

# Needling, lasers, and Meso-Botox for hypertrophic and keloidal scars: A comprehensive review study on promising procedural treatments

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## ABSTRACT

Scars are among the most prevalent referral cases of dermatology clinics, including atrophic, hypertrophic, or keloidal scars. Approach to scar usually needs a holistic trend, attention to individualized characteristics, and combination therapy. Scars usually need multiple sessions of therapy and the use of combination therapeutic approaches to reach the most acceptable outcomes by safe modalities. Studies on scars are always one of the most important fields of research in medicine, especially in dermatology. For writing this review study, we searched all the databases to find the most relevant and the newest studies related to our topic, because based on expert opinion, this topic may be really practical and interesting for dermatologists and all physicians of various specialties or subspecialties who manage and treat various kinds of scars, including hypertrophic scars and keloids. Based on our results, we concluded that different procedures, which basically use needling, lasers, especially pulsed dye laser (PDL) and carbon dioxide (CO<sub>2</sub>) laser, and MesoBotox (micro-injection of botulinum toxin), are really promising therapeutic options for hypertrophic and keloidal scars and a combination of these therapies results in more efficacy and lesser side effects in the field of scar management.

**Keywords:** Botulinum Toxin, laser, microneedling, needling, scar

## Introduction

Scars are among the most prevalent referral cases of dermatology clinics, including atrophic, hypertrophic, or keloidal scars. The approach to a scar usually needs a holistic trend, attention to

individualized characteristics, and a combination therapy.<sup>[1-8]</sup> Scars in dermatology are usually caused by trauma, burn, surgery, or as a sequel of inflammatory mucocutaneous disorders, wounds, or ulcers, especially as a consequence of severe nodulocystic acne vulgaris.<sup>[1,2,5-8]</sup> Each of these etiologies could result in any type of scar or even concurrent forms of scar. Various therapeutic methods have been used for the treatment of scars, and there are many systematic reviews and/or meta-analyses which discuss the results of these studies. Some recent promising procedural therapies have been given less attention or have a lower level of evidence for some types of scars, which means lesser existing original studies

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or clinical trials, which we have tried to approach in this narrative review article. We know that for the hypertrophic or keloidal scars, lasers (mostly pulsed dye laser [PDL], carbon dioxide [CO<sub>2</sub>] laser), needling, and MesoBotox are among the most important modalities which need to be known more clearly or in more detail.<sup>[3,4,9]</sup> For this purpose, we aimed to search for articles and write a comprehensive narrative review based on our topic of interest.

## Materials and Methods

For writing this review study, we searched the database to find the most relevant and the newest studies related to our topic. A search was carried out in Medline (PubMed) (<http://ncbi.nlm.nih.gov/pubmed>), Scopus (<http://www.scopus.com>), Web of Science (<http://webofknowledge.com>), and Google Scholar (<https://scholar.google.com>).

## Results and Discussion

### Needling

There are a lot of studies about the positive effects of needling on the healing process of atrophic scars (e.g., acne scars) and reduction of complications of scars, so it could be considered as a well-tolerated and minimal method with a high level of patient satisfaction.<sup>[1,2,5-8]</sup> There are few studies about the positive effects of needling on the hypertrophic and keloidal scars.<sup>[3,4]</sup> The related review articles suggest examining needling as a promising adjuvant therapy for non-atrophic, hypertrophic, or keloidal scars, which needs more studies and long-term follow-up periods in comparative trials conducted on resurfacing modalities.<sup>[3,4]</sup>

A combination of needling and topical therapies, or even the microneedle patch,<sup>[9]</sup> is the most important promising option for hypertrophic scars and keloids.<sup>[10,11]</sup> Needling with intralesional treatments or mesotherapies is the other therapeutic option for these kinds of scars.<sup>[12]</sup> Based on some studies, needling could perform even better than the routine laser therapy for scars, so the authors recommend to use it in combination with other medical and procedural treatments, however, more research on the effect of needling as combination or single therapy is needed for approaching hypertrophic scars and keloids.<sup>[13]</sup>

