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ORIGINAL CONTRIBUTION

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Potentials for implementing pressure-controlled jet injection in management of keloids with intralesional 5FU and corticosteroids

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Abstract

Background: Needle-free jet injection implements kinetic energy of liquid jet for transcutaneous delivery of drugs into soft tissues. Combination therapy of intralesional 5-fluorouracil and triamcinolone offers efficacious treatment for keloids with a reduced adverse effect of the drug monotherapy. This study evaluates safety and efficacy of the drug combination administered to keloid scars via intralesional jet injections.

Methods: A retrospective analysis of the keloid treatments was performed. Efficacy was assessed by reviewing pre- and post-treatment scores of the Vancouver Scar Scale (VSS) and Patient and Observer Scar Assessment Scale (POSAS) and by comparing baseline and photographs taken 3 months after the treatments. Safety and tolerability were collected and analyzed.

Results: Twenty-one subjects (M/F = 11/10) with 39 keloids received the treatments. Treatments were well-tolerated by all patients at mean injection pain of 2.0 ± 1.0 per Numeric Pain Rating Scale (NPRS). Self-resolved lesion ulceration was observed in 4 patients. Post-treatment evaluation demonstrated a 53% decrease in total VSS score ($P < 0.05$) and in all sub-categories. Mean patient score of POSAS decreased in the color, stiffness, thickness, and irregularity components. Pain and pruritus lessened by 69% and 79% ($P < 0.05$ in both), respectively, among the patients with complaints prior to the treatment. Independent reviewers reported an average 51%-75% reduction in keloids.

Conclusions: Improved appearance of keloids and symptomatic relief was achieved by intralesional administration of combined 5-fluorouracil and corticosteroid through the high-pressure jet injections. The synergy between the drug combination and the jet physical impact provided clinical effect.

KEYWORDS

5-fluorouracil, EnerJet, intralesional injection, jet injection, keloid

1 | INTRODUCTION

Keloids present a substantial source of distress for patients and can be a challenge for management. The first-line of intralesional therapy includes corticosteroids (CSs) and 5-fluorouracil (5FU) administered either through traditional needle injections or by innovative laser-assisted modality.

Despite its simplicity, the needle injections may be physically challenging due to the density of keloids and are associated with significant injection pain, nonhomogenous distribution, and risk of inadvertent injection into surrounding normal tissue.[1] Fractional lasers break protective skin barriers and create channels for subsequent distribution of the drugs to the tissue. Despite proven clinical results, this method relies on passive diffusion and lacks precision in

controlling the depth of diffusion, dosing, and exposure to the delivered substance.[2]

Transcutaneous needle-free jet injection implements kinetic energy of liquid jet for active injection of drugs into soft tissues. A pressurized and accelerated stream of fluid penetrates the skin through a small entry point and dissipates inside spreading the droplets in a multidirectional pattern that can reach 1 cm in diameter (Figure 1).[3] In nonscarred skin, it generates micro-trauma which stimulates fibroblasts and activates neocollagenesis resulting in dermal remodeling.[4,5]

Jet injections of hyaluronic acid were previously shown to be effective in treating atrophic scars.[6,7] It was further demonstrated that needless pressure injections of steroids into hypertrophic scars and keloids markedly decrease scar thickness and improved associated symptoms without pain of traditional intralesional needle injections.[8] Our study evaluated efficacy, safety, and tolerability of the 5-fluoruracil and corticosteroid combination (5FU:CS) administered into keloids in serial jet injections.

2 | METHODS

A retrospective analysis was performed for the data extracted from the charts of the patients who received the jet treatment of keloids in two clinics specializing in plastic surgery (AL) and procedural dermatology (OA). Patients selected for analysis of the treatment results had keloid lesions exceeding 1 cm in diameter and were originally planned for intralesional injections of 5FU:CS mixture. Patients voluntarily agreed to be treated with the drugs via jet injection treatment as an effective alternative to treat their keloids pain-free. Prior to the treatments, all the patients signed an informed consent in which they declared to be aware of the treatment method and allowed the use of photographic records for scientific publications. Patients were indicated for the treatment if they did not have a history of coagulation disorders; renal, hepatic, or respiratory failure; bone marrow depletion; chronic use of systemic corticosteroids or immuno-suppressants; and pregnant or lactating females. Collection and management of the patient data were conducted in accordance with the ethical guidelines and principles of the 1975 Declaration of Helsinki. Retrieved data (demographics, history, treatment information, efficiency measures, patient questionnaires, and photographs) were analyzed by the physicians who directly treated the patients. Etiology and distribution of keloids are presented in Table 1.

