there was no statistical difference in the penetration degree of lidocaine when the number of channels was 450 and 900 at 6 h or 300, 450 and 900 at 24 h. Therefore, it is speculated that there is a "minimum pore density", at which the cumulative permeability of the drug can reach a peak. On this basis, even if the pore density is increased, the permeability of the drug will not increase.[24]

The depth of the channel

Bachhav et al.[24] after gradually increasing the laser energy, used confocal scanning laser and standard microscope to observe the pig skin samples. It was found that the larger the laser energy was, the deeper the pores were generated. However, when the pore density was constant, increasing the energy could not improve the cumulative permeability of lidocaine. Christina et al.[25] also reached the same conclusion through research: they used CO^2 dot array laser combined with amino acid to study the degree of transdermal penetration of Yorkshire pig skin. It was found that the intensity of fluorescent substances produced in all layers from superficial to deep skin was similar despite different energies being applied at the same time. That is, the depth

of the hole created by the laser penetrating the skin does not affect the penetration and concentration of the drug.

Application of laser-assisted transdermal drug delivery

Actinic keratosis

Togsverd-Bo et al.26 evaluated laser-assisted solar photodynamic therapy (PDT) with methyl ALA as a drug for organ transplantation in patients with actinic keratosis. Sixteen patients were divided into four treatment groups: laser + heliostatic PDT, heliostatic PDT, conventional PDT and single laser therapy. The results showed that after three months of treatment, the complete reaction rate of the combined laser and daylight PDT was 74%. The proportion was higher than that of daylight PDT group (46%), conventional PDT group (50%) and laser group (5%). Eleven of the patients reported no pain and five reported minimal to moderate pain.

Bowen's disease

Twenty-one patients with Bowen's disease participated in a clinical study of erbium-lattice laser-assisted photodynamic therapy.[27] It was found that the effective rate of laser assisted PDT was up to 94%, while that of standard PDT was (73%). The recurrence rate was 7% in the laser-assisted group and 32% in the non-laser group. There was no significant difference in appearance and safety between the two groups.

Stubborn psoriasis

Laser-assisted drug absorption also helps to improve stubborn psoriasis lesions.[28] Five patients received laser therapy followed by topical calcium potriol ointment. The psoriasis PASI (psoriasis area and severity index) was 10–11 before treatment, but the score decreased to 4–5 after routine topical treatment with calcium potriol ointment. After lattice laser treatment, PASI scores in the topical group could be reduced to 2–3. The side effects of laser therapy are limited to pigmentation, which may resolve after three months.

Basal cell carcinoma

Laser-assisted transdermal therapy is a method of treating basal cell carcinoma that involves the use of lasers to remove cancerous cells. The laser is used to destroy the cancerous cells while leaving the surrounding healthy tissue intact. This method has been shown to be effective in treating basal cell carcinoma.[29,30]

Azzopardi et al.[31] discuss the use of laser-assisted transdermal therapy in combination with methyl aminolevulinic acid (a photosensitizing agent) for the treatment of basal cell carcinoma. The study is the largest study in this regard and reports a 5 year follow up of 100 patients or so, where the success rate is 93.6% for basal cell carcinoma.[31] It provides evidence for the effectiveness of laser-assisted transdermal therapy in combination with methyl aminolevulinic acid for the treatment of basal cell carcinoma. Twenty-eight patients[32] were treated with CO^2 dot matrix laser assisted 5-FU for superficial basal cell carcinoma and squamous cell carcinoma. After 10 m J laser irradiation in the lesion area, the histological clearance rate of basal cell carcinoma and squamous cell carcinoma (5%) was 71% and 100%, respectively, and the patients could tolerate the local stimulation.

