Objective: To compare the clinical response of keloidal and hypertrophic scars after treatment with intralesional corticosteroid alone or combined with 5-fluorouracil (5-FU), 5-FU alone, and the 585-nm flashlamp-pumped pulsed-dye laser (PDL).

Design: Prospective, paired-comparison, randomized controlled trial.

Setting: A private ambulatory laser facility.

Patients: Ten patients with previously untreated keloidal or hypertrophic median sternotomy scars at least 6 months after surgery that were considered problematic by the patients.

Interventions: Five segments were randomly treated with 4 different regimens: (1) laser radiation with a 585-nm PDL (5 J/cm²); (2) intralesional triamcinolone acetonide (TAC) (20 mg/mL); (3) intralesional 5-FU (50 mg/mL); and (4) intralesional TAC (1 mg/mL) mixed with 5-FU (45 mg/mL). One segment of each scar received no treatment and served as a control.

Main Outcome Measures: Scar height, erythema, and pliability were evaluated before and every 8 weeks after treatment. Patients’ subjective evaluations were tabulated. Histologic sections of segments were examined in 1 biopsy sample per segment at week 32.

Results: There was a statistically significant clinical improvement in all treated segments. No significant difference in treatment outcome vs method of treatment was noted. However, intralesional formulas resulted in faster resolution than the PDL: scar induration responded better to intralesional formulas, scar texture responded better to the PDL, and scar erythema responded the same as the control with all treatments. Adverse sequelae, including hypopigmentation, telangiectasia, and skin atrophy, were observed in 50% (5/10) of the segments that received corticosteroid intralesionally alone. No long-term adverse sequelae were demonstrated in the segments treated with other modalities.

Conclusions: Clinical improvement of keloidal and hypertrophic scars after treatment with intralesional corticosteroid alone or combined with 5-FU, 5-FU alone, and PDL seemed comparable, with the exceptions of the incidence of adverse reactions, which were most common with intralesional corticosteroid. Intralesional 5-FU is comparable to the other therapies.

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PATIENTS AND METHODS

PATIENTS

Ten patients (6 women and 4 men) aged 25 to 74 years with skin phototypes I (n = 1), II (n = 5), III (n = 2), and VI (n = 2) were enrolled in the study after providing informed consent. All participants had a median sternotomy scar of at least 6 months’ duration that was not healing to their satisfaction, and none had received previous treatment.

STUDY DESIGN AND INTERVENTION

Each scar was divided equally into 5 segments, with an untreated area of 1 cm between individual treated segments to avoid the global effect of PDL and intralesional formulas on the adjacent treated segments and to have a well-defined segment for observation of each treatment modality. Before treatment, each scar was mapped with a permanent marker on a flexible, transparent sheet using natural landmarks such as moles, lentigines, or other anatomic sites as references. Five segments of each scar were randomly treated with 4 different regimens: (1) laser irradiation with a 585-nm PDL (Photogenica V; CynoSure Inc, Bedford, Mass) at an energy density of 5 J/cm² with a 7-mm spot without cooling for 6 treatment sessions at 4-week intervals (the detailed technique of scar treatment with PDL has been previously described11,12 and involves a single pass of spots overlapping 10%-20%); (2) intralesional TAC (Kenalog; Westwood-Squibb, Buffalo, NY) at a concentration of 20 mg/mL every 4 weeks for a total of 6 treatments; (3) intralesional 5-FU (Roche, Nutley, NJ) at a concentration of 50 mg/mL for a total of 10 treatments (every 2 weeks for the first 8 treatments and every 4 weeks for the last 2 treatments); and (4) intralesional TAC (1 mg/mL) mixed with 5-FU (45 mg/mL) for a total of 10 treatments (every 2 weeks for the first 8 treatments and every 4 weeks for the last 2 treatments). No local or topical anesthesia was used in conjunction with any treatment. The injection technique has been described in detail in a previous study4 and involves injection into the center of the scar mass using a 30-gauge needle. One segment of each scar received no treatment and served as a control. The assignment of modality per segment was sequentially rotated from superior to inferior in each patient to adjust for effects of location. Immediate treatment reactions and adverse sequelae on all treated segments were also observed at every follow-up visit.