In a comparative clinical trial regarding combination of needling and silicone gel in 20 patients with different combination methods, the authors found that the combination of needling and silicone gel for treatment of hypertrophic scars and keloids is really safe and effective (more than 60%), and also, use of the needling is better than silicone gel alone.<sup>[9]</sup>

In another trial, the authors found that microneedling seemed to be an effective method to improve hypertrophic burn scars, with better scores in the physical characteristics of scar and patients' satisfaction compared to CO<sub>2</sub> laser at the 3-month follow-up.<sup>[13]</sup>

Based on their experience in needling therapy in several dermatologic entities and clinical settings, especially scars and

active acne,<sup>[13-21]</sup> and other review studies, the authors believe that it is a proper time to give more focus on needling applications in hypertrophic and keloidal scars.<sup>[13]</sup>

### Lasers

Today, two types of lasers (PDL and fractional CO<sub>2</sub> laser [FX CO<sub>2</sub>]) are the most prominent methods used in the treatment of hypertrophic and keloidal scars, including similar burn-related scars.<sup>[22-24]</sup> PDL affects the scar tissue through selective photothermolysis. The emitted laser is absorbed by the chromophores that are primarily found in hemoglobin and is converted in to thermal energy, causing coagulation necrosis. It has been suggested that laser-induced ischemia affects collagen and collagenase by causing microvascular damage, thereby reducing wound scarring; for example, after PDL treatment, it has been observed that keloidal scars will have looser collagen fibers and are more morphologically similar to normal skin.<sup>[25]</sup> In the treatment of keloidal and hypertrophic scars, PDL is primarily associated with improving scar flexibility and reducing redness and itching. This treatment seems to be very promising because its side effects (ecchymosis and bruising, petechial lesions, and temporary change of pigmentation) are minimal; also, most patients can tolerate mild PDL pain.<sup>[25-28]</sup>

In FX CO<sub>2</sub> laser treatment, the CO<sub>2</sub> laser penetrates the tissue in the form of light columns and destroys or shreds it by heating the water inside the tissue and existing cells. The tissue of this area is then regenerated.<sup>[29]</sup>

While clinical studies often report positive results and significant effects following PDL treatment<sup>[25,30]</sup> and FX CO<sub>2</sub>,<sup>[31-36]</sup> a number of studies have found no effect on scar appearance.<sup>[37-39]</sup> Recent studies, mostly conducted in China, have reported the effect of combining the two therapies, but there is insufficient information on the efficacy of PDL or FX CO<sub>2</sub> alone compared with the combination therapy.

A number of studies published in 2010 and 2014 have shown that PDL has a positive effect on the appearance of scars by reducing the redness and thickness of hypertrophic or keloidal scars. It is also effective in reducing scar itching.<sup>[25,30]</sup> Others, however, did not see a clear effect of PDL on the appearance of scars between 2003 and 2004 and only reported improvement in the patients' pruritus after treatment.<sup>[37-39]</sup>

There are many reports of the effectiveness of FX CO<sub>2</sub> laser in the treatment of hypertrophic scars, especially burn scars, which confirm that this laser can improve redness, thickness, texture, color, and symptoms of scars.<sup>[31-36]</sup>

Subsequently, we discuss the results of some mentioned articles in detail.

Hultman *et al.*<sup>[32]</sup> reported a 19-year-old female patient who had a deep partial-thickness burn with grease on her chest. After she

developed a hypertrophic scar along the sternum, she received two times PDL and two times CO<sub>2</sub> laser. Her redness, itching, and paresthesia completely improved after treatment.

Another patient was a 5-year-old girl who had intermediate partial-thickness burns due to hot fluids on the scalp and back of the neck. She underwent excision and allograft treatment, but developed a severe hypertrophic scar on the back of her neck and scalp with chronic folliculitis and partial alopecia. All the symptoms of the patient completely improved after four sessions of PDL without steroid injection.

Another patient was a 25-year-old worker with full-thickness burn, who had been electrocuted while working on the roof and had a hypertrophic scar on his hands despite early excision and grafting. He received two sessions of PDL, steroid injections, and two sessions of CO<sub>2</sub> laser, as well as a small full-thickness skin graft to free up the web space. As a result of the treatment, he returned to normal functioning and to his original work with minimal restrictions.