Each keloid lesion received series of bi-weekly treatments at which 4 mL 50 mg/mL fluorouracil (Pharmachemie, Haarlem, The Netherlands) was mixed 9:1 with 0.5 mL of 40 mg/mL methylprednisolone acetate (Depo-Medrol, Pfizer) or 40 mg/mL triamcinolone acetonide (Kenalog-40, Bristol-Myers Squibb). Additionally, 0.5 mL of 2% lidocaine (B. Braun Melsungen AG) was added to the mixture to achieve a concentration of 0.1% for analgesia. The drugs were mixed in one syringe and injected intralesionally by jet injection device (EnerJet2.0, PerfAction Technologies) in aseptic conditions. The injections were spread in a 1-cm grid covering entire lesion. Each injection contained 0.1 mL of the mixture, so every 1 cm^2 of the treated area received 4.5 mg of 50 mg/mL 5FU and 0.4 mg of 40 mg/mL steroid. The total injected volume of 5FU:CS mixture varied from 0.5 to 10 mL, depending on the total surface of the lesion. Nevertheless, the total dose never exceeded the recommended safety levels—daily 60 mg for CS and bi-weekly 500 mg for 5FU.[9]

The depth of penetration was controlled through the device software and was adjusted according to the keloid height. The

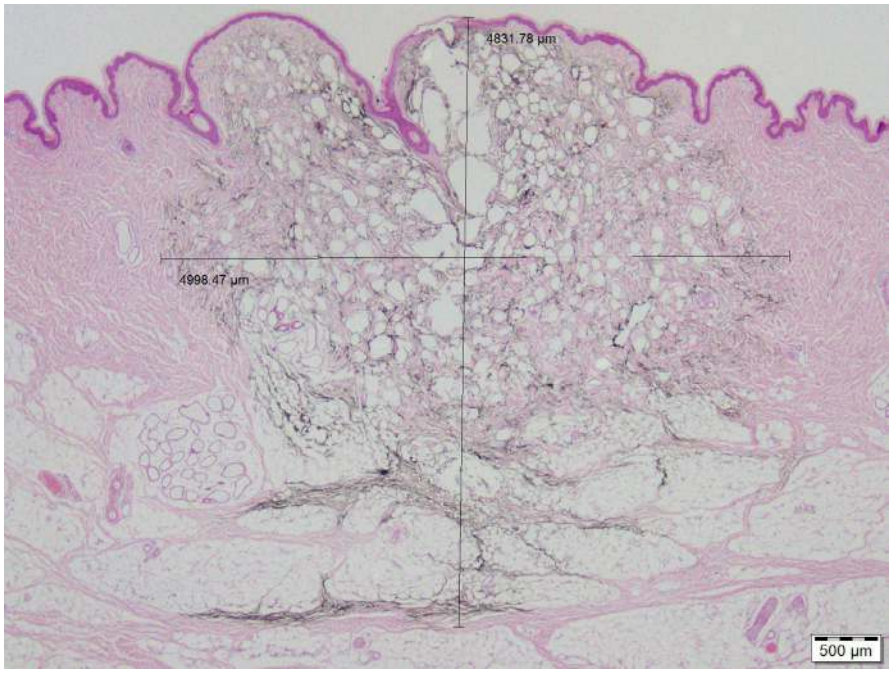

FIGURE 1 Intradermal distribution of the Indian ink solution jet injected into porcine skin. Focal vacuolation suggests mechanical separation of collagen bundles due to dispersion of the solution droplets within dermis and adipose panniculus (H&E, ×300)

TABLE 1 Scar location and etiology

Keloid etiology							
No.	Acne	Burns	Piercing	Spontaneous	Surgery	Trauma	
	12	10	3	2	11	1	
Keloid locations							
No.	Head/earlobe	Chest	Arm/shoulder	Sternum	Knee	Abdomen	Back
	4	11	11	2	1	1	9

bulky lesions were treated in 2-tiered "pressure sandwich" by injecting at low (3.5-4.0 bars) and then at higher pressure (5.0-5.7 bars) and, respectively, reaching superficial portion and the central core of keloid (Figure 2). Less prominent keloids were injected at the single pressure ranging at 3.0-3.7 bars. The treatments continued until the scar's initial volume was subjectively reduced at least by 70%.