EVALUATION PROCEDURE

Scar Height, Erythema, and Pliability

A dial caliper (Mitutoyo Corporation, Kawasaki, Japan) was used to determine scar height by measuring the maximum vertical elevation of the scar above normal skin. Scar erythema was measured using a handheld colorimeter (ChromaMeter CR-200; Minolta, Ramsey, NJ). A higher erythema value indicates increased saturation toward red.13 The mean of 3 measurements obtained from each area under study was used. Scar pliability was rated according to a standard scale used to assess functional mobility of the scar related to contracture and the elastic texture of the scar.14

Patient Self-assessment

At the end of the study (week 32), self-assessment of overall scar improvement was subjectively graded by patients as being completely clear (100% improvement) or was placed in a category of 25% increments compared with a standardized photograph taken before treatment.

Histologic Examination

Punch biopsy samples were obtained from 2 representative patients at week 32: 2 from the PDL- and TAC-treated segments of one patient and 2 from the TAC+5-FU and control segments of another patient. Each biopsy sample stained with hematoxylin-eosin was examined for the pattern, arrangement, and characteristics of collagen bundles and fibroblasts and the vascularity features of individually treated segments.

STATISTICAL ANALYSIS

Mean values for scar height, erythema, and pliability were considered significant at P < .05. The percentage of scar flattening and lightening was defined as the percentage of scar height and erythema reduction after treatment compared with baseline height and erythema, respectively. Repeated-measures analysis of variance and standard 2-tailed, paired t-test analyses were performed between means of scar height and erythema of baseline, control, and all treated segments and were used to compare the percentage of flattening and lightening. Scar pliability of baseline, control, and all treated segments was also compared using Friedman and Wilcoxon signed rank tests. The mean scar height, erythema, and pliability values of each treated segment (PDL, TAC alone, TAC+5-FU, and 5-FU alone) and the control segment were also compared based on the aforementioned statistical formulas at each follow-up visit.

RESULTS

BASELINE CHARACTERISTICS OF SCARS

Mean scar duration at the onset of treatment was 7 months (range, 6.0-11.5 months). In all median sternotomy scars, there were no statistically significant differences in thickness, erythema, and pliability for any segments from all patients.

SCAR HEIGHT

All hypertrophic portions of the treated segments showed significant flattening compared with baseline and control segments in all patients (Figure 1 and Figure 2). Laser-irradiated segments showed significant flattening compared with baseline at week 16 (4 weeks after the fourth treatment, P = .01) and compared with control segments at week 32 (12 weeks after the sixth treatment, P = .005). The TAC-treated segments showed significant flattening compared with baseline at week 8 (4 weeks after the second injection, P = .003) and compared with control segments at week 16 (4 weeks after the fourth injection, P = .02). Segments treated with 5-FU showed significant flattening compared with baseline at week 8 (2 weeks after the fourth injection, P = .02) and compared with control segments at week 16 (2 weeks after the eighth injection, P = .003). The TAC+5-FU-treated segments showed significant flattening compared with baseline at week 8 (2 weeks after the fourth injection, P = .004) and compared with control segments at week 8 (2 weeks after the fourth injection, P = .02).

Scar flattening was maintained at all subsequent follow-up visits through week 32 in all treated segments. Control segments showed a slight increase in scar height at week 32 compared with baseline. No statistically significant difference in the mean scar height of all treated
segments vs each other was noted at all follow-up visits through week 32. However, there was a trend toward all intralesional formula therapies providing a greater percentage improvement compared with laser treatment (Figure 3).

**ERYTHEMA**

Compared with baseline, the degree of scar erythema was significantly reduced at week 32 (12 weeks after the sixth treatment) at the laser-irradiated segments ($P=.02$), at week 16 (2 weeks after the eighth injection) at the 5-FU–treated ($P=.01$) and control ($P=.03$) segments, and at week 24 (2 weeks after the tenth injection) at the TAC+5-FU–treated segments (Figure 1 and Figure 4). However, there was no significant difference in the degree of erythema at the TAC-treated segments at baseline vs all follow-up visits.

In this study, only the red tone representing the scar erythema was recorded by the colorimeter. Isolated telangiectatic vessels would not be expected to have a predictable measurable impact on this measurement. In addition, there was mild hypopigmentation in 2 of 10 patients after receiving 2 and 6 TAC injections, respectively. This might have an effect on the recorded measurement as well.

No significant differences in scar erythema were shown among treatment modalities at all follow-up visits through the end of the study. There also was no significant difference in degree of erythema lightening between each treated segment and the control segments.

