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Laser-Assisted Drug Delivery in Early Post-Burn Hypertrophic Scars: Review Article

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Abstract

Hypertrophic scars and keloids arise from an excessive healing process and frequently cause considerable distress to patients. Fractional ablative lasers generate tiny channels in the skin and penetrate scar tissue, prompting a natural regeneration reaction in the damaged areas.

Laser-assisted drug delivery (LADD) is a promising therapeutic technique that involves the direct application of drugs that alter scars within the scar tissue via small channels.

Burn injuries stem from numerous etiologies, with hot liquids, solids, and flames being the most common culprits. These injuries pose a significant source of morbidity and can impact on a patient's quality of life, psychosocial well-being, and socioeconomic burden. While advances in burn management have reduced mortality rates, they have also led to a growing number of patients experiencing sequelae, notably hypertrophic scars (HTSs).

An overly accelerated healing process might result in hypertrophic scars and keloids, which can sometimes cause significant patient issues. One cutting-edge technique for accurately distributing medications under the skin is laser-assisted drug delivery, or LADD. LADD has proven to be quite successful in treating burn injuries and scarring. They enable a speedy recovery, are minimally intrusive, and have a low risk of adverse consequences. Consequently, they are incorporated into certain therapy protocols with other conservative and surgical methods, which can be quite effective but also have a greater likelihood of complications.

Key Words: *Laser-Assisted Drug Delivery – Post-Burn – Hypertrophic – Scars.*

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Introduction

Hypertrophic scars and keloids arise from an excessive healing process and frequently cause considerable distress to patients. Fractional ablative lasers generate tiny channels in the skin and penetrate scar tissue, prompting a natural regeneration reaction in the damaged areas. Laser-assisted drug delivery (LADD) is a promising therapeutic technique that involves the direct application of drugs that alter scars within the scar tissue via small channels [1].

Laser technology has shown substantial effectiveness in scar therapy. Laser technology has undergone thorough investigation to determine its efficacy in treating a wide range of scars, such as those resulting from acne, surgical procedures, injuries, and keloids. However, the research on laser therapy for burn-related complications is limited and it is not generally available in most hospitals [2,3].

Over 1000 burn injury incidences per 100,000 people were reported worldwide in 2017. The necessity for dermatologists in their treatment is highlighted by the fact that most burns affected less than 20% of the body's surface area and mostly caused skin damage [4].

Burn scars can significantly affect the patients' quality of life. The presence of four contractures and deformity significantly impair functionality, diminishes mobility, and induces pain and irritation. Furthermore, the prominent emotional aspect linked to this particular injury can result in societal disapproval, particularly when the face and neck are affected, and contribute to feelings of unease, sadness, and low self-esteem [5].

In the past, several conservative methods have been used to treat burn scars, such as silicone gel, pressure therapy, corticosteroid injections, and therapeutic massages [6]. These techniques often need surgical operations, which may involve scar removal, wound closure, horizontal incisions, Z-plasty, flap techniques, or skin grafting. The text is enclosed with the tags [7].

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Burn injuries:

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The HTSs formed in this aberrant healing process are characterized by erythema, contracture, stiffness, restricted range of motion, pain, and itch. Addressing the consequences of HTSs demands significant healthcare resources. Moreover, diminished satisfaction with one's appearance harms self-esteem, resulting in psychological distress and social anxiety, motivating patients to seek treatment **[9]**.

Therapies to address scar symptoms include intralesional injections, laser-assisted drug delivery (LADD) of corticosteroids and/or 5-fluorouracil (5-FU), radiotherapy, and cryotherapy. However, the most promising treatment for HTSs is laser therapy, specifically fractional ablative CO_2 laser (FLSR), which has demonstrated effectiveness with no major adverse effects **[10]**.

Evaluation of the Scar:

Because of variations in thickness, erythema, texture, and pigmentation, burn scars often cause aberrant skin healing in over 70% of instances. Examples of burns that may need laser therapy include second- or third-degree burns, which affect the deeper layers of the dermis. Superficial burns that don't penetrate the reticular dermis seldom result in aberrant scarring and often don't cause problems **[11]**.

Scars can be categorized based on their thickness, specifically as hypertrophic, keloids, and atrophic scars. Additionally, they can be classified by their pigmentation, with some being hypopigmented and others hyperpigmented compared to surrounding healthy skin. Erythema is frequently observed, particularly in active and newly formed scars.