Post-treatment digital images and the data documented in patients' charts 3 months after the last treatment were compared to baseline. The Vancouver Scar Scale (VSS) was used for the assessment of the lesion's vascularity, pigmentation, pliability, and height. Additionally, patients used the Patient and Observer Scar Assessment Scale (POSAS) for self-evaluation of keloid appearance (color, stiffness, thickness, irregularity) and relief of the scar-related symptoms (pain and itchiness). Injection pain was rated by the 0-10 Numeric Pain Rating Scale (NPRS). Statistical probability was calculated by Student's *t* test.

Pictures of keloids before and after the treatment were independently compared and scored by a study-independent panel of 3 physicians (two plastic surgeons and one dermatologist) according to a 5-grade scale. Physicians were blinded to the patient identifying information. The scale reflected their subjective opinion on reduction of keloid bulk in comparison with pretreatment: 0—no change; 1—diminished by <25%; 2—diminished 25%-50%; 3—diminished by 51%-75%; and 4—absence or near absence of keloid lesion. Agreement between the reviewers was not assessed.

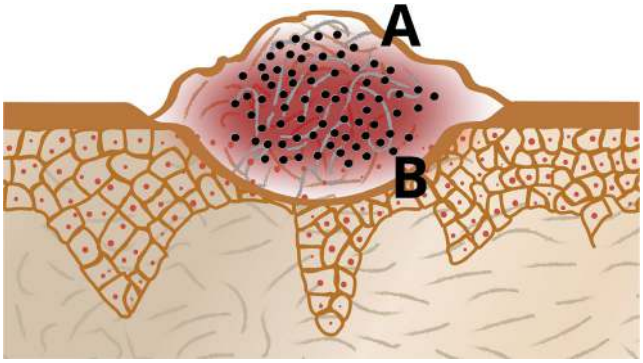

FIGURE 2 A schematic representation of the "sandwich" injections for bulky keloids: (A) low injection pressure applied for superficial layer; (B) high injection pressure applied for keloid's core

One year after, a telephone interview was conducted. The patients were asked if their jet-treated keloids recurred during the last 12 months.

3 | RESULTS

Twenty-one subjects (M/F = 11/10, aged 15-68 years old) with keloids (n = 39) who received jet injection treatments from March 2016 to August 2018 were included in the analysis. Mean age of keloids before the treatment was 3.12 years: 41%—<1 year and 58%—more than 1 year. The lesions varied in the range of 2-20 cm in maximum diameter distance.

Prior to the treatment, 13 patients were naïve to any keloid therapy and 8 patients failed previous steroid intralesional injections or had recurrence after surgical excision. Thirty-three percent of patients had complaints of pain and pruritus related to their keloids.

Twenty patients completed the treatments. One patient interrupted the course and was lost to follow-up due to the long-term hospitalization not related to the therapy. The treatment aimed at decreasing keloid bulk and improving the symptoms;

TABLE 2 Number of treatments and achieved keloid reduction

Age	Average number of treatments (min-max)	Average reduction score[a]
Keloid location		
Chest	7 (1-14)	3.0
Arm/shoulder	6.9 (3-12)	2.8
Head/earlobe	7.2 (4-12)	2.8
Sternum	7 (7)	2.5
Knee	3 (3)	2.4
Abdomen	3(3)	3.0
Keloid etiology		
Acne	7.2 (6-8)	2.8
Burn	6.8 (3-12)	2.8
Piercing	7.7 (7-12)	2.8
Spontaneous	4 (4)	2.5
Surgery and trauma	7.0 (1-14)	2.8

[a]0—no change; 1—diminished by <25%; 2—diminished by 25%-50%; 3—diminished by 51%-75%; 4—absence or near absence of keloid lesion.

therefore, the number of treatments varied according to patient's clinical needs and keloid assessment. The average number of sessions required to successfully treat keloids was 7 (range 1-14; Table 2). The maximum 14 treatments were performed for post–skin-grafting keloid, although only moderate improvement was achieved.