**PLIABILITY**

All patients showed significant softening of the hypertrophic portions of their scars vs baseline at all intralesional-treated segments (Figure 5). Significant softening was initially seen as early as week 8 at TAC-treated (4 weeks after the second injection, $P=.02$) and TAC+5-FU–treated (2 weeks after the fourth injection, $P=.02$) segments and by week 16 (2 weeks after the eighth...
injection, \( P = .02 \)) at 5-FU–injected segments. No statistically significant softening of the laser-irradiated segments vs baseline was seen, whereas significant softening of the control segments vs baseline was initially noted at week 24 (\( P = .046 \)), but it was not maintained through the week 32 follow-up visit.

**IMMEDIATE TREATMENT REACTION AND ADVERSE SEQUELAE**

Mild to moderate discomfort or pain described as similar to the sensation of a rubber band snapping was reported in 90% (9/10) of the patients during laser pulsing at the PDL-treated segments, whereas mild to moderate pain during injection was noted in 100% (10/10) of the patients at the TAC–, 5-FU–, and TAC+5-FU–treated segments. There was no difference in the initial pain of injection of TAC vs 5-FU, but a burning discomfort from 5-FU was reported to last 30 minutes to several hours. Spots of purpura were seen at the 5-FU and TAC+5-FU injection sites in 20% to 30% (2/10 to 3/10) of the patients at each follow-up visit. One of the 10 patients developed localized superficial tissue slough at the TAC+5-FU injection site after the first treatment visit, but this reaction was not observed after the subsequent treatments. Purpuric discoloration was seen at the laser-irradiated segments of all patients. Erosion secondary to blistering was observed on some areas treated with laser in 2 patients with skin phototype VI.

Adverse sequelae, including hypopigmentation (20%, 2/10), telangiectasia (20%, 2/10), and skin atrophy (10%, 1/10), were seen in 50% (5/10) of the segments that received TAC injection alone. Some of these adverse effects were initially noted as early as week 8 (4 weeks after the second injection), and all persisted through 32-week follow-up. No persistent adverse sequelae were demonstrated in segments treated with the other modalities.

**PATIENT SELF-ASSESSMENT**

Figure 6 summarizes the percentage of improvement using each treatment modality as assessed by patients at the end of the study (week 32). Fifty percent improvement or higher was rated by 80% (8/10) of the patients at the laser-irradiated segments, 100% (10/10) at the TAC-treated segments, 100% (10/10) at the 5-FU–treated segments, and 90% (9/10) at the TAC+5-FU–treated segments. Control segments were graded as less than 50% improvement by 60% (6/10) of the patients. An improvement in skin texture toward that of adjacent normal skin was also noted in all laser-irradiated segments but in no other segments.

**HISTOLOGIC FINDINGS**

At the week 32 follow-up visit, 4 biopsy specimens were obtained from 2 of the 10 patients: 2 from a laser- and a TAC-treated segment of one patient and 2 from a TAC+5-FU–treated and a control segment of another patient (Figure 7). There were subtle differences among the treated segments but a more dramatic difference between all treated areas and the control segment. The thick condensed collagen bundles of the untreated segment particularly contrast with the finer, more loosely woven fibers of the treated segments.
Figure 7. Histologic findings from 2 representative patients. A and B, Pulsed-dye laser–irradiated segment. Note the significantly finer and loosely interwoven collagen bundles parallel to the epidermis in the more superficial locations and the more dense and larger bundles in the deeper dermis. The vessels are significantly smaller throughout (original magnification ×40). C and D, Triamcinolone acetonide–treated segment. Note the dense and thick collagen bundles throughout the dermis, although less condensed than in the control. Predominant visibility and number of vessels stream through the collagen throughout (original magnification ×40). E and F, Triamcinolone acetonide– and 5-fluorouracil–treated segment. Fine interwoven collagen with small dark nuclei of fibroblasts are in the upper dermis, and more condensed and larger collagen bundles with more plump fibroblasts are in the deeper dermis (original magnification ×40). G and H, Control segment. Note the thick condensed bundles of collagen with large oval basophilic fibroblasts in the middle to lower dermis and the finer bundles of collagen in the superficial dermis (original magnification ×40).
Although the basis for keloid and hypertrophic scar formation has not been fully delineated, an imbalance of matrix degradation and collagen biosynthesis resulting in excess accumulation of collagen in the wound has been postulated to be the primary biochemical features of these skin lesions.\(^5\)\(^,\)\(^15\) Fibroblasts construct new extracellular matrix components, initiate collagen synthesis, and provide wound edge tension through contractile proteins, actin, and desmin. Keloid- and hypertrophic scar-derived fibroblasts produce increased amounts of collagen per cell compared with normal fibroblasts.\(^16\) Thus, suppression of the overwhelming and uncontrolled fibroblast activity in keloids and hypertrophic scars may be essential in therapeutic approaches to this abnormal wound response.

