Laser Assisted Drug and Cosmeceutical Delivery System of the Skin

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Lasers have been used to enhance the delivery of topical agents. In laser assisted delivery, fractional technology is used in maintaining a mainstream laser method. Targeting cutaneous lesions requires precise parameters for achievement of both efficacy and safety. Facilitating systemic absorption through the skin requires deeper penetration by lasers and the retention of the agents is also an important factor. Optimization with matching the agents and proper laser channels are another ongoing challenge.

Key words

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INTRODUCTION

Skin is an originally protective organ of human body from external environment and delivering topical agent through skin needs specified conditioning. The epidermis is the major barrier to entry. Stratum corneum is composed of hydrophilic keratinocytes or corneocytes, and keratin derived from these cells. Other hydrophobic lipids including ceramics, cholesterol and free fatty acids consist extracellular matrix of the stratum corneum, resulting in unique "brick-and-mortar" structure. This findings are most important in the barrier function of the skin or the epidermis. Bypassing this layer is the rate-limiting step of absorption when a agent is topically applied. Because there are lacunae-like aqueous channels can exist in these layers, transport system is available for hydrophilic agents nevertheless the bioavailability is extremely low in lower layer of the skin.^{1,2,3}

When transepidermal transport is achievable, upper dermal structures have lower resistance to simple diffusion. Extracellular space is more larger in size, and systemic absorption happens through vascular and lymphatic plexus. Some agents (e.g. triamcinolone) can diffuse and remain in the adipose tissue.³

To enhance penetration in the epidermal layers, simple removing of stratum corneum is a way of barrier destruction. As an example tape stripping is a simple, efficient, and controllable method to remove stratum corneum for preclinical experiments,^{3,4} nonetheless it is not clinically available for most of the cases because of irritation and difficulty in recovering. Iontophoresis, sonophoresis and transfollicular positive-pressure delivery are other enhancing methods by facilitating the function of existing channels. Laser-assisted delivery (LAD) has its own property that the user can directly adjust the character of the channels, with predictable and controllable manner.

LASER'S

Wavelengths

The Absorption rate to the water and lipid determines the basic property of the channels created by laser. In laser-assisted delivery, wavelengths have been commonly used were 2,940 nm and 10,600 nm.⁴ These wavelengths make ablative or sub-ablative channels from the stratum corneum. Erbium:yttrium-aluminum-garnet (Er:YAG) laser has 2,940 nm wavelength highly absorbed in the water, which enables precise ablation and minimized heat generation into the surrounding tissues. Carbon dioxide (CO₂) laser has 10,600 nm wavelength with high absorp-

tion rate of the water and the adipose tissues. With other parameters controlled, the difference of the absorption rate determines the shape and the composition of channel walls.⁴ Recently 1,927 nm Thulium was introduced with unique histologic changes, with ablation of the epidermis with higher water concentration and coagulation formed under ablated space.⁵

Fractionation

Fractional photothermolysis is a tissue remodeling mechanism by making multiple vertical columns. For rejuvenation and other indications, fractional photothermolysis is eventually used to make debulking abnormal or aged tissues, and remodeling by remaining tissues.^{4,5,6} Meanwhile, in LAD, fractionated laser channels enables controllable delivery, by making microscopic necrotic columns (MNC). Compared to other resurfacing lasers exploiting stratum corneum or epidermis, laser fractionation can make the LAD procedure more quantitatively controllable, which is critical in clinical application.⁶

Channel size

By the difference in absorption efficiency, each wavelength makes tissue interactions resulting in different shape of the channel.^{4,5,6} With same fluence irritated, Er:YAG shows minimal penetration depth and heat diffusion. CO₂ laser makes more consistent and greater heat generation to the target and adjacent tissue. Er:YAG laser and Thulium lasers can make proportional ablation on upper layer of treatment area, meanwhile the amount of ablation is not increasing proportionally by the increase of fluences.⁷ In the MNC's by Thulium lasers underlying coagulation increases more in size by increased irradiation. Stacking pulses is another method to increase penetration depth for Er:YAG Lasers, which is not efficiently working in CO₂ and Thulium lasers because the coagulation formed from initial pulses is lack of the chromophores (water and lipid) and heat dispersion is more greater, making low efficiency to make ablative channels. It also causing unwanted tissue damage to the adjacent skin.^{6,7,8}