Treatments were well-tolerated by all patients. Injection pain was scored at mean 2.0 ± 1.0 per NPRS. No severe adverse reactions or systemic side effects were documented. Superficial ulceration was observed in 4 scars, all of them treated at the single pressure settings (vs variable pressure "sandwich"); it self-healed once the time between the treatments was increased from 2 to 4 weeks.

Post-treatment evaluation demonstrated a 53% decrease in total VSS score ($P < 0.05$), with a reduction in keloid vascularity (from 1.81 ± 0.96 to 1.11 ± 0.85, $P < 0.05$), pigmentation (0.81 ± 0.92 to 0.63 ± 0.74, $P < 0.05$), pliability (3.04 ± 0.85 to 1.11 ± 0.97, $P = 0.13$), and height (2.93 ± 2.70 to 0.74 ± 0.66, $P < 0.05$; Figure 3).

Overall patient score of the POSAS significantly decreased (39.54 ± 5.31 to 19.63 ± 6.30, $P < 0.05$). Significant reduction ($P < 0.05$) was found in all POSAS components including keloid color (from 8.07 ± 2.04 to 4.11 ± 1.55), stiffness (8.70 ± 1.46 to 4.44 ± 1.78), thickness (8.48 ± 1.55 to ± 4.44 ± 1.72), and irregularity (9.26 ± 1.20 to 5.19 ± 2.24). Among the patients with complaints prior to treatment, pain and pruritus lessened by respective 69% and 79% ($P < 0.05$ in both). Independent panel reported an average 51%-75% reduction in keloids on post-treatment photographs (Figures 4-6). Out of 50% of patients available for the follow-up interview, none reported a recurrent growth of the jet-treated keloids in the past 12 months.

4 | DISCUSSION

We implemented innovative intralesional treatment of keloids of a different etiology, location, and age. A retrospective analysis revealed a fast improvement of keloids after jet injection of 5FU:CS combination. Values of POSAS and VSS scores have been statistically decreased from baseline to 3 months after the therapy ($P < 0.05$).

Current guidelines for intralesional management of keloids include injections of 5FU in combination with CS.[10,11] The anti-inflammatory effect of corticosteroid suppresses fibroblast proliferation, reduces vascular permeability, and inhibits production of chemical intermediates that reduce itch and pain.[12] 5FU interferes with DNA synthesis and causes fibroblast apoptosis and inhibition of the rapidly proliferating cells.[13] Studies suggest that combination of 5-fluorouracil and corticosteroids provides fast clinical response and has fewer side effects compared to the drug monotherapy.[10,11,14] Although clinical efficacy was proven for 5FU:CS combination, no consensus was established for the ratio and treatment regimen.[13,15] We achieved symptomatic relief and cosmetic improvement of keloids at the drugs ratio 9:1 and bi-weekly injection schedule.[13]

Synergy between the jet impact and the jet-injected drugs was previously demonstrated to remodel the nonkeloid scar tissue.[6,7]

