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Pentoxifylline for the Prevention of Postsurgical Keloid Recurrence

Andrea Tan, BS,

Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas

Orlando Martinez Luna, BS,

Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas

Donald A. Glass II, MD, PhD

Department of Dermatology and McDermott Center for Human Growth and Development,
University of Texas Southwestern Medical Center, Dallas, Texas

Keloids are abnormal overgrowths of dermal fibrous tissue due to an exaggerated wound healing response after cutaneous insults. Although surgical excision is a common treatment option, recurrence rates after surgery can be high, especially without postoperative treatment modalities.¹ The current postoperative standard of care is to administer monthly intralesional triamcinolone injections. However, even for patients with a high disease burden (e.g., with multiple symptomatic keloids), there are no systemic treatments typically employed.²

Pentoxifylline is a methylated xanthine derivative and a nonspecific phosphodiesterase inhibitor used to treat claudication from peripheral artery disease by reducing inflammation and increasing blood flow. Pentoxifylline has also been shown to inhibit the proliferation and rate of collagen synthesis of fibroblasts from keloids, scleroderma, and morphea in vitro.^{3,4} Although not labeled for use in the treatment of keloids, pentoxifylline has been noted to decrease pain and itch and halt growth in severely symptomatic keloids.⁵

To assess the clinical efficacy and side effect profile of oral pentoxifylline in keloid treatment, a retrospective, open-label pilot study analyzing postsurgical keloid recurrence rates was conducted. The primary goal of the present study was to determine whether the administration of postoperative oral pentoxifylline in patients who underwent keloid excision is associated with a decrease in keloid recurrence.

Methods

The Genetic Causes of Keloid Formation Study (GCKFS) is a University of Texas Southwestern Medical Center Institutional Review Board– approved research study. A retrospective study was performed on participants enrolled in the GCKFS; inclusion criteria included a diagnosis of keloids and at least one keloid surgically removed in 1 of 2 dermatologic clinics from October 2012 to December 2016. Exclusion criteria included

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contraindications for pentoxifylline administration such as breast-feeding, concurrent anticoagulation therapy, or history of stroke.

Prior to surgery, patients were triaged by disease burden as either low risk or high risk of postoperative keloid recurrence, based on factors including multiple symptomatic keloids, history of recurrence, and family history (Table 1). All patients received 40 mg/mL of intralesional triamcinolone acetonide monthly for 6 months postsurgery as per standard of care. High-risk patients were additionally prescribed pentoxifylline 400 mg by mouth 3 times a day for 6 months postsurgery. High-risk patients who completed the 6-month course of pentoxifylline were designated as “High-Risk Treated Group,” whereas high-risk patients who could not tolerate pentoxifylline and discontinued treatment within the first 2 weeks or who had preexisting contraindications were designated as “High-Risk Control Group” (Figure 1). Patients who were considered low risk for recurrence, for whom pentoxifylline was not indicated, were designated as “Low-Risk Control Group,” and received no additional treatment besides intralesional triamcinolone. Clinical factors assessed at each follow-up included treatment compliance, tolerability and side effects of pentoxifylline, and whether the keloid recurred. Data were collected at 1, 3, and 6 months after keloid excision.

Results

A total of 67 unique keloids from 45 patients who met inclusion criteria were surgically excised. Thirty-nine keloids were considered high risk, of which 2 were not prescribed pentoxifylline because it was contraindicated due to breast-feeding; the remaining 37 were started on pentoxifylline. Twenty-eight keloids were considered low risk and were not prescribed pentoxifylline. At the 6-month follow-up, there were 19 keloids total in the “High-Risk Treated Group,” 6 keloids in the “High-Risk Control Group,” and 9 keloids in the “Low-Risk Control Group.” The “High-Risk Control Group” was composed of keloids that did not take 6 months of pentoxifylline due to side effects or contraindications—3 from nausea, 1 from menorrhagia, and the 2 previously mentioned due to breast-feeding. The remaining patients with keloids were lost to follow-up over the 6-month period.

Keloid Recurrence Rates

At the 6-month follow-up, the Low-Risk Control Group (for which pentoxifylline was not indicated) had 2 of the 9 keloids recur (22.2%). The High-Risk Control Group (which could not tolerate pentoxifylline) had 4 of 6 keloids recur (66.7%). In contrast, the High-Risk Treated Group only had 2 of 19 keloids recur (10.5%) after 6 months. The demographics of those who recurred, those who did not, and those lost to follow-up are listed in Table 2.

A Fisher exact test was performed to determine whether there was a significant association between keloid recurrence and treatment with pentoxifylline in high-risk patients; a p -value of .015 was obtained and found to be significant at $\alpha = 0.05$. The strength of the relationship was further assessed by calculating the odds ratio (0.0588) and phi coefficient (20.5614). Based on these results, a substantial negative relationship between treatment with pentoxifylline and recurrence of keloids in high-risk patients could be concluded.

Discussion

In this pilot study, there was a statistically significant decrease in postsurgical keloid recurrence rate at 6 months for the High-Risk Treated Group (10.5%) versus the High-Risk Control Group (66.7%). Furthermore, the recurrence rate in the High-Risk Treated Group was even lower than that of the Low-Risk Control Group (22.2%), for which pentoxifylline was not prescribed given the lower disease burden and likelihood of recurrence.