Channel shape

Wide, shallow channel and Narrow, deep channel can make same amount of diffusion area theoretically. Increased penetration by MNCs' total area can be understood using Fick's first law⁷

$$J = Km * Dm * \Delta C/L$$

(J, the degree of flux of molecule. Km, a reflection of the number of molecules in diffusion across a barrier. Dm,

a reflection of the inherent diffusibility of a molecule. ΔC , concentration difference of that molecule on either side of that barrier. L , the path length in the membrane or the wall).

In laser-treated skin, the increased permeability by ablative lasers increase K_m , therefore increasing overall flux of the molecule. As molecular size of the agent increases, there is greater frictional resistance and D_m decreases, decreasing overall flux.^{7,8} Heat generation by laser also has the influence on K_m and D_m . L can be different on the thickness of the coagulation surrounding wall.⁹

Wide, shallow channel and narrow, deep channel can make same amount of diffusion area theoretically. The target depth can be adjusted with a same diffusion rate, to a certain depth of the layer.

Channel numbers

The density or the rate of the spots in treatment area can determine the areas of permeation for fractional lasers. More density can make more diffusion by increased permeation area. This increase is not permanently proportional, because the maximal tissue concentration can be limited.^{10,11,12} Clinically the density of the spots is closely related to the risk of complication and the optimization for proper amount of delivery is very important.

Channel wall character

Coagulation and ablation are two main laser-tissue interactions in LAD. Many debates have been issued how the coagulative wall in MNC's act as a barrier to the diffusion or not. By simple heat generation, the extracellular space can be widened and the export channel can be altered. Dense coagulation is believed to be an obstacle for most of the agents in diffusion by making compact, degenerated protein wall. Longer pulse duration for CO₂ lasers can make char, additional barrier for LAD.⁶

OTHER FACTORS

Because ablation is believed to be a main tissue reac-

tion in making channels for LAD, other derivatives from laser-tissue interaction can influence the efficacy. Kositratna et al.¹³ reported Fibrin clots formed in the ablative channels by fractionated CO₂ lasers, resulting in blocking the passage. This change showed time-dependent manner making more than 90% of coverage of the channels in 90 minutes after laser irradiation. This result suggests the clinical protocol requires a consideration of different laser-tissue interactions can influence the efficiency in LAD. Exudate from the tissue can make negative result by diluting and washing out the agents out of the skin. Fresh 'Wet' channel by micro needling or time-elapsd channels by the laser or other energy delivery devices cannot be free from this issue.

Additional devices can be used simultaneously with LAD. Iontophoresis, sonophoresis and positive pressure injection devices has been used clinically but lack of comparison studies. Erlandsson et al reported an enhancement of LAD by combining altered application of pressure and vacuum suction. Addition of this steps induced rapid filling of the agent in the columns, enabling faster and uniform uptake.¹⁴

AGENTS

Topical steroids

Topical steroids are commonly used agents for inflammatory skin lesion and the scars. Especially body parts with thicker skin (e.g. palm and sole) and thickened lesions by lichenification makes the drug penetration Triamcinolone acetonide is a long-acting steroid can be used as a controlled releasing agents with minimal mineralocorticoid action. Because triamcinolone is only emulsified temporally to the water, usually it is delivered by the painful intra-lesional injection.