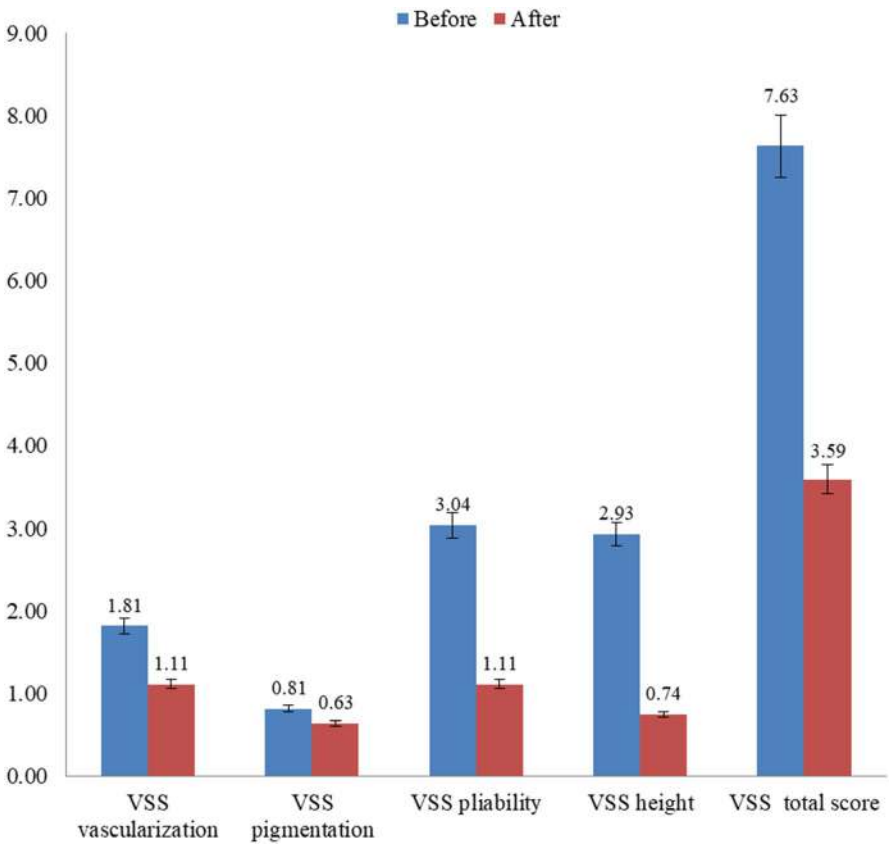

FIGURE 3 Mean pre- and post-treatment scores of Vancouver Scar Scale

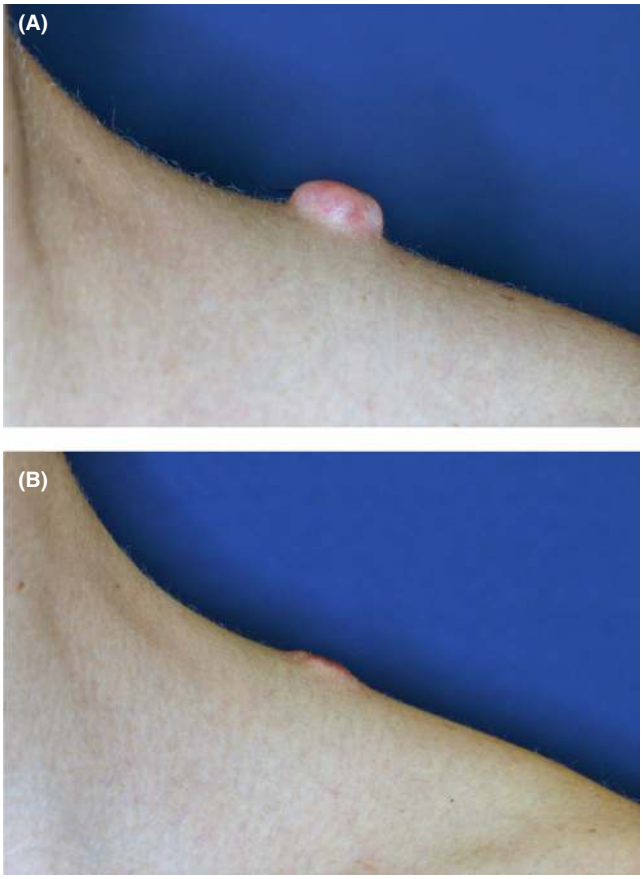

FIGURE 4 A 24-y-old male with postacne keloid in low axillary region demonstrates flattening of the lesion after seven treatments: (A) before the treatment and (B) 3 mo after the treatment