Other patient was a 35-year-old man who had burns in about 60% of his entire body after an industrial explosion in a food factory. Also, he suffered from inhalation damage. He developed severe hypertrophic scars that were accompanied by excruciating itching, shortening of the upper lip, and chronic folliculitis on the chin, lips, and scalp. He was treated with two times Alexandrite laser and two times CO<sub>2</sub> laser without steroid injections. Following this treatment, his symptoms resolved to near normal and also led to a decrease in peripheral stiffness and lengthening of the patient's upper lip.

In another case, a 17-year-old woman was reported to have burned 50% of her entire body due to a propane grill explosion, causing hypertrophic rings on her chest, limbs, neck, and face, causing her forehead, eyebrows, and lips to deviate. The top and bottom and the area around the ear were damaged. She underwent a series of tissue rearrangements with steroid injections, five times PDL, and three times CO<sub>2</sub> laser. She is currently a senior at UNC-Chapel Hill, working as a show host and producer on the college cable news station.

In 2018, Xie *et al.*<sup>[40]</sup> evaluated the clinical effect of consecutive PDL and FX CO<sub>2</sub> laser treatments on early-stage hypertrophic burn scars. They enrolled 221 patients with 228 hypertrophic scars in all parts of the body, who had their wounds healed at least 6 months ago. For the first time, all patients received PDL and repeated PDLs at 1-month intervals until the scar vascularity score dropped to 2 points. Then, they were started on FX CO<sub>2</sub> laser treatment, which was repeated after 3 months. Patients with self-made scar rating scale were evaluated for vascularity, thickness, and pliability. Patients were also evaluated for age, scar location, time to start treatment, and number of repetitions. There was no significant relationship between patients' age and the number of repetitions of treatment with improvement of hypertrophic burn scars. In terms of scar location, only

differences in pliability were reported. A significant correlation was observed between the start time of treatment and scar improvement in all scoring cases. In general, consecutive PDL and FX CO<sub>2</sub> laser treatments were effective, and the effectiveness may increase with earlier onset and increase in frequency. Laser was also very satisfying for the doctor and the patient as it reduced the symptoms, especially itching.

In one study, 56 patients with erythematous hypertrophic scars were randomly divided into control and treatment groups. The control group received 595 nm PDL and the treatment group received Fractional CO<sub>2</sub> laser. Based on Vancouver scar scale (VSS) score, melanin, height, vascularity, and pliability scores showed a significant decrease in both groups. But the effect on total VSS score was greater in the control group than in the treatment group. In this study, a combination treatment of PDL and FX CO<sub>2</sub> on hypertrophic erythematous scars was recommended due to its clinical efficacy and lesser side effects.<sup>[41]</sup>

Zhang *et al.*<sup>[42]</sup> performed a randomized controlled trial (RCT) in which the combined effect of narrow-spectrum intense pulsed light (IPL) and FX CO<sub>2</sub> was investigated for pruritus in hypertrophic scars. Ninety patients were divided into two groups of 45 patients each. The control group received IPL twice at intervals of 1 month. The treatment group received a combination of IPL and FX CO<sub>2</sub> therapy for the first time, and a month later, the patients underwent IPL once. Before and 3 months after treatment, they were evaluated by visual analog scale (VAS) and pruritus questionnaire. Before treatment, there was no difference in the degree of itching of the scar and its distribution between the two groups. After treatment, in the control group, the scar itching score decreased in terms of the amount and frequency of recurrences; but no effect was observed on itching distribution and location, or improvement of sleep in these patients. While in the treatment group that received a combination of IPL and FX CO<sub>2</sub>, a clear effect was reported on all scoring items, including their amount, frequency of repetition, location, and improvement of sleep.

In 2018, Li *et al.*,<sup>[43]</sup> with the aim of comparing the efficacy and safety of PDL and ultra-pulsed fractional carbon dioxide laser (UFCL) in the treatment of hypertrophic scars after burns, studied 201 patients (two groups with 122 and 99 patients, respectively). The group with 122 patients received PDL treatment every 3–4 weeks and the other group received UFCL treatment every 6–12 weeks, and both groups continued treatment for 12 months. Results of this study showed that PDL and UFCL both have a definite effect on hypertrophic scars, but PDL is preferred in terms of low pain, minor scarring, and rapid recovery time, especially in children and those who do not tolerate pain.