Deep hemangioma

Nine children aged one to six months with deep hemangioma were treated with CO^2 dot laser combined with 5% timolol.[33] After treatment, there were four cases with abnormal therapeutic effect (44.4%), four cases with good reaction (44.4%) and one case with moderate reaction. A recent study reinforces these findings; It investigated the treatment scores of 30 deep IHs at Er: YAG laser application at two-week intervals and subsequent local occlusion application at 0.5%, four times daily for 30 min, 24 weeks.[34] Of these patients, 76.7% had excellent regression, 13.3% had good regression, and 10% had moderate regression. Therefore, dot array laser assisted drug transdermal absorption may be a safe and effective treatment for deep hemangioma.

Stretch marks

Treatment of distention marks remains a challenge for dermatologists. Issa et al.[15] used exfoliative dot matrix radiofrequency combined with 0.05% retinoic acid ointment and sound pressure ultrasound to treat the white phase dilatation of breast. Results showed that all patients experienced significant improvement with fewer side effects and high patient satisfaction.

Local anesthesia

Many dermatological treatments need to be done under local anesthesia, and a single external application of anesthetics requires a long encapsulation time and the effect is not very satisfactory. Arne et al.[35] combined two commonly used local anesthetics with ablative lattice laser respectively: (1) Attecaine hydrochloride 40 mg/mL + epinephrine solution (AHES solution); and (2) Lidocaine 25 mg /g + 25 mg /g ointment (EMLA ointment) was applied to the skin, and their osmotic effect and anesthetic effect were evaluated. The results showed that AHES solution anesthesia after dot-array laser pretreatment can produce anesthesia effect in 10 min with low parameter setting, greatly reducing anesthesia time and pain. The anesthesia effect of AHES solution was better than that of EMLA ointment after combined dot array laser treatment.

Refractory keloid

Topical or intradermal hormone injections have long been considered the gold standard for treating keloids. A retrospective study was conducted to evaluate the efficacy of a wavelength of 2 940 nm dot array laser combined with betamethasone ointment in the treatment of keloid.[36,37] Results showed that the average response rate was 50%, especially for hypertrophic scar formation after acne (response rate was 77%), and the average patient satisfaction rate was 70%.

Hypertrophic dermatitis

Neurodermatitis, chronic eczema and other hypertrophic dermatitis have complex etiology and long course of disease, which are difficult to cure. Although there are many therapeutic methods in clinics, the therapeutic effect is not obvious. One treatment of chronic eczema and neurodermatitis was stripping erbium laser combined with topical hormone.[2,38] The treatment course was three weeks, and the curative effect was observed 1, 2 and 3 weeks after operation. The results showed that 35 patients in the combined treatment group were cured, 38 cases were effective, the cure rate was 87.5%, the effective rate was 97.5%. Therefore, lattice laser combined with external hormone treatment of chronic eczema, neurodermatitis significant effect.

Alopecia

Alopecia, a scalp hair follicle disease, has a high incidence and is difficult to treat. Hair follicles are located in the dermis of the skin, and the therapeutic effect of single external drug is not ideal. Laser ablation allows local drugs to be efficiently delivered to and uniformly distributed in the dermis.[34] Fractionated CO^2 laser combined with triamcinolone acetonide spray (10 mg/mL) was used to treat 10 patients with refractory alopecia areata. Of the eight patients who completed treatment, seven had a complete recovery in the treated area.[39] Forty-five patients with male androgenic alopecia were treated with CO^2 graded laser combined with minoxidil, CO^2 graded laser alone or minoxidil alone. The effect is best when ablative fraction CO^2 laser is used alone or combined with minoxidil. This study provides an experimental basis for the treatment of alopecia with laser assisted topical drugs in clinic.

Vitiligo

The efficacy of topical tacrolimus ointment was enhanced by CO^2 dot matrix laser in 45 patients with vitiligo.[40] The skin color improvement was 51% in the laser-assisted group, but only 20% in the non-laser control group. In the laser-assisted group, 52 of 65 patients had rehyperpigmentation in the lesions, which was higher than that in the control group (44/80).