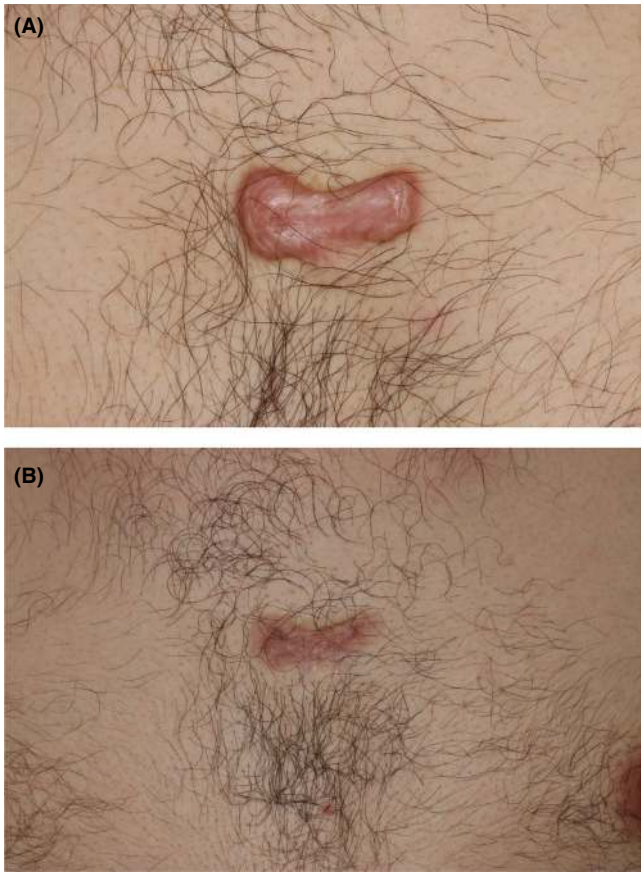

FIGURE 5 A 32-y-old male with postsurgery chest keloid demonstrates reduction and color normalization after nine treatments: (A) before the treatment and (B) 3 mo after the treatment

The jet's physical effect exerted on keloids is thought to enforce the drugs' effect by several mechanisms. The jet's fluence of 260 J/cm^2 applied on the spot size of 0.2 mm allows the liquid to easily penetrate and disperse inside keloid, mechanically breaking fibrotic strands and disrupting pathological collagen bundles. Each injection produced instant blanching in keloids—similar to the hyperthermia blanching generated by ablative fractional CO_2 lasers on hypertrophic scars and leading to tissue hypo-perfusion and hypoxia.[16] We assume that the jet forcefully penetrating the scar may lead to immediate, and at least temporary, shutdown of excessive microcirculation typically present in keloids—similar to the beneficial action of a pressure garment.

Traditional intralesional needle injections are painful and require significant amounts of pressure and experience to provide effective infiltration of the material in keloids. Insufficient and nonuniformed spread results in uneven distribution depth, surface atrophy, and prominent telangiectasia associated with a high recurrence rate up to 50%.[17] Recently developed laser-assisted drug delivery (LADD) is thought to increase homogeneity and enhance bioavailability of pharmaceutical agents in keloid. Fractional laser resurfacing creates micro-channels which permit topically applied 5FU:CS bypass epidermal barriers and be deposited into keloid. Although the therapeutic effect mainly depends on passive uptake, current LADD data show improvement and a low rate of recurrence.[2,18] Still, the exact amount of the drug supplied to the tissues is not uniformed and depends on the material rheological properties and the channel-closure time.[2,19]

The pressurized liquid jet allows controlled, deep, and even penetration through the full thickness of the scar—which cannot be achieved either by manual injection or by the absorption mechanism of LADD. A direct relation between jet injection pressure and its penetration depth was validated in the literature[20] and implemented for variable-pressure injections into full thickness of keloid (Figure 2). An ability to reach the full depth of the scar was demonstrated as the major factor for lowering keloid recurrence rate.[18] Partially obtained feedback from the patients revealed no recurrence within the post-treatment 12 months.