Another study published in 2020 examined the effect of combining PDL and UFCL treatments in the early stages on large scars in children. In this, 120 children entered the 6-month course of treatment, which included two single PDLs and a combination

of PDL and UFCL. The PDL repeat interval was 1 month, and the UFCL repeat interval was 3 months. Combination therapy had a significant effect on reducing the duration of treatment and reducing complications. Combination therapy can also reduce symptoms and increase the quality of life in children.<sup>[44]</sup>

In a systematic review study conducted in 2011, the effects of various laser treatments on hypertrophic scars were studied. It showed that 595 nm PDL with a moderate effect on hypertrophic scars was superior to other types of lasers, including PDL 585 nm, fractional non-ablative laser 1540 nm, and CO2 laser 10,600 nm, since it was more effective.<sup>[45]</sup> Based on the results of an RCT with low risk of bias, PDL 595 nm with a pulse duration of 4.5 ms was found to be much more efficient than PDL 595 nm with a pulse duration of 40 ms and had better effects on the volume and flexibility of hypertrophic scars.<sup>[46]</sup> In the same study, CO2 laser 10 600 nm, according to a controlled clinical trial (CCT) in 2006 with a high risk of bias, was reported to show moderate improvement of hypertrophic burn scars according to the VSS and self-assessment scale.<sup>[47]</sup>

In another systematic review conducted in 2018, studies on the invasive and noninvasive treatments of hypertrophic scars were reviewed, and based on the studies performed on PDL, its definite effect on the improvement of hypertrophic scars was reported.<sup>[48]</sup> Asilian *et al.*<sup>[49]</sup> considered three groups in their trial: the first group was treated with 5-fluorouracil (5-FU), the second group with 5FU + triamcinolone, and the third group with 5FU + triamcinolone + PDL. Addition of 585 nm PDL with a pulse duration of 250 ms, energy density equal to 5–7 J/cm, and spot size equal to 5 mm showed more improvement in hypertrophic scars in terms of size, height, color, redness, and itching, compared to the first and second groups. Also, by conducting 28 clinical trials and having sufficient evidence, it was shown that PDL is recommended as an effective treatment option for the improvement of hypertrophic scars.

### MesoBotox (Micro-Botox)

Mesotherapy or microinjection of diluted botulinum toxin has been examined with acceptable success for treatment of scars, and hypertrophic or keloidal scars are not an exception. Recently, MesoBotox has been used for some dermatological indications, including both types of depressed atrophic scars like acne scar and hypertrophic scars, as an adjuvant therapy in combination with other widely used procedures.<sup>[50,51]</sup>

In recent years, botulinum toxin type A (BTA) has been used to treat hypertrophic scar lesions. This toxin affects acetylcholine exocytosis and indirectly blocks neuromuscular transmission, which ultimately leads to muscle relaxation. It is widely used to treat facial wrinkles and is also an effective way to treat hyperactive muscles in facial expression. Some studies have also suggested that this toxin can minimize the formation of facial scars by reducing muscle tension and subsequently affecting the cell cycle distribution of scar-derived fibroblasts.<sup>[52]</sup> The results

of previous studies indicate the relative and limited effect of this toxin in relieving symptoms and preventing recurrence of lesions.<sup>[53]</sup> In another study, the use of botulinum toxin by injection into facial muscles combined with the removal of facial scars was considered a useful way to improve the appearance of scars;<sup>[54]</sup> however, there are some controversies among the results of different studies.<sup>[55,56]</sup>

Combinations of lasers, especially PDL, CO<sub>2</sub>, or both, with other methods, especially topical or intralesional injection of steroids, have been evaluated in various studies, but we do not know much about mesotherapy with botulinum toxin for treatment of hypertrophic scars or keloids. Here, we discuss about more relevant studies in this regard.