Dynamic wrinkles

Expression muscle injection of Botox neurotoxin is used to reduce dynamic wrinkles. Gart et al.[41] studied the transdermal delivery of CO^2 dot matrix laser-assisted botulinum toxin, a large molecule drug, and found that CO^2 dot matrix laser formed micropores with a depth of about 50μm on the skin surface. The effect of laser assisted botulinum toxin external use group on wrinkles was better than that of laser alone use group, and the subjects in the laser group had higher satisfaction. No obvious side effects were observed.

Other applications

In addition, LADD is not only widely used in the above fields, but also shows excellent application prospects in other aspects.[42] Firstly, it has shown potential for enhancing wound healing by delivering growth factors, antimicrobial agents, or other wound healing-promoting substances directly to the site of the wound. It can also be used for the treatment of hyperpigmentation conditions, such as melasma or post-inflammatory hyperpigmentation.[43] By delivering

depigmenting agents, such as hydroquinone or kojic acid, directly to the affected skin, LADD can help reduce the appearance of dark spots or patches. Furthermore, it can aid in the treatment of nail fungal infections (onychomycosis) by enhancing the delivery of antifungal medications to the nail bed. This approach can improve the penetration of the drugs and increase their efficacy in combating the infection.[44] LADD has shown promise in the treatment of pruritus, a common symptom associated with various skin conditions. By delivering anti-itch medications directly to the affected areas, LADD can provide targeted relief and reduce itching sensations.[45] In addition, Junsuwan was treated patients with botulinum toxin type A (BTX-A) for primary palmar hyperhidrosis.[13,46] Thus, Fractional CO^2 laser enhanced transmission of BTX-A, resulting in a reduction in sweat volume. The results show that the method has a good clinical effect.

LADD safety: Systemic reactions and toxicity

LADD has been used to deliver analgesics, antineoplastic drugs and even bone marrow stem cells into systemic circulation.[18,47] Correspondingly, drug delivery enhancement of pores or channels created by the laser raises concerns about systemic toxicity, especially when treating larger skin areas. Laser preconditioning purposefully destroys the epidermis and cuticle, thereby facilitating drug entry into the dermis and its vascular system. According to Fick's diffusion law, the rate of diffusion of a substance is directly proportional to its concentration gradient. Therefore, careful consideration of drugs and dosages is essential for effective diffusion. Marra et al.[48] reported a case of lidocaine poisoning of the face and neck pretreated with 30% lidocaine after fractional photothermal decomposition using a 1550 nm diode pumped erbium fiber laser. Subsequent clinical studies showed that no systemic toxicity was found after 6% lidocaine was applied to the whole face with CO^2 or Er: YAG laser, although serum lidocaine levels were detected.[49] In addition, Tian and colleagues[50] studied the application of fractional Er: YAG laser pretreatment in increasing the analgesic effect of compound lidocaine cream and noted positive results without systemic toxicity. But only 3-4 cm^2 of skin were treated.[50] These studies showed that lidocaine was toxic after fractional photothermal decomposition.

Potential hazards and limitations

In the process of determining the safety and efficacy of transdermal drug delivery, there are still many unknown factors worth further exploration. Therefore, it is prudent to retain LADD in the topical body surface area, use drugs or products suitable for topical injection, or use topical compounds of as pure a formulation as possible. It is also prudent for physicians to use a dose not higher than the intradermal dose, bearing in mind that even intradermal injections can produce systemic side effects, such as Cushing's reaction after steroid treatment in cicatricial lesions.[51] Finally, clinicians should be aware of the systemic side effects and toxic doses of all drugs used for LADD. Therefore, in a known therapeutic area and assuming 100% absorption at a standard dose, clinicians can confidently apply the drug and any systemic absorption will be within the therapeutic and safety range of the drug. Currently, some drugs, especially hydrophilic molecules and macromolecules, have limited skin penetration problems, which can be solved with laser aid. This effect has led to the wider use of local administration. As laser can significantly increase the accumulation of drugs in the skin, it is expected to improve the treatment efficiency of skin diseases. Most LADD studies have focused on in vitro or animal platforms. Most patients who require laser-assisted intervention have skin lesions with impaired barrier function. The penetration enhancement effect of laser on skin lesions can be reduced. How lasers can still effectively enhance drug penetration of diseased skin should be understood in the near future. Of course, many clinical trials have demonstrated the effect of laser-assisted drug administration on the treatment of skin diseases, however, some clinical studies lack appropriate controls and the number of patients is limited. In order to determine the efficacy of laser-assisted drugs, it is urgent to design clinical trials carefully in the future.