Therapy should be initiated and monitored after evaluating the extent of the scarring. The most prevalent method is the Vancouver Scar Scale, assessing blood vessel formation, thickness, pliability, and skin tone. The Patient and Observer Scar Assessment Scale (POSAS) is considered the most comprehensive, as it encompasses subjective symptoms like pain and itching in its assessment. Proper evaluation enables the selection of the most suitable laser for treatment. To select the correct device and settings, we need to consider the patient's characteristics, such as skin phototype and any comorbidities, as well as the location of the scar, for example, on the head, neck, or limb **[12]**.

Lasers:

Recently, lasers have revealed effectiveness in the management of burn injuries. These procedures are characterized by their minimal invasiveness, low likelihood of undesirable side effects, and quick recovery time. As a result, they are included in targeted treatment plans that involve fairly effective non-invasive methods and surgical procedures, which can offer significant benefits but also come with a noteworthy risk of complications **[13]**. Although lasers do not completely substitute surgery, they can minimize the treatment area, resulting in a decrease in postsurgical problems **[14]**.

Fractional Ablative CO2 Laser:

Fractional CO2 (FXCO2) has been utilized successfully by other groups to treat HTS. Within 6 months of treatment, all ten individuals with hypertrophic burn scarring who received fractional CO2 laser treatment shown significant improvement in their Vancouver scar scale (VSS), Patient and Observer Scar Assessment Scale (POSAS) score, and quality of life evaluations **[15]**.

Surprisingly, after just one session, a 30% decrease in scar stiffness was noted. When 40 HTS patients got fractional CO2 laser therapy during four monthly sessions, the VSS indicated a statistically significant improvement. Before and after treatment, a skin sample revealed a thinner stratum corneum, thicker epidermis, and new collagen fibrils that were well-organized in lieu of the asymmetrical collagen bands. Significantly less transforming growth factor (TGF)-b1 was expressed after laser treatment **[16]**.

A second study of ten patients with mature, hypertrophic, full thickness, burn scarring managed with a fractional CO2 laser provides more insight into the therapeutic process. Types I and III procollagen mRNA levels were significantly reduced following treatment, based on a reverse transcription polymerase chain reaction examination of fresh tissue samples (obtained both before and 48 hours after the initial treatment). This is in addition to the remarkable improvement shown as measured with VSS and POSAS **[17]**.

Following two months, the ratio of type III to type I collagen also rises in FXCO2-treated skin, suggesting that collagenogenic processes are initially suppressed and then "reset," with subsequent collagen deposition more nearly resembling the subtype proportions observed in healthy skin. Following treatment, Matrix metalloproteinases (45MMP-1) and miR-18a and miR-19a expression were also markedly increased [17]. The activity of the metalloprotease is likely to account for some or all of the CO2 laser's capacity to improve lesion pliability for both keloid and HTS [18].

Three months later, scars were treated using a fractional CO2 laser that delivered 70mJ of energy in either a single pulse or stack across three consecutive pulses. At regular intervals before and after FXCO2 therapy, the skin's functional and aesthetic characteristics, including erythema and trans-epidermal water loss, were recorded [19].

It was revealed that triple stacking of FXCO2 pulses only minimally increased the depth and width of the microthermal zone (MTZ). Surprisingly, both treatment procedures demonstrated that the skin had re-epithelialized after 48 hours, and that local inflammation indicators had reverted to baseline levels by 1 week after the surgery. As was previously established, contracture is still a dreaded and crippling result of pathological scarring that affects a joint. One group showed efficacy in treating constrictive pediatric scar contractures with an ablative micro-fractionated 600nm CO2 laser in a published case series of two kid patients [19].

Nonablative fractional lasers:

Nonablative fractional lasers induce heat damage within the dermis through distinct columns of coagulation, all while preserving the uppermost epidermal layer. This mechanism enables minimization of surface damage, and the intensity of heat applied to the skin, resulting in a shorter recovery time. The most frequently utilized type is the 1540-nm or 1550-nm erbium-doped glass (Er: glass) laser [20].

Near-infrared lasers (NAFLs) heat the skin to a temperature of around 50-70 degrees Celsius and penetrate to a shallower depth of approximately 1.8 millimeters compared to Ablative Fractional laser (AFLs). Studies investigating the 2 lasers for treating scars are scarce, and yet NAFLs result in less thermal damage, yet they are also less effective and necessitate more treatment sessions [20].

Taudorf et al. discovered a noticeable improvement in burn scars' thickness, flexibility, and texture, along with collagen normalization in histological analysis, but this advancement came with a drawback - a decrease in the effectiveness of the treatment on hypertrophic scars [21].