The efficacy of corticosteroid injections in the treatment of keloids and hypertrophic scars has been well-established. Suppressive mechanisms of corticosteroids on wound healing include (1) interruption of the inflammatory process by inhibition of inflammatory cell migration and phagocytosis, (2) a vasoconstriction effect resulting in disruption of the oxygen and nutrient supply to the wound, and (3) antimitotic activity on fibroblasts and keratinocytes, which may be the most important mechanism.\(^17\) The most commonly used corticosteroid is TAC. The dosage and treatment interval have arbitrarily varied from 10 to 40 mg/mL administered at intervals of 4 to 6 weeks for several months or until the scar is flattened. Although intralesional TAC administration has shown clinical efficacy, the outcome has been uncertain and associated with multiple adverse effects, including atrophy, telangiectasia, and pigmentedary changes.\(^15\)\(^,\)\(^18\) Recently, the combined use of intralesional TAC and 5-FU in the treatment of inflamed hypertrophic scars has been reported to be effective and can avoid these potential complications.\(^4\) 5-Fluorouracil, a pyrimidine antimetabolite, has been used as an adjunct to glaucoma filtering surgery, a procedure in which inhibition and prevention of postoperative scarring is essential for achieving surgical success.\(^5\)\(^,\)\(^10\)\(^,\)\(^16\)\(^,\)\(^17\) 5-Fluorouracil inhibits fibroblast proliferation in vitro\(^5\) and in vivo.\(^1\) Long-term follow-up studies\(^10\) of the ophthalmic surgery using 5-FU confirm its efficacy and safety.

The effectiveness of PDL in the treatment of keloids and hypertrophic scars has been well documented\(^11\)\(^,\)\(^19\) and has been thought to be mediated by selective damage of the microvasculature of the scar.\(^20\) A fluence-dependent inhibition of hypertrophic scar implants in mice was proportional to the fluence from 6 to 10 J/cm\(^2\) using a candela PDL. In contrast, previous clinical studies\(^11\)\(^,\)\(^21\) on the PDL treatment of scars noted no significant difference in the treatment outcome vs minor variations in fluence used (6.0-7.5 J/cm\(^2\)). Similarly, our recent controlled study\(^22\) noted no statistically significant fluence dependence of the clinical improvement of keloidal and hypertrophic median sternotomy scars after PDL treatment. However, a trend toward better response with lower fluence was observed. A dose-response study\(^23\) of treatment of striae distensae demonstrated enhanced response at lower fluence. This response was speculated to be mediated by stimulation of elastic tissue.\(^22\)

A recent study\(^23\) of the efficacy of the 585-nm PDL in treatment of hypertrophic scars showed that the clinical improvement in scar sections treated with 4 PDL irradiations at 8-week intervals was no different than that in control sections. Several factors were postulated to affect this difference in clinical results from other previous studies: differences in the range of patient skin phototypes, a tendency for partial spontaneous resolution of scars less than 1 year old in previous studies, and a global effect of PDL on the adjacent sections used as a control in the recent study.\(^23\) This was in contrast to an average improvement in nonfacial scars of 81% after 2.5 treatments with PDL reported by Goldman and Fitzpatrick.\(^11\) This positive result is confirmed by the present study as there was statistically significant flattening of the scars at the PDL-irradiated segments vs baseline as early as week 16 (4 weeks after the fourth treatment) and vs the control at week 32 (12 weeks after the sixth treatment). In addition, a significantly higher percentage of scar flattening was noted after more than 2 treatments. Therefore, multiple sequential treatments may be essential for achieving a better clinical response. The increase in epidermal melanin in dark-skinned individuals is a competitive chromophore to the hemoglobin at the 585-nm wavelength of the PDL. Four patients with darker skin (2 patients with skin phototype III and 2 with skin phototype VI) were also included in the present study. Although the number of patients was too small to assess the statistical difference in clinical improvement compared with fair-skinned patients (skin phototypes I and II), the mean scar height of these type III and VI patients was also substantially decreased at the PDL-irradiated segments. A global effect of PDL on adjacent nontreated scar tissue might explain the indifference in clinical improvement between PDL-treated and adjacent control sections reported in the study by Wittenberg et al\(^23\) as we also observed this improvement effect at the adjacent nontreated segments in our patients.