The introduction of compact, portable laser devices has revolutionized the field of LADD, enabling widespread use in outpatient clinics. These portable devices have overcome the inconvenience associated with larger lasers, making it easier to administer LADD treatments in non-hospital settings. With the combined efforts of biomedical and mechanical engineering experts, it is necessary to further develop small devices that are convenient for application. Non-ablative laser enhanced drug delivery is rarely used in clinical studies. Non-ablative laser

has obvious advantages because it has little damage to skin surface.

Discussion

Cuticle barrier is the main barrier to percutaneous absorption of topical drugs. There have been many studies using various methods to destroy the cuticle to enhance the penetrating effect of topical drugs, including ionization, low-frequency ultrasound, point-like acupuncture, repeated adhesive tape, etc. However, these methods have a variety of disadvantages, such as uncontrollable depth, poor repeatability, unknown side effects.[24,52] By adjusting different parameters, dot array laser can point strip tissues at different depths. Using laser that penetrates only the cuticle and superficial epidermis can increase the transdermal absorption of drugs and avoid other side effects.[37] Because the penetration depth is shallow and the repair speed is fast, skin trauma will not be caused. There are no visible erythema, edema and other inflammatory reactions at the treatment site, and no other side effects will be caused.

Lattice laser parameters, including laser wavelength, laser energy, MTZ density and aperture radius, have a great impact on the efficiency of drug transdermal absorption. In addition, the physical and chemical properties of the drug itself, including molecular weight, lipophilicity, ionization properties and whether there is a nanoparticle carrier in the spatial structure, also have an impact on the drug transdermal efficiency. To optimize this parameter and find a higher and more stable laser-assisted drug transdermal system is worth further exploring and expanding its advantages.

The waveform of a laser pulse is generally not as important as its wavelength in determining its effectiveness for a particular application. However, the waveform can affect the way that energy is delivered to the target and can have an impact on the efficiency of the laser. Superpulsed lasers can emit several thousand bursts of power per second, with each burst lasting only a few nanoseconds. The waveform of these lasers is typically described as a "shark-tooth" pattern. While this waveform has been associated with an increased risk of burns in some applications, it may be more effective for other applications such as cancer treatment. In terms of ablative works, such as cancer treatment, the waveform of the laser pulse may be less important than other factors such as the fluence (energy per unit area) and pulse duration. LADD is an increasingly studied and applied methodology for drug delivery. It has been used in a wide variety of clinical applications.

Most studies on dot-matrix laser-assisted drug transdermal penetration focus on in vitro or on animals, and generally use complete and healthy skin to evaluate the effect of laser assisted dermal penetration. However, in clinical practice, most skin patients requiring dot-matrix laser-assisted drug administration have various functional disorders in the skin lesions, and the effect of dot-matrix laser-assisted drug transdermal penetration may be changed in these skin lesions. At present, many clinical studies have demonstrated the therapeutic effect of LADD on skin diseases, but there are also problems such as low total number of patients (less than 100) and lack of appropriate control group. In addition, the cellular and molecular mechanisms of the laser-assisted drug osmosis mode remain unclear, and further efforts are needed to elucidate the effect of dot matrix laser irradiation on cuticle and keratinocytes.

Compared with other methods, dot array laser has more advantages in assisting the transdermal absorption of macromolecules in a less invasive way. Compared with traditional laser, dot array laser causes less damage to the skin and can restore the skin barrier function more quickly, so it is increasingly used to assist drug delivery. At present, many basic studies have proved the effectiveness and safety of dot array LADD, and this method needs to be further applied in clinical treatment of diseases in the future.