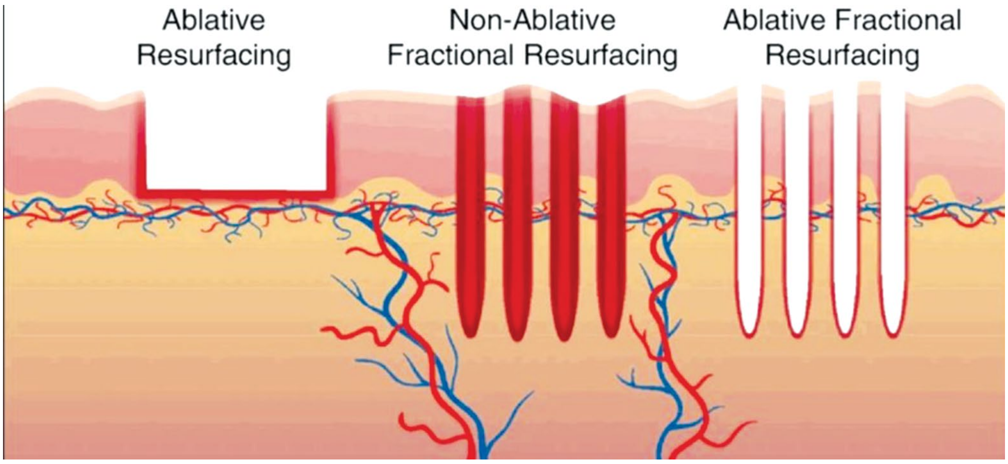

Fig. (1): Schematic figure for the zone of damage in ablative and fractional lasers [22]. Trans-Epidermal Drug Delivery (TDDS).

TDDS is a non-painful method for administering drug formulations to unblemished skin to achieve systemic medication delivery. The drug first penetrates the stratum corneum without collecting in the dermal layer, then progressing to the deeper layers of the dermis and epidermis. A medicine may be systemically absorbed by the dermal microcirculation after penetrating the dermal layer. TDD has several advantages compared to conventional pharmaceutical administration methods [23].

Ablative radiofrequency (RF) generates micro-sparks by oxygen ionisation (micro-plasma), resulting in the formation of epidermal microchannels. A low-frequency, high-pressure ultrasonography (US), termed impact US, was launched to enhance medication penetration when combined with ablative techniques. These US waves function by driving molecules through designated channels. A novel course of action is proposed, contingent upon the prior utilise of an ablative approach [24].

Jet injection is a viable method for transdermal medication administration; nevertheless, research has shown possible drawbacks, including discomfort and infection [25]. Iontophoresis and electroporation are often safe and efficient methods for augmenting the skin and cellular permeability of pharmaceuticals; nevertheless, they carry a risk of skin irritation and potential cell damage or necrosis [26].

Transdermal patches are applied to the skin and release medications by passive diffusion. They are non-invasive and safe; nevertheless, they are less efficient and may cause skin irritation and contact dermatitis. Sonophoresis is the use of ultrasound waves to augment medication absorption via the skin, using a broad spectrum of ultrasonic frequencies ranging from low (20–100 kHz) to high (2–16 MHz) to improve the skin or percutaneous permeability of pharmaceuticals. Adverse occurrences, including heat damage or burns, have been documented but were determined to be small and transient. This method is generally regarded as safe and extremely successful [27].

High-intensity focused ultrasound (HIFU) is a non-invasive therapeutic modality that has garnered significant attention in recent years for cancer therapies, including tumour ablation and targeted medication administration. HIFU employs US radiation within the frequency range of 0.8–20 MHz and an intensity of 1000–25,000 W/cm^2. HIFU plays a vital role in cancer treatment, enhancing outcomes for many malignancies, including those of the brain, breast, kidneys, liver, prostate, and rectum. In this context, HIFU was shown to enhance the aggregation and absorption of drug-loaded nanocarriers and to release the drug at the targeted site. Nonetheless, the use of HIFU technology in transdermal medication administration remains inadequately understood [28].

Microneedle devices, including Dermaroller and Dermapen, generate microtunnels ranging from 0.5 to 2.5mm in depth. Similar to lasers, the microneedling method was developed to penetrate the stratum corneum, facilitating the effective delivery of active chemicals to the skin. These microchannels impose no restrictions on the size of molecules that may traverse them. The microchannels measure in microns, but the supplied macromolecules are often in nanometers [29].

Laser-assisted drug delivery (LADD):

The standard approach for treating tiny hypertrophic burn scars involves injecting antimitotic medications, such as corticosteroids and 5-fluorouracil, directly into the scar tissue [30].