The improvement in skin texture of scars treated with PDL is an interesting observation because it adds a significant cosmetic element to the improvement seen. Textural changes such as this are thought to be the result of collagen remodeling and are the basis of the improvement seen with treatment of photoaged skin with nonablative resurfacing.\(^24\)\(^-\)\(^27\) It is not surprising that this effect would be observed with this treatment as well.

The average time to onset of action of scar flattening of all intralesional formulas was comparable and was seen at an earlier follow-up period than that of PDL (week 8 vs week 16). However, the number of treatments required for achieving the onset of this therapeutic response varied from 2 treatments at 4-week intervals with TAC to 4 treatments at 2-week intervals with 5-FU and TAC + 5-FU to 4 treatments at 4-week intervals at the PDL-irradiated segments. Onset of action of scar softening was seen as early as week 8 at the TAC- and TAC+ 5-FU-treated segments at week 16 at the 5-FU-treated segments. Although no significant scar softening was noted at the 5 J/cm\(^2\) PDL-irradiated segments, there was a trend toward pliability score reduction after each treatment session. The study by Alster and Williams\(^19\) and our recent study\(^12\) also found statistically significant improvement in scar pliability after treatment with PDL at fluences of
The fact that scar pliability was a subjective evaluation might affect the accuracy of its assessment. All treatment modalities provided significant improvement in scar height and pliability but not scar erythema. In addition, the improvement was sustained through the week 32 follow-up visit (10-12 weeks after the last treatment). Because the natural history of spontaneous improvement of scars during the first 6 to 12 months after integumental injury, especially in terms of erythema, may complicate the interpretation of treatment evaluation, it was not surprising that there was no significant improvement in scar erythema noted with any treatment modalities compared with controls. These particular scars were all of 6 to 12 months’ duration, a time during which improvement is to be expected.

All intralesional formulas seemed to have comparable effectiveness in scar flattening and had a trend toward a higher degree of effectiveness than laser treatment. However, because the treatment of scars is often undertaken for at least some cosmetic concerns, the treatment should be free of adverse sequelae in addition to being judged effective. Transient burning sensation or discomfort was the most common immediate adverse effect reported by all patients at the TAC + 5-FU- and 5-FU-treated segments, and purpuric discoloration usually lasting 7 to 10 days was seen in all patients at the laser-irradiated segments. At week 32, adverse sequelae were seen only at the TAC-treated segments in half of the patients, whereas no adverse effects were found at the segments treated with the other modalities. Atrophy, telangiectasia, and hypopigmentation are not acceptable adverse effects for most patients.

Inactive fibroblasts were seen on all the biopsy specimens obtained at laser-, TAC-, and TAC + 5-FU-treated segments. The tissue vascularity of the laser-irradiated segment was particularly less prominent than that of the TAC-treated segment. This hypovascular state of the TAC-treated segment may result from the adverse effect of the intrallesional corticosteroid, which presents clinically in the form of telangiectasia. The TAC-treated segment seemed to have altered tissue effects throughout the depth of the specimen, which is probably because of the depot effect and diffusion of action.

In summary, clinical improvement of keloidal and hypertrophic scars was seen after treatment of hypertrophic and keloidal sternotomy scars with intrallesional corticosteroid alone or combined with 5-FU, 5-FU alone, and 585-nm PDL; overall, the end results were comparable. Use of the intrallesional formulas provided a more rapid response, but intrallesional corticosteroid therapy is much more likely to cause adverse effects. Use of intrallesional 5-FU is a reasonable alternative. The histologic findings of each treatment reflect the clinical findings. Management of these lesions should be individualized according to the patient’s desires and expectations. Some patients may not respond to any single treatment modality, and the use of multiple treatment modalities may be the best approach for maximizing therapeutic success.

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