Conclusions

The prospect of topical application of therapy, bypassing the gastrointestinal and venous pathways, is an attractive approach that may have fewer systemic side effects. However, when administered through its intended route, clinicians can expect to be relatively reliable in dose and effect, thanks to the rigorous pharmacological studies and oversight that lead to the continued production of drugs and their vectors. This consistency between patient and doctor is a luxury for LADD, not a necessity. The efficacy and safety of LADD depend on the type of laser, the laser setting, the size of the treatment area, the biology of the treatment area, and the nature and concentration of the drug used. The clinician must have a firm grasp of the expected adverse effects of laser ablation, as well as the local and systemic effects of the drug or compound. For LADD to make a seamless transition from the laboratory to clinical practice, further research

is needed to illuminate nuances and knowledge gaps.

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ORCID iD

Fuyang Wang https://orcid.org/0000-0001-9773-8666

References

1. Kakar P, Li Z, Li Y, et al. Laser facilitates week-long sustained transdermal drug delivery at high doses. *J Control Release* 2020; 319: 428–437.
2. Sklar LR, Burnett CT, Waibel JS, et al. Laser assisted drug delivery: a review of an evolving technology. *Lasers Surg Med* 2014; 46: 249–262.
3. Nieboer MJ, Meesters AA, Almasian M, et al. Enhanced topical cutaneous delivery of indocyanine green after various pretreatment regimens: comparison of fractional CO^2 laser, fractional Er:YAG laser, microneedling, and radiofrequency. *Lasers Med Sci* 2020; 35: 1357–1365.
4. Wenande E, Olesen UH, Nielsen MM, et al. Fractional laser-assisted topical delivery leads to enhanced, accelerated and deeper cutaneous 5-fluorouracil uptake. *Expert Opin Drug Deliv* 2017; 14: 307–317.
5. Lim HK, Jeong KH, Kim NI, et al. Nonablative fractional laser as a tool to facilitate skin penetration of 5-aminolaevulinic acid with minimal skin disruption: a preliminary study. *Br J Dermatol* 2014; 170: 1336–1340.
6. Waibel JS, Wulkan AJ and Shumaker PR. Treatment of hypertrophic scars using laser and laser assisted corticosteroid delivery. *Lasers Surg Med* 2013; 45: 135–140.
7. Taudorf EH, Lerche CM, Vissing AC, et al. Topically applied methotrexate is rapidly delivered into skin by fractional laser ablation. *Expert Opin Drug Deliv* 2015; 12: 1059–1069.
8. Lee WR, Shen SC, Aljuffali IA, et al. Erbium-yttrium-aluminum-garnet laser irradiation ameliorates skin permeation and follicular delivery of antialopecia drugs. *J Pharm Sci* 2014; 103: 3542–3552.
9. Erlendsson AM, Doukas AG, Farinelli WA, et al. Fractional laser-assisted drug delivery: active filling of laser channels with pressure and vacuum alteration. *Lasers Surg Med* 2016; 48: 116–124.
10. Nelson JS, McCullough JL, Glenn TC, et al. Mid-infrared laser ablation of stratum corneum enhances in vitro percutaneous transport of drugs. *J Invest Dermatol* 1991; 97: 874–879.
11. Omland SH, Wenande EC, Svane IM, et al. Laser immunotherapy: A potential treatment modality for keratinocyte carcinoma. *Cancers (Basel)* 2021; 13: 5405.