Corticosteroids and 5-fluorouracil are frequently delivered through intralesional injection using a fine needle. Nevertheless, if the medication is administered directly into the dense tissue of the scar, it has the potential to accumulate in that specific region. For instance, the authors intend to examine particular outcomes, such as tissue shrinkage, small white spots, widened blood vessels, and loss of skin color, that arise from the deliberate application of corticosteroids through injections directly into the affected area [31].

Furthermore, corticosteroids and 5-fluorouracil are rarely applied to a wider surface of the skin and are often only injected into moderate hypertrophic scars. LADD is necessary to safely and effectively apply and distribute these medicines to burn scars of varying sizes. Utilizing fractional laser treatment immediately following surgery facilitates the transportation of drugs through the outermost layer of the skin and ensures even dispersion of medication in the deeper layer of the skin. This method enables the creation of accurate and consistent columns of tissue vaporization. The use of LADD of corticosteroids into scars has been observed in multiple case series. These studies have shown that this technique improves the effectiveness of topically applied medications, as proven by other experiments conducted on animals [31]. LADD of corticosteroid is a common practice in the majority of burns hospitals [32,33].

Consequently, it raises the question of whether positive outcomes are due to the precise and evenly administered corticosteroids, 5-fluorouracil, or the laser treatment itself, which will be the main focus of our investigation [32,33].

Previous studies on administering medicines with AFL have primarily employed devices emitting fractional carbon dioxide (CO2; wavelength 10,600nm) or erbium-doped yttrium aluminum garnet (Er: YAG; wavelength 2,940nm) lasers. CO2 lasers cause more residual thermal damage per unit of energy compared to Er: YAG devices, due to their lower absorption by water at a wavelength of 10,600nm (800cm-1), in contrast to the higher absorption by water at 2,940nm (12,800 cm-1) (221) [34].

The magnitude of thermal injury is of outmost importance in the context of LADD, as it directly affects the degree of tissue coagulation, leakage, bleeding, and discomfort following exposure to AFL [35].

Nevertheless, it is not fully precise to make broad statements regarding the relative advantages of erbium -doped yttrium aluminum garnet (Er: YAG) or CO2 devices for drug administration, as both lasers can generate identical channel geometries based on the selected settings. Er: YAG and CO2 devices have facilitated direct and definitive comparisons of LADD [35].

In practice, three criteria regulate AFL-assisted delivery:

1- Channel density is a measure of the proportion of breadth and quantity of micro-channels produced per unit of skin area.

2- The channel depth is primarily dictated by the quantity of laser energy provided.

3- The coagulation zone (CZ) which is a circular region of tissue that has undergone thermal coagulation. The region surrounding certain microchannels can exhibit varying thickness.

After topical application, drugs penetrate the skin via three pathways [36]:

1- The intercellular pathway occurs entirely within the extracellular matrix. The intercellular pathway exclusively takes place within the extracellular matrix.

2- The transcellular pathway involves a direct passage across corneocytes through the intermediate extracellular space. The transcellular pathway refers to the direct passage across corneocytes and the intermediary extracellular space.

3- The appendageal pathway runs through sweat glands and hair follicles. The appendageal pathway, which traverses sweat glands and hair follicles.

Carbon Dioxide (CO2) Laser and Erbium:

The two laser devices commonly examined for LADD are the CO2 laser and the Er: YAG laser. The CO2 laser produces light with a 10,600nm wavelength, leading to cells rapidly heating up and subsequently vaporizing and coagulating. Following this, the proteins outside the cell undergo denaturation, and the collagen beneath them contracts due to the heat. Studies of scar tissue after ablative fractional CO2 laser treatment showed complete skin regeneration within 48 hours. The Er: YAG laser system operates at a wavelength of 2940nm, ensuring precise energy transfer and minimizing thermal injury to the adjacent tissue. This process fosters accelerated wound healing and the regrowth of the dermis. CO2 devices generate more extensive heat dissipation to the surrounding tissue, whereas the Er: YAG system exhibits a reduced hemostatic effect [37].

The fractional CO2 laser and the fractional Er: YAG laser show similar differences compared to their full-field counterparts, with the CO2 systems causing more noticeable residual thermal damage. Research has demonstrated that the use of fractional Er: YAG laser leads to considerably reduced residual thermal skin impairment, which in turn leads to quicker healing and lower redness following the treatment, when compared to the use of fractional CO2 laser. The Er: YAG/CO2 laser system, when utilized in a combined mode, can provide the advantageous amalgamation of ablative and coagulation effects, under appropriate circumstances. Both lasers are effectively utilized in scar therapy, resulting in positive clinical results. Both fractional CO2 and Er: YAG treatments yielded similar results, however some studies suggested that the fractional CO2 system was associated with a greater level of practical discomfort. Assessing the superiority of the two modalities is challenging because of the variation in clinical situations and the absence of a comparison research design [37].