Photodynamic therapy (PDT) agents

5-aminolevulinic acid (ALA) and methylaminolevulinic acid (MAL) are two most widely used agents. Because thickened and large actinic keratosis (AK) and basal cell carcinoma (BCC) needs enough tissue concentration, LAD has been tried from early times. Other thickened

Table 1. Summary of the laser-assisted topical steroid delivery studies

Study by	Laser	Agent	Remarkable findings	Reference
Issa et al.	Fractional CO ₂	Triamcinolone acetonide	Scars in the face and the knee were nearly resolved in one to four sessions.	[15]
Waibel et al.	Fractional CO ₂	Triamcinolone acetonide	Average clinical improvement: 2.73/3.0	[16]
Yu et al.	Fractional Er:YAG	Prednisone	Significantly increased delivery dependent on the channel depth and numbers	[17]
Cavalié et al.	Fractional Er:YAG	Betamethasone	50% of median improvement of keloid lesions in 3 to 18 months	[18]

Table 2. Summary of laser-assisted PDT agent delivery studies

Study by	Laser	Agent	Remarkable findings	Reference
Foster et al.	Fractional Er:YAG	ALA	13.8-fold increase in penetration	[19]
Lee et al.	Fractional Er:YAG	ALA	3- to 260-fold increase in penetration	[20]
Haedersdal et al.	Fractional CO ₂	MAL	Significantly increased permeation in whole skin layers	[21,22]
Togsverd-Bo et al.	Fractional CO ₂	MAL	Lesion response was 20% and 29% higher in grade I and grade II-III AK's at 3 months compared to the non-LAD PDT group	[23]
Foster et al.	Conventional Er:YAG	ALA	7.3-fold increase in the penetration	[19]
Lee et al.	Fractional Er:YAG	ALA	27- to 124- fold increase in penetration	[20]
Helsing et al.	Fractional CO ₂	MAL	Lesion clearance was 42% greater compared to the non-LAD PDT group	[24]
Yoo et al.	Fractional CO ₂	MAL	100% of clearance in 90% of periungual warts	[25]
Song et al.	Fractional CO ₂	MAL	LAD reduced the incubation time for the AK's	[26]
Kim et al.	Fractional CO ₂	MAL	LAD reduced the incubation time for the Bowen's disease lesions	[27]
Lippert et al.	Fractional CO ₂	ALA	Response rate of BCC was superior by 12.5% compared to the non-LAD PDT group	[28]
Haak et al.	Fractional CO ₂	MAL	LAD reduced the incubation time for various depths	[29]

Table 3. Summary of laser-assisted cell delivery studies

Study by	Laser	Remarkable findings	Reference
Waibel et al.	Fractional CO ₂	28.5% of engrafted cells survived after 3 weeks.	[4]

Table 4. Summary of laser-assisted vaccine delivery studies

Study by	Laser	Agent	Remarkable finding	Reference
Lee et al.	Conventional Er:YAG	Lysozyme vaccine	3-fold increase in serum antibody production	[30]
Chen et al.	Fractional CO ₂	Ovalbumin vaccine	28- to 538- fold increase in serum antibody production	[31]

warty lesions can be treated with same manner. Other photodynamic agents like indocyanine green is still lack of previous reports.

Living cells

Living allogenic stem cells has been introduced for radiation induced immunosuppressed mice skin. Allogenic fibroblast with minimal antigenicity is believed to be next subject in the trial for the defective congenital skin diseases. There are still huddles for laser-assisted cell transfer, in bypassing recipient immune system and in securing cell survival in the target tissue.

Vaccines

Vaccines were tried in early years. Needle patches and other formulations are rapidly replacing device-driven delivery. LAD for vaccines requires deeper penetration depth by lasers to induce sufficient immune reaction in the tissue. Subepidermal diffusion is essential.

Topical anesthetics

Laser-assisted anesthetics delivery has been reported

to have several advantages compared to the topical application or injection. Rapid absorption can facilitated preparation time for the procedure. Avoiding multiple site injection with needles is another benefit. Saving the amount of dosage is to be considered to avoid overt systemic absorption and its complication.

Chemotherapeutic agents

Topically applied chemotherapeutic agents are used to treat precancerous, cancerous, proliferative and infectious lesions. Thickening and hyperkeratosis are common secondary changes in those lesions to abbreviate the absorption of topically applied agents. Lee et al and Gomez et al reported an universal improvement of the absorption by different, non-ablative wavelengths such as Q-switched Nd:YAG or Ruby lasers, suggesting simple mechanical or physical alteration of stratum corneum can make permeation changes, for a certain agents like 5-fluorouracil (5-FU).^{38,39}

Antialopecia drugs

Anti-alopepic agent has limited application reports.