One of the most common treatments for hypertrophic scars is intralesional injection of corticosteroids, including triamcinolone acetonide, which has been used in several studies alone or in combination with other treatments. In 2013, the effectiveness of intramuscular injection of 10–20 mg/ml of triamcinolone in combination with ablative fractional laser in hypertrophic scars caused by burns, surgery, or trauma was evaluated. In this study, in 15 patients, the combination treatment was performed in three to five sessions with intervals of 2–3 months. Following treatment, overall healing was observed in the lesions, where dyschromia showed the least improvement and the texture of the lesion showed the highest recovery. Therefore, it was concluded that the combined treatment of corticosteroids and fractional laser can be an effective, safe, and efficient for limited and hypertrophic skin scars. One of the other treatment methods used in studies to treat hypertrophic scars is the use of laser therapy by PDL. In a 2004 study conducted in the dermatology department of Hong Kong Hospital to evaluate the role of PDL therapy in the treatment and prevention of hypertrophic scars in Chinese patients, PDL with a wavelength of 585 nm, pulse duration of 1.5 ms, spot size of 5 mm, and energy of 7–8 J/cm<sup>2</sup> was applied in 29 patients and for a total of 35 scars in the arm area in three to six sessions with an interval of 8 weeks. The results of this study showed that according to the designed questionnaire, 66% of patients reported improvement in lesions. The itching rate of the lesion was also significantly reduced. Although there was a decrease in thickness and improvement in the viscoelasticity of scars, it was not significant compared to the control group. Also, lightening of the lesions occurred significantly after treatment.<sup>[38]</sup>

In 2016, a randomized clinical trial study examined the effects of two types of PDL with a wavelength of 585 nm and Nd:YAG with a wavelength of 1064 nm on hypertrophic and keloidal scars. For this purpose, in 22 patients, each lesion was divided into two parts and each part was treated with each of the lasers. Each patient received six sessions of laser treatment at 1-month intervals. The results of this study showed that in both types of lasers, after 1 month of analysis, VSS showed a significant improvement in lesions, which was 55.14% in PDL and 65.44% in Nd: YAG. However, there was no significant difference between the two lasers.<sup>[57]</sup> In some studies, laser treatment has been used

in conjunction with other treatments for hypertrophic scars. In a clinical study by Alster *et al.*,<sup>[58]</sup> PDL treatment alone (585 nm) was evaluated with combination PDL therapy (intralesional injection of triamcinolone [10–20 mg] immediately after laser) in 22 female patients with bilateral inflammatory hypertrophic scars. Therapeutic sessions were performed at 6-week intervals. At the end of the treatment sessions, all lesions showed clinical improvement along with increased flexibility and reduced itching. In both groups, a decrease in sclerosis was observed in the lesions. The results of this study showed that treatment of these lesions with PDL causes clinical and histological improvement, while the addition of intralesional injection of triamcinolone does not significantly improve the clinical results. Another study performed by Ouyang *et al.*<sup>[41]</sup> in 2017 compared the clinical effects of PDL therapy alone and in combination with FX CO<sub>2</sub> laser. In this study, 56 patients were randomly divided into two groups; in one group, PDL with a wavelength of 585 nm, energy of 7–15 J/cm<sup>2</sup>, and a pulse width of 1.5–3 ms was given, and in the other group, PDL with the above-mentioned features and FX CO<sub>2</sub> laser with an energy of 30–50 mJ, frequency of 300 Hz, and density of 5% was applied following PDL. According to the VSS scale, melanin, height, vascularity, and flexibility decreased significantly in both groups. However, this reduction was significantly greater in the PDL alone group than in the combination group of PDL and CO<sub>2</sub> laser treatment.

In a comparative clinical study of 2014, PDL treatment in new surgical scars with purpura-inducing settings (1.5 ms) and non-purpura-inducing settings (10 ms) improved their clinical appearance. Treatment was performed in three sessions at 1-month intervals, and recovery was compared using the VSS scale. The results of this study showed that there was significant improvement of lesions in both groups. Non-purpura-inducing adjustments resulted in significant improvements in the appearance of surgical scars, improved vascularity, and flexibility. Purpura-inducing adjustments also led to comparable improvement on the VSS scale, and thus could be a new method used for the recovery of these lesions.<sup>[59]</sup>