The treatments were easily tolerated by the patients. Jet injections have been reported to produce minimal pain and discomfort, without pretreatment or local anesthesia.[7,21] High velocity of the liquid jet significantly reduces the momentum of skin propagation (estimated as 30 msec) and eventually decreases activation of dermal pain receptors. In comparison, conventional needle injection or LADD is painful, requires additional local anesthesia, and is not

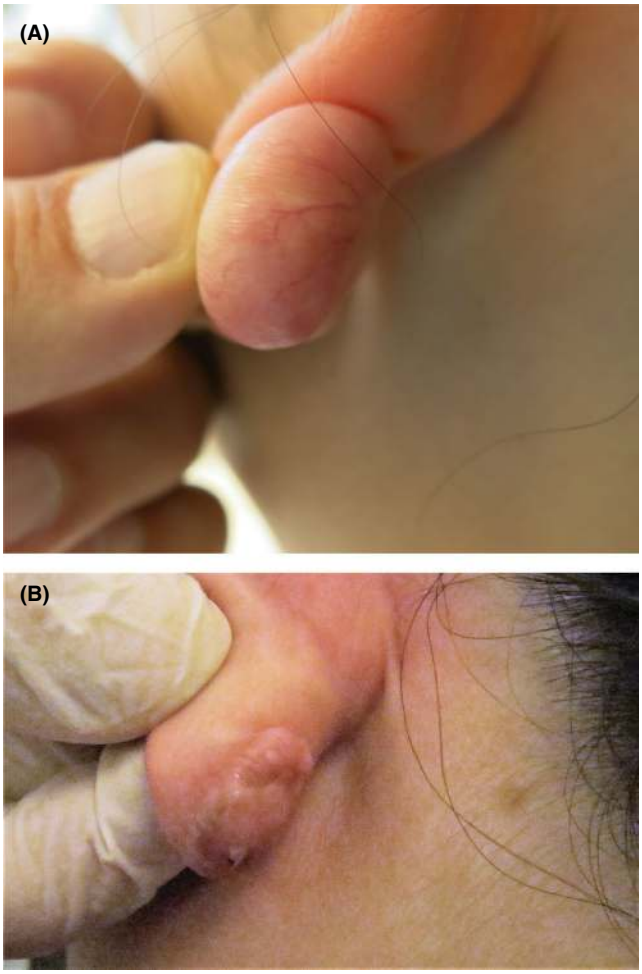

FIGURE 6 A 20-y-old female with postpiercing earlobe keloid: (A) before the treatment and (B) 3 mo after the treatment

easily tolerated by the patients, especially with very large or multiple keloids.[22,23] Unlike fractional lasers and other energy-based devices, the jet injection achieves skin penetration through a 200-μm epidermal entry point, without disrupting skin-protective barriers and lowering the risk of infection and hypersensitivity reactions.[24,25] A small number of observed superficial ulcerations (10% of treated keloids) were associated with the drug-related skin reaction and appeared at significantly lower rate than 60%-65% reported in the literature.[9,15,18]

To our knowledge, this is the first trial exploring management of keloids with jet-assisted delivery of 5FU and steroid. Although statistically significant therapeutic response was achieved in all patients, the study has several limitations. As a retrospective observational trial, it did not include a control group for more objective assessment. The population lack homogeneity in the keloid location, etiology, and age. Patient compliance was low for the longer follow-ups, so we were limited in reviewing longevity of the treatment effect.

Although our results demonstrated potential of the jet injections in keloid management, more investigation is needed. A controlled comparative investigation with large uniformed population and at least 18-month follow-up will be required to further validate and optimize the treatment approach. The efficacy measures should include instrumental tools (ie, sonography) to evaluate precise changes in the lesions. It would be also beneficial to compare efficacy of the jet injections to traditional needle.

5 | CONCLUSION

Improved appearance of keloid scars and symptomatic relief was achieved by intralesional administration of combined 5-fluorouracil and corticosteroid through pressure-controlled jet injections. The treatment presents a good potential for management of keloid scars through the synergy between the jet impact and drugs. Safety and efficacy of the approach were demonstrated in all patients 3 months after the last treatment.

CONFLICT OF INTEREST

There is no any conflict of interest.

AUTHORS CONTRIBUTION

Alex Levenberg received honorarium fee from PerfAction Technologies. Yuri Vinshtok is an employee of PerfAction Technologies. Ofir Artzi received honorarium fee from PerfAction Technologies.

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