Table 5. Summary of laser-assisted anesthetic delivery studies

Study by	Laser	Agent	Remarkable finding	Reference
Oni et al.	Fractional Er:YAG	Lidocaine	Depth-dependent increase of absorption	[32]
Koh et al.	Fractional Er:YAG	Lidocaine	2.0 to 3.5 J/cm ² were effective and safe fluence for enough effect and minimized side effect	[33]
Bachhav et al.	Fractional Er:YAG	Lidocaine	Absorption efficacy was maximum at 150 pores, without difference with larger number of pores	[34]
Meesters et al.	Fractional CO ₂	Articain hydrochloride + Epinephrine	LAD induced faster anesthesia	[35]
Meesters et al.	Fractional CO ₂	Lidocaine + Prilocaine	Formulation of the agent was suggested to have influence on LAD efficacy - Liquid was thought to be superior than a cream	[35]
Yun et al.	Conventional Er:YAG	Lidocaine	Decreased pain in full-face resurfacing with LAD pretreatment	[36]
Baron et al.	Conventional Er:YAG	Lidocaine	Decreased pain by 61% on the needle prick in 5 minutes	[37]
Singer et al.	Conventional Er:YAG	Lidocaine	Decreased pain by IV cannulation in 5 minutes	[38]

Table 6. Summary of laser-assisted chemotherapeutic delivery studies

Study by	Laser	Agent	Remarkable finding	Reference
Lee et al.	Q-switched ruby	5-FU	5- to 10- fold increase	[38]
Lee et al.	Conventional Er:YAG	5-FU	53- to 133- fold increase	[38]
Lee et al.	Conventional CO ₂	5-FU	36- to 41- fold increase	[38]
Waibel et al.	Fractional CO ₂	5-FU	Decrease in scar height, less side effect than triamcinolone acetonide	[4]
Gomez et al.	Q-switched Nd:YAG	5-FU	Significantly enhanced transepidermal influx	[39]
Taudorf et al.	Fractional Er:YAG	Methotrexate	7- to 10- fold increase, needs incubation time for saturation	[40]
Lee et al.	Conventional Er:YAG	Methotrexate	3- to 80- fold increase	[41]

Table 7. Summary of laser-assisted antialopecia drug delivery studies

Study by	Laser	Agent	Remarkable finding	Reference
Lee et al.	Conventional Er:YAG	Minoxidil	6-fold increase in hair follicle uptake	[42]
Lee et al.	Conventional Er:YAG	Diphencyprone (DPCP)	Less enhancement than minoxidil	[42]
Goo et al.	Fractional CO ₂	Nano-liposomal finasteride	1.7-fold increase	[43] [Unpublished]
Goo et al.	Fractional CO ₂	Nano-liposomal dutasteride	1.4-fold increase	[43] [Unpublished]
Goo et al.	Fractional Er:YAG	Nano-liposomal finasteride	2.4-fold increase	[43] [Unpublished]
Goo et al.	Fractional Er:YAG	Nano-liposomal dutasteride	1.8-fold increase	[43] [Unpublished]

Table 8. Summary of laser-assisted topical immunomodulator studies

Study by	Laser	Agent	Remarkable change	Reference
Lee et al.	Imiquimod	Fractional Er:YAG	0.4% imiquimod with LAD acheived same tissue concentration with 5% without LAD	[44]
Braun et al.	Ingenol mebutate	Fractional Er:YAG	Significantly more inflammatory action after 3 weeks	[45]

Current systemic agents have limitation in topical formulation. Technically, laser irradiation in the hair-bearing scalp needs special attention even with sparse hairs.

Immunomodulators

Topical immunomodulators has multiple actions on the various skin lesions. Unlike chemotherapeutic agents, immunomodulators induce host immune reaction targeting agent-bearing skin lesion, resulting in destructive

changes including apoptosis.

Cosmeceuticals

Hydrophilic vitamins and other formulas have been tried. 1,927 nm thulium laser was used for precise epidermal penetration and retention.