These preliminary findings suggest that pentoxifylline could potentially play a role in keloid treatment by decreasing recurrence rates after surgical excision. Pentoxifylline is well suited to serve as an adjunctive systemic agent to decrease keloid recurrence: it has already received approval from the Food and Drug Administration, is relatively safe, and does not require laboratory monitoring. The drug was tolerated well by the majority of those prescribed it—only 4 of the 37 keloids initially treated with pentoxifylline experienced adverse effects (3 from nausea and 1 from menorrhagia).

Limitations of this study include a small sample size and lack of random assignment given its retrospective nature. As such, the High-Risk Treated Group and High-Risk Control Group differed in the rates of previous recurrences and the locations of keloids, which could have influenced the study results. The data analysis was not performed with an intention to treat; in addition, many patients were lost to follow up. Designation of patients as high risk or low risk was accomplished through clinical triage by a single surgeon at a single academic site because there is not yet a widely accepted keloid-specific severity index. Larger prospective studies using other validated scar assessment tools, such as the Patient and Observer Scar Assessment Scale or a keloid-specific severity index, are needed to confirm these findings, especially with longer-term treatment duration and follow-up over the span of several years.

In summary, the significant decrease in postsurgical recurrence rate for high-risk patients taking pentoxifylline suggests that pentoxifylline may be a useful adjunct for keloid treatment. Future studies should continue to explore the role of pentoxifylline as a treatment modality for keloids.

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Figure 1.

Flowchart of assessed Keloid lesions. Flowchart demonstrating the categorization of keloid lesions into the High-Risk Treated Group, High-Risk Control Group, and Low-Risk Control Groups. PTX, pentoxifylline.

TABLE 1.

Demographics by Treatment Group

Characteristic	High-Risk Treated (n = 19)	High-Risk Control (n = 6)	Low-Risk Control (n = 9)
Age, mean (SD), yr	52.5 (16.2)	35.8 (7.4)	45.7 (12.4)
Sex, no. (%)			
Male	13 (68.4)	1 (16.7)	1 (11.1)
Female	6 (31.6)	5 (83.3)	8 (88.9)
Ethnicity, no. (%)			
African American	16 (84.2)	6 (100)	5 (55.6)
Hispanic	3 (15.8)	0 (0)	4 (44.4)
Painful, no. (%)	13 (68.4)	5 (83.3)	5 (55.6)
Pruritic, no. (%)	19 (100.0)	4 (66.7)	8 (88.9)
Previous recurrence, no. (%)			
Yes	7 (36.8)	3 (50.0)	3 (33.3)
No	12 (63.2)	3 (50.0)	6 (66.7)
Family history, no. (%)			
Yes	8 (42.1)	1 (16.7)	0 (0)
No	4 (21.1)	1 (16.7)	4 (44.4)
Unknown	7 (36.8)	4 (66.7)	5 (55.6)
Keloid area, mean (SD), cm ²	11.2 (11.3)	9.2 (10.2)	10.1 (9.5)
Keloid location, no. (%)			
Scalp	2 (10.5)	0 (0)	0 (0)
Face	1 (5.3)	0 (0)	0 (0)
Ear	6 (31.6)	2 (33.3)	6 (66.7)
Neck	0 (0)	1 (16.7)	2 (22.2)
Shoulder	1 (5.3)	0 (0)	1 (11.1)
Chest	0 (0)	2 (33.3)	0 (0)
Trunk	7 (36.8)	1 (16.7)	0 (0)
Groin	2 (10.5)	0 (0)	0 (0)

TABLE 2.

Demographics by Treatment Outcome

Characteristic	Recurred (<i>n</i> = 8)	Not Recurred (<i>n</i> = 26)	Lost to Follow-up (<i>n</i> = 33)
Age, mean (SD), yr	41.0 (8.2)	49.8 (16.3)	38.7 (16.2)
Sex, no. (%)			
Male	3 (37.5)	12 (46.2)	9 (27.3)
Female	5 (62.5)	14 (53.8)	24 (72.7)
Ethnicity, no. (%)			
African American	8 (100)	19 (73.1)	21 (63.6)
Hispanic	0 (0)	7 (26.9)	11 (33.3)
Caucasian	0 (0)	0 (0)	1 (3.0)
Painful, no. (%)	6 (75.0)	17 (65.4)	24 (72.7)
Pruritic, no. (%)	6 (75.0)	25 (96.2)	27 (81.8)
Previous recurrence, no. (%)			
Yes	4 (50.0)	9 (34.6)	8 (24.2)
No	4 (50.0)	17 (65.4)	25 (75.8)
Family history, no. (%)			
Yes	2 (25.0)	7 (26.9)	3 (9.1)
No	2 (25.0)	7 (26.9)	14 (42.4)
Unknown	4 (50.0)	12 (46.2)	16 (48.5)
Keloid area, mean (SD), cm ²	9.1 (9.3)	11.1 (10.9)	4.9 (6.3)
Keloid location, no. (%)			
Scalp	0 (0)	2 (7.7)	1 (3.0)
Face	1 (12.5)	0 (0)	1 (3.0)
Ear	1 (12.5)	13 (50.0)	27 (81.8)
Neck	2 (25.0)	1 (3.8)	0 (0)
Shoulder	1 (12.5)	1 (3.8)	1 (3.0)
Chest	2 (25.0)	0 (0)	0 (0)
Trunk	1 (12.5)	7 (26.9)	2 (6.1)
Groin	0 (0)	2 (7.7)	1 (3.0)