12. Prignano F, Bonciani D, Campolmi P, et al. A study of fractional CO^2 laser resurfacing: the best fluences through a clinical, histological, and ultrastructural evaluation. *J Cosmet Dermatol* 2011; 10: 210–216.
13. Mahmoud BH, Burnett C and Ozog D. Prospective randomized controlled study to determine the effect of topical application of botulinum toxin A for crow's feet after treatment with ablative fractional CO2 laser. *Dermatol Surg* 2015; 41: S75–S81.
14. Bedi VP, Chan KF, Sink RK, et al. The effects of pulse energy variations on the dimensions of microscopic thermal treatment zones in nonablative fractional resurfacing. *Lasers Surg Med* 2007; 39: 145–155.
15. Issa MC, de Britto Pereira Kassuga LE, Chevrand NS, et al. Transepidermal retinoic acid delivery using ablative fractional radiofrequency associated with acoustic pressure ultrasound for stretch marks treatment. *Lasers Surg Med* 2013; 45: 81–88.
16. Ibrahim O, Wenande E, Hogan S, et al. Challenges to laser-assisted drug delivery: applying theory to clinical practice. *Lasers Surg Med* 2018; 50: 20–27.
17. Chuang SY, Lin YK, Lin CF, et al. Elucidating the skin delivery of aglycone and glycoside flavonoids: How the structures affect cutaneous absorption. *Nutrients* 2017; 9(12): 1304.
18. Alegre-Sanchez A, Jimenez-Gomez N and Boixeda P. Laser-assisted drug delivery. *Actas Dermosifiliogr (Engl Ed)* 2018; 109: 858–867.
19. Ali FR and Al-Niaimi F. Laser-assisted drug delivery in dermatology: from animal models to clinical practice. *Lasers Med Sci* 2016; 31: 373–381.
20. Hsiao CY, Sung HC, Hu S, et al. Fractional CO2 laser treatment to enhance skin permeation of tranexamic acid with minimal skin disruption. *Dermatology* 2015; 230: 269–275.
21. Lin CH, Aljuffali IA and Fang JY. Lasers as an approach for promoting drug delivery via skin. *Expert Opin Drug Deliv* 2014; 11: 599–614.
22. Wong TW. Electrical, magnetic, photomechanical and cavitational waves to overcome skin barrier for transdermal drug delivery. *J Control Release* 2014; 193: 257–269.
23. Baleg SM, Bidin N, Suan LP, et al. The effect of CO2 laser treatment on skin tissue. *J Cosmet Dermatol* 2015; 14: 246–253.
24. Bachhav YG, Summer S, Heinrich A, et al. Effect of controlled laser microporation on drug transport kinetics into and across the skin. *J Control Release* 2010; 146: 31–36.
25. Haak CS, Bhayana B, Farinelli WA, et al. The impact of treatment density and molecular weight for fractional laser-assisted drug delivery. *J Control Release* 2012; 163: 335–341.
26. Togsverd-Bo K, et al. Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients A randomized controlled trial. *Br J Dermatol* 2015; 172: 467–474.
27. Ko DY, Kim KH and Song KH. A randomized trial comparing methyl aminolaevulinate photodynamic therapy with and without Er:YAG ablative fractional laser treatment in Asian patients with lower extremity Bowen disease: results from a 12-month follow-up. *Br J Dermatol* 2014; 170: 165–172.
28. Li R, et al. 2940-nm Er: YAG fractional laser enhanced the effect of topical drug for psoriasis. *Lasers Med Sci* 2017; 32: 1393–1397.
29. Ahluwalia J, Avram MM and Ortiz AE. The evolving story of Laser therapeutics for basal cell carcinoma. *Dermatol Surg* 2020; 46: 1045–1053.
30. Kash N and Silapunt S. Laser therapy for the treatment of basal cell carcinoma. *Basal Cell Carcinoma: Advance Treat Res* 2020: 213–232.