Laser-assisted cosmeceutical delivery is differentiated with laser-assisted drug delivery. Although the procedure is performed and supervised by the doctor, the

Table 9. Summary of laser-assisted cosmeceutical delivery studies

Study by	Laser	Agent	Remarkable finding	Reference
Trelles et al.	Fractional CO ₂	Cosmeceuticals	69% improvement in overall cosmetic outcome. Additional 10% improvement in acoustic pressure ultrasound combination Tx group.	[46]
Hsiao et al.	Fractional CO ₂	Vitamin C	Fractional CO ₂ laser showed same permeation and less side effect than conventional CO ₂ resurfacing	[47]
Waibel et al.	Fractional CO ₂	Vitamin C, E, Ferulic acid	Faster healing after fractional CO ₂ laser resurfacing	[48]
Waibel et al.	Fractional CO ₂	Vitamin C, E, Ferulic acid	Decreased side effect by fractional CO ₂ laser resurfacing, increased basic fibroblast growth factor (bFGF)	[49]

Table 10. Comparison of laser-assisted drug delivery and laser-assisted cosmeceutical delivery

	Laser-assisted drug delivery	Laser-assisted cosmeceutical delivery
Application	For damaged or diseased skin / For systemic absorption enhancement	For normal skin: Acceptable for damaged or diseased skin
Regulatory issues	Positive listing of ingredients, only for the designated indications	Negative listing, to generally normal skin condition

Table 11. Summary of laser-assisted miscellaneous agents studies reported

Study by	Laser	Agent	Remarkable finding	Reference
Lee et al.	Conventional Er:YAG	Morphine, nalbuphine, buprenorphine	10- to 35- fold increased influx	[50]
Mahmoud et al.	Fractional CO ₂	Botulinum toxin A	Significantly reduced wrinkles in Crow's feet	[4]
Bachlav et al.	Fractional Er:YAG	Diclofenac	13-fold increased influx	[51]

cosmeceuticals have different quality control standard compared to the drugs. Cosmeceuticals usually have less limitation in ingredients, which is used for healthy skin. Mostly the cosmeceuticals has additional ingredient to the effective molecules and side effects when large amount of ingredients are transferred into the skin. Any laser treatment used for the cosmeceutical delivery should have precisely controllable parameter adjustment function for epidermal permeability alteration. The quality of the cosmeceuticals should be strictly controlled.

Micellaneous

Analgesics were tried for LAD to deliver the drug systemically through the skin, avoiding multiple injections and other side effects from long-term use. Botulinum toxin for intradermal administration was also tried to avoid multiple injections.

Future formulation

Most of the previous studies has similar designs comparing the delivery efficiency of a topical agent is tested before and after using LAD. Since optimized or specially designed agents are being introduced, such as nano-sized molecules and liposomal agents enables more efficient delivery not only to the untreated skin, but also to

the laser-treated skin, reaching to deeper skin structures and systemic absorption can be facilitated.⁵³

COMPLICATION AND LIMITATION

Pain on laser treatment is most common complain as a side effect. Superficial ablation at low fluences usually enables painless treatment. For deeper ablation, local anesthesia is necessary. Anesthesia by air-cooling can significantly decrease patient discomfort.⁵² Irritation and erythema are most common complications. Prolonged swelling and dyspigmentation are following. Laser treatment can make these as a single modality, while the combination of the agents can make unexpected degree of the skin reaction. Other serious complications include scarring and general laser surgery complications.

Increased permeability achieved by LAD can make larger accumulation of drug than expected. Topical immunomodulators and chemotherapeutic agents can make serious cutaneous side effects when accumulated, and resulting in increased side effects.⁴⁵ Increased absorption of topical agent can lead to systemic toxicity, as reported with lidocaine,⁵⁴ as well as in transdermal systemic drug delivery. Similarly to systemic administration, regular checking serum level is necessary.

CONCLUSION

LAD is a powerful and useful method to enhance less-permeable agents including the drugs and the cosmeceuticals. Ablative lasers have superiority in efficiency. Controlling the side effect and the complications remains as the issues need clinical attention.

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