The mechanism of ablative fractional LAAD [37] is as follows:

Ablative fractional lasers produce a laser beam with high intensity, resulting in the formation of many distinct columns of thermal damage. Ablative fractional photothermolysis (AFP) devices generate MTZs by completely vaporizing scar tissue, potentially penetrating into the deep dermis. Columns modified in structure by MTZs are surrounded by a peripheral region of thermal denaturation, which is substantial enough to cause collagen coagulation. In addition, thermal radiation triggers the formation of new collagen nuclei to enable the rearrangement of collagen. Research has shown that elevated production of heat shock proteins (HSPs) leads to an anti-inflammatory response following ablative laser therapy for scar tissue. There is also a noticeable shift in the levels of MMPs and the tissue inhibitors of metalloproteinases (TIMPs), accompanied by an increase in growth factor expression. The improvement in the visual appearance of scars is linked to the unique production of anti-inflammatory compounds and cytokines. MTZs enhance the absorption of topically administered medications and other biologically active substances by serving as an alternate route for delivering pharmaceuticals via the skin.

Post-AFXL therapy, the appearance of scars is often enhanced. This is likely due to the removal of a portion of the fibrotic scar, resulting in a partial restoration of the collagen's structure and composition. Waibel evaluated fifteen individuals with burns, injuries, or trauma resulting in hypertrophic scars. Each patient received up to five therapies of CO2-AFXL (10–15% density) utilising the Ultra Pulse Lumenis machine, followed by the administration of topical triamcinolone (10 or 20mg/mL) [38]. Six months post-final treatment session, 23 blinded evaluators noted enhancements in texture, hypertrophic degree, and dyschromia [39].

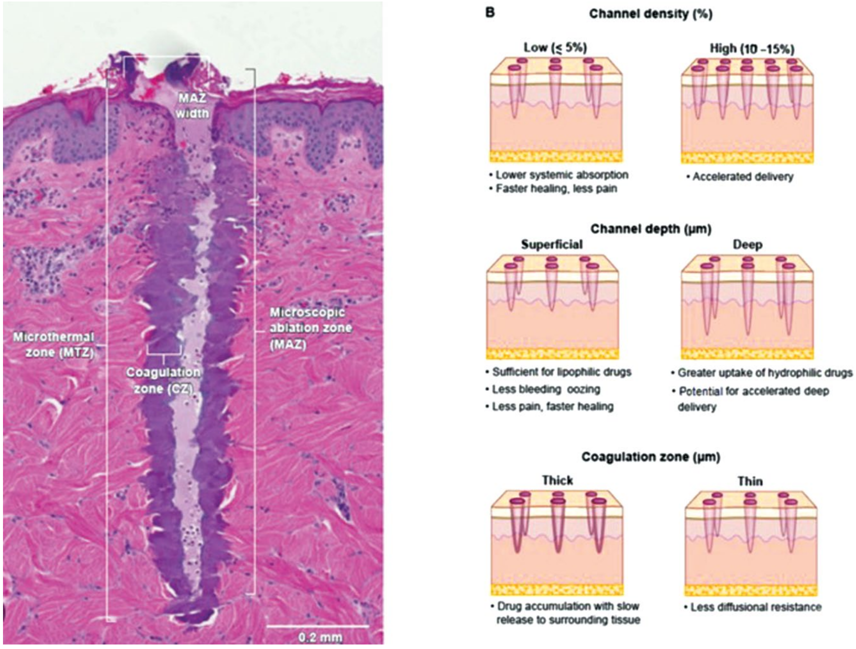

Fig. (2): Laser channel morphology – definitions and impact on topical drug delivery **[36]**.

In conclusion, while Laser-Assisted Drug Delivery (LADD) has demonstrated promising efficacy in the treatment of post-burn hypertrophic scars, offering benefits such as enhanced drug penetration and reduced scar formation, its application is not without limitations. The technique leverages laser energy to improve the absorption of therapeutic agents, thereby potentially accelerating scar resolution and improving both functional and aesthetic outcomes. However, the effectiveness of LADD can be influenced by factors such as laser parameters, patient skin type, and scar maturity, which require careful consideration to optimize results. Moreover, challenges such as the risk of side effects like hyperpigmentation, prolonged erythema, and the need for specialized equipment and expertise highlight the technique's limitations. Therefore, while LADD holds significant promise as a therapeutic modality for hypertrophic scars, further well-controlled clinical trials are essential to better define optimal treatment protocols, minimize adverse effects, and fully establish its role in post-burn scar management.

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