31. Azzopardi EA, Abdelrahman W, Azzopardi E, et al. Treatment of cutaneous basal cell carcinoma with combined laser extirpation and methyl aminolevulinic acid: five-year success rates. *Ann R Coll Surg Engl* 2021; 103: 263–271.
32. Nguyen BT, et al. Treatment of superficial basal cell carcinoma and squamous cell carcinoma in situ on the trunk and extremities with ablative fractional laser-assisted delivery of topical fluorouracil. *J Am Acad Dermatol* 2015; 72: 558–560.
33. Ma G, Wu P, Lin X, et al. Fractional carbon dioxide laser-assisted drug delivery of topical timolol solution for the treatment of deep infantile hemangioma: a pilot study. *Pediatr Dermatol* 2014; 31: 286–291.
34. Sun L, Wang C, Cao Y, et al. Fractional 2940-nm Er:YAG laser-assisted drug delivery of timolol maleate for the treatment of deep infantile hemangioma. *J Dermatolog Treat* 2021; 32: 1053–1059.
35. Meesters AA, Bakker MM, de Rie MA, et al. Fractional CO2 laser assisted delivery of topical anesthetics: a randomized controlled pilot study. *Lasers Surg Med* 2016; 48: 208–211.
36. Elsaie ML. Update on management of keloid and hypertrophic scars: a systemic review. *J Cosmet Dermatol* 2021; 20: 2729–2738.
37. Truong K, Prasidha I and Wain T. A systematic review of randomised controlled trials investigating laser assisted drug delivery for the treatment of keloid and hypertrophic scars. *Lasers Med Sci* 2023; 37: 47–59.
38. Klifto KM, Asif M and Hultman CS. Laser management of hypertrophic burn scars: a comprehensive review. *Burns Trauma* 2020; 8: tkz002.
39. Majid I, Jeelani S and Imran S. Fractional carbon dioxide Laser in combination with topical corticosteroid application in resistant alopecia areata: a case series. *J Cutan Aesthet Surg* 2018; 11: 217–221.
40. Chen W, et al. Preliminary study on the treatment of vitiligo with carbon dioxide fractional laser together with tacrolimus. *Lasers Surg Med* 2018; 50: 829–836.
41. Gart MS and Gutowski KA. Overview of botulinum toxins for aestheticuses. *Clin Plast Surg* 2016; 43: 459–471.
42. Alegre-Sánchez A, Jiménez-Gómez N and Boixeda P. Laser-Assisted drug delivery. *Actas Dermosifiliogr (Engl Ed)* 2018; 109: 858–867.
43. Ng WHS and Smith SD. Laser-assisted drug delivery: a systematic review of safety and adverse events. *Pharmaceutics* 2022; 14: 2738.
44. Jeong WY, Kwon M, Choi HE, et al. Recent advances in transdermal drug delivery systems: a review. *Biomater Res* 2021; 25: 24.
45. Wenande E, Erlendsson AM and Haedersdal M. Opportunities for laser-assisted drug delivery in the treatment of cutaneous disorders. *Semin Cutan Med Surg* 2017; 36: 192–201.
46. Junsuwan N, Manuskiatti W, Phothong W, et al. Fractional CO(2) laser-assisted Botulinum toxin type A delivery for the treatment of primary palmar hyperhidrosis. *Lasers Med Sci* 2021; 36: 233–236.
47. Fang JY, Liu PF and Huang CM. Decreasing systemic toxicity via transdermal delivery of anticancer drugs. *Curr Drug Metab* 2008; 9: 592–597.
48. Marra DE, Yip D, Fincher EF, et al. Systemic toxicity from topically applied lidocaine in conjunction with fractional photothermolysis. *Arch Dermatol* 2006; 142: 1024–1026.
49. Oni G, Rasko Y and Kenkel J. Topical lidocaine enhanced by laser pretreatment: a safe and effective method of analgesia for facial rejuvenation. *Aesthetic Surg J* 2013; 33: 854–861.
50. Tian T, Luo Y, Jiang T, et al. Clinical effect of ablative fractional laser-assisted topical anesthesia on human skin: a randomized pilot study. *J Cosmet Laser Ther* 2016; 18: 409–412.
51. Fredman R and Tenenhaus M. Cushing's syndrome after intralesional triamcinolone acetonide: a systematic review of the literature and multinational survey. *Burns* 2013; 39: 549–557.
52. Waibel JS and Rudnick A. Laser-assisted delivery to treat facial scars. *Facial Plast Surg Clin North Am* 2017; 25: 105–117.

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