In another clinical study of 2012, Bailey *et al.* compared the effects of compression therapy (CT) and a combination of CT and early treatment with PDL in children with burn scars who underwent scar reconstruction with split-thickness scarring. For this purpose, laser treatment was applied at 6-week intervals until clinical recovery was achieved. The results showed that the combination of CT with PDL reduced erythema and height and also increased tissue elasticity after two or three sessions. Based on the VSS scale, it further improved lesions in terms of vascularity, flexibility, pigmentation, and height.<sup>[60]</sup>

In a randomized clinical trial conducted in 2008, the effect of single-dose PDL application during suture removal on the clinical appearance of surgical scars was investigated. For this purpose, PDL with a wavelength of 585 nm, energy of 7 J/cm<sup>2</sup>, and a pulse duration of 1.5 ms was applied during the suture collection session (usually 2 weeks later). This laser was applied within 1 cm

of the scar with a 10% overlap between the spots. Immediately after laser treatment, purpura was created at the site. Six weeks later, compared with the control group (without any therapeutic intervention), no significant differences were observed in terms of clinical appearance, erythema, hyperpigmentation, hypopigmentation, induration, and atrophy. Therefore, they concluded that the addition of one-session laser treatment had no positive clinical effect on the appearance of scars.<sup>[61]</sup>

In another randomized clinical trial by Soroosh *et al.*,<sup>[62]</sup> in 2018, the prophylactic use of PDL with a wavelength of 585 nm in the 2 weeks after surgery was investigated in reducing the severity of thyroidectomy scars. For this purpose, in 60 patients, PDL treatment with a pulse duration of 1.5–1 ms, energy of 7–8 J/cm<sup>2</sup>, spot size of 7 mm, and overlap of 10% was applied, and then, the lesions up to 2 months after the last laser session were examined through the VSS scale. The results showed that 2 months after the third laser session, there was a significant improvement compared to the control group in terms of vascularity, flexibility, pigmentation, and height. Therefore, PDL can be considered a suitable and safe way to heal scars caused by thyroidectomy.

Lin *et al.*,<sup>[63]</sup> in their recent study in 2018, evaluated the efficacy and safety of dual-wavelength Nd: YAG and PDL combination laser treatments on hypertrophic scars. In this study, 25 patients received combination laser treatment at intervals of 4–6 weeks. The results showed that after several sessions of laser treatment, the lesions significantly improved and no adverse side effects were observed. Due to its high safety and satisfaction, combination laser treatment can be an effective and safe treatment option for hypertrophic scars.

Another clinical study by Deng *et al.*<sup>[64]</sup> in 2020 examined the effect of PDL treatment on immature hypertrophic scars in terms of erythema, circulation, and scar thickness. In this 3-month one-blind study, 45 Asian patients (22 patients in PDL group and 23 patients in the control group) were included. Patients in the PDL group received three sessions of laser treatment 4 weeks apart. The Patient and Observer Scar Assessment Scale (POSAS) and objective evaluation of the lesions, including erythema, blood circulation, and lesion thickness, were used to evaluate the treatment results. After 3 months of treatment with PDL, vascularity, pigmentation, thickness, erythema, blood circulation, and overall score on the POSAS scale improved significantly. But this improvement was not observed in the control group. In the PDL group, the thickness of scars did not increase during treatment, while in the control group, it increased significantly.

In a recent study conducted by Alexander *et al.*<sup>[65]</sup> in 2018, the effects of combining intralesional steroid injection (10 mg/ml) with FX CO<sub>2</sub> laser and intralesional steroid injection alone on hypertrophic scars and keloids was compared. In this study, 50 patients were randomly divided into two groups. The results of this study showed that in all patients, there was a significant improvement in the height and length of the lesions, so that

hypertrophy was reported more than 50% in 40% of lesions, dyschromia more than 50% in 33.4% of lesions and texture was seen as with the least amount. The rate of recovery was more than 50% in 30% of lesions. The rate of improvement of these parameters in the group receiving intralesional steroids alone was significantly lower than in the group receiving combination steroid and fractional laser therapy. Therefore, the results of this study confirm that the addition of laser to intralesional steroid treatment will increase the effectiveness of treatment.

In a similar clinical study conducted by Shin *et al.*<sup>[66]</sup> in 2019, the efficacy of combination therapy of intralesional steroid injection with non-ablative fractional laser in the treatment of hypertrophic scars and keloids was evaluated. In this study, 21 patients received triamcinolone acetonide injection (40 mg/ml at a rate of 0.1 ml/cm<sup>2</sup>) alone (control group) and 17 patients received erbium-glass fractional laser treatment in addition to steroid injection. They received a wave of 1550 nm. In the end, the number of treatment sessions required in combination therapy was less than that required in the control group. The rate of recurrence of lesions was 38.1% in the control group and 35.3% in the combination therapy group, and there was no significant difference between the two groups. In general, combination therapy resulted in better therapeutic results in scars and keloids, with fewer treatment sessions, longer recovery periods, and greater patient satisfaction. Therefore, this study also emphasizes the benefits of adding laser to intralesional steroid injection therapy.

Studies with a special focus on botulinum toxin for hypertrophic scars and keloids are discussed subsequently. A study was conducted in 2019 by Rasaii *et al.*<sup>[67]</sup> to compare the effects of intralesional triamcinolone alone and in combination with botulinum toxin in the treatment of keloidal scars. Twenty patients with a total of 40 keloids were studied. The results of this study showed that there was no significant difference between the two treatments in terms of vascular score, flexibility, and pigmentation. However, the addition of botulinum toxin resulted in a significant improvement in symptomatic pain and pruritus compared with triamcinolone treatment alone.

In a randomized clinical trial conducted by Shaarawy *et al.*<sup>[68]</sup> in 2015 to compare the efficacy and safety of intralesional injection of BTA with intralesional corticosteroid therapy in the treatment of keloids, 24 patients with keloids were randomly divided into two equal groups. Patients in group A received intralesional steroids every 4 weeks for six repetitive sessions and in group B received BTA 5 IU/cm<sup>3</sup> every 8 weeks for three sessions. Scar parameters (stiffness, height, and redness), complaints (itching, pain, and tenderness), patient satisfaction, and side effects were evaluated. In both groups, there was a significant reduction in the volume of lesions after treatment. Significant softening of lesions was also observed, which was significant in the first group. There was a significant decrease in lesion height and erythema score compared to baseline, but no significant difference was observed between the two groups. All patients reported a significant

reduction in their complaints, which was more pronounced in group B. Skin atrophy and telangiectasia were evident in three patients of group A. Therefore, in this study, the effectiveness and safety of BTA treatment were found to be clearly more than those of intralesional corticosteroids.

In addition to the methods mentioned, in several studies, intralesional injection of BTA has been used for keloids and hypertrophic scars. In a prospective clinical study conducted in 2016 by Elhefnawy *et al.*,<sup>[69]</sup> in 20 patients with hypertrophic ulcers, intralesional injection of BTA was performed once a month for 3 months with a 6-month follow-up period. Each lesion was injected until partial paleness developed. Patient and physician satisfaction was recorded. Lesions were evaluated for erythema, pruritus, and flexibility and each item was evaluated on a 5-point scale. Satisfaction was recorded in 14 patients as “good” and in the remaining six patients as “excellent.” The mean score of erythema decreased from 3.2 to 0.1, the mean of flexibility decreased from 3.3 to 0.8, and the mean score of pruritus decreased from 2.7 to 0.7; all the mentioned changes were statistically significant.

In a study conducted in 2009 by Zhibo *et al.*,<sup>[70]</sup> BTA (Botox) was injected at a concentration of 35 units per milliliter into the lesion. The total number of patients was 12. The interval between each injection was 3 months, and the total period of Botox injections was 9 months. Patients were followed up for 1 year, and the treatment results were divided into several categories: cases with a good response (five patients), cases with an average response (four patients), and cases with an excellent response (three patients) to treatment, and no recurrence was reported. The mean redness decreased from 3.41 to 1.23. The average consistency of the masses decreased from 3.85 to 0.78 and pruritus decreased from 3.5 to 0.83. Nevertheless, this study emphasizes that further studies should be conducted to prove this effect.

In a clinical trial conducted by Kim *et al.*<sup>[71]</sup> in 2019, the effect of BTA injection on scar formation was investigated. For this purpose, 45 patients with forehead ulcers were included in the study. Twenty-four patients were randomly injected with BTA in the dermal layer at a concentration of 5 units/ml and in 21 patients (control group), normal saline was injected at the wound site. Patients were then followed up in the first, third, and sixth months and scars were assessed using POSAS and VAS scales. The results of this study showed that in all patients the lesions improved, but this improvement was significantly higher in the intervention group. Skin biopsy also showed less collagen storage in the dermis layer of the botulinum group. Therefore, injection of BTA improves the lesion esthetically, functionally, and psychologically, and this treatment can be used to prevent hypertrophic scars following burns, trauma, or surgery.

Another clinical study conducted in 2013 by Ziade *et al.*<sup>[72]</sup> examined the effect of early injection of BTA on facial ulcers. In this study, 30 patients were enrolled and randomly divided

into control and intervention groups (injection of BTA 72 h after surgery in the facial lesions with a direct or indirect role in increasing the width of the scar). After 1 year of follow-up, lesions were assessed using POSAS, VSS, and VAS scales. Twenty-four patients were referred for follow-up after 1 year. There were no statistically significant differences between the two groups in terms of POSAS and VSS scales. However, the mean VAS score by the evaluators was 8.25 in the intervention group and 6.35 in the control group, which was a significant difference between the two groups. Therefore, botulinum injection can be useful for healing facial wounds in young patients by reducing the pressure lines on the facial skin.

In another clinical trial by Huang *et al.*<sup>[73]</sup> conducted in 2019, BTA injection was used to treat epicanthoplasty scars. In 43 patients receiving epicanthoplasty, 5 units of BTA or a similar volume of normal saline was randomly injected 6–7 days after surgery. Lesions were assessed by VAS and VSS at 1, 3, and 6 months after treatment. In botulinum-treated lesions, a significant improvement in VSS score was observed and the highest improvement was observed at 3-month follow-up. Among the different scales, height and flexibility showed the highest improvement. VAS score also decreased significantly in the intervention group, and 86.7% of patients were highly satisfied with the treatment. Therefore, early treatment following epicanthoplasty with injection of BTA will reduce the formation of hypertrophic scars and improve surgical results.

Similar to intralesional injection of corticosteroids, injection of BTA has been combined with other treatments in various studies to increase its effectiveness in healing hypertrophic scars. In a 2015 study by Lee *et al.*,<sup>[74]</sup> two cases of traumatic scars on the chin were successfully treated with a combination of 595 nm PDL therapy and intramuscular injection of botulinum toxin. After treatment, good esthetic results were obtained in both patients. The only side effect during and after treatment was mild pain, which resolved within a few days without any additional treatment. As a result, a combination of 595 nm PDL and botulinum toxin injection was shown to be a safe and effective treatment for trauma-induced chin scars.

In a double-blind, prospective, randomized clinical trial by Chang *et al.*,<sup>[75]</sup> 60 patients were randomly divided into two groups. In the intervention group, Botox at a concentration of 2.5 units per 0.1 ml and at a dose of 1 unit per kilogram of neonatal weight was injected at the site of surgery in the orbicularis oris muscle immediately after surgery and in the control group, same volume of normal saline was injected. After 6 months of follow-up, the findings were evaluated based on VSS, VAS, and photographic measurement of lesion width. The results showed that in the intervention group, the width of the lesions significantly decreased and the VAS score improved. However, the VSS score was similar between the two groups. Therefore, intralesional injection of botulinum toxin improves the appearance and width of the scar, but has no effect on the pigmentation, vascularity, flexibility, or height of the scar.

## Conclusion

Based on our results, we concluded that different procedures which basically use needling, lasers, especially PDL and CO<sub>2</sub> laser, and MesoBotox (micro-injection of botulinum toxin) are really promising therapeutic options for hypertrophic and keloidal scars and combination of these therapies results in more efficacy and less side effects in the field of scar management. In combination therapy, a combination of two or more modalities is usually better than applying each one alone, but the efficacy of different combination regimens depends on the type of therapies combined. Needling, laser, and MesoBotox could be arms of different comparative or combination trials to be conducted in future for treating scars, especially hypertrophic and keloidal scars.

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## Conflicts of interest

There are no conflicts of interest.

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