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Keloid Intralesional Excision Reduces Recurrence: A Meta-analytic Study of the Available Literature on 608 Keloids

Nathan G. Lawera, MD*
Jules Madzia, PhD*
Liann C. Casey, MD*
Rodney L. Guyton, MD*
Kiersten C. Woodyard De Brito, BS*
Alexandra Kinzer, MD*
Raquel M. Ulma, MD, DDS*
Brian S. Pan, MD*
Ann R. Schwentker, MD*
Angelo A. Leto Barone, MD*†

Background: The objective of this meta-analysis was to examine the effectiveness of keloid intralesional excision (KILE) in preventing recurrence. Treatment of keloids using surgical excision alone leads to high rates of recurrence. To date, there are no widely accepted guidelines for keloid treatment, and a multitude of adjunctive therapies are used to reduce recurrence. Despite these efforts, recurrence remains high. In this study, we conducted a meta-analysis of the existing literature on KILE to determine its role in recurrence reduction.

Methods: A literature review using PubMed, Scopus, and Web of Science databases was performed. Two authors independently evaluated studies for eligibility. Incidence of keloid recurrence was recorded, and a comprehensive meta-analysis was performed to assess the pooled keloid recurrence rate, as well as the effect of additional therapies.

Results: Twenty-two studies evaluating intralesional excision of 608 keloids were included in the study. Average time to follow-up was 19.2 months (range 6–35 months). A meta-analysis of proportions was conducted, demonstrating a pooled recurrence rate of 13% (95% confidence interval, 9%–16%). There was no evidence that using therapies in addition to KILE had a significant effect on the overall pooled recurrence rate.

Conclusions: A meta-analysis of 608 keloids shows that KILE is an effective technique in preventing keloid recurrence, with a pooled recurrence rate of 13% compared with previously reported rates of 45%–100% after complete excision. Although there are no standard guidelines for keloid treatment, our meta-analysis shows that KILE is promising in recurrence reduction. *(Plast Reconstr Surg Glob Open 2024; 12:e5652; doi: 10.1097/GOX.0000000000005652; Published online 8 March 2024.)*

INTRODUCTION

Keloids are reported to occur in 11% of all cases of scarring.[1] They are raised, rubbery, nodular benign growths that result from abnormal wound healing. Keloids extend beyond the area of skin injury, rise above the skin level, and have histological characteristics that are distinct from hypertrophic scars.[2] They do not regress, and treatment with surgical excision alone leads to recurrence rates ranging from 45% to 100%.[3] They affect darker skinned populations disproportionately: studies show that keloids occur in 4.5%–16% of skin injury in darker pigmented populations.[4]

Arising as a complication of wound healing, bulky keloid lesions cause severe mental and physical morbidity, and a decreased quality of life.[5] Many treatment options and combinations of treatments exist. A recent review described various current treatment strategies for keloids including occlusive and compressive dressings,

*From *Division of Pediatric Plastic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and †Division of Plastic and Craniofacial Surgery, Nemours Children's Hospital, Orlando, Fla.*

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Drs. Lawera and Madzia contributed equally to this work.

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intralesional steroids, topical imiquimod, topical mitomycin C, intralesional and topical 5-fluorouracil, interferons, bleomycin, skin grafts, cryotherapy, radiation therapy, and laser treatments, although none of these treatments have a high efficacy.[6] In fact, the number of and wide range of treatment modalities indicates that consensus on effective treatment is lacking, and no standardized guidelines exist in the US for keloid treatment.

Widely used outside the United States, keloid intralesional excision (KILE) and core excision (CE) of keloids are predominant in Europe, Asia, and Africa. In KILE the large majority of the keloid is excised as a wedge, leaving a rim of keloid tissue on each side which is then primarily closed (Fig. 1). CE entails the extirpation of the central bulk of the lesion, leaving a portion of the pathologic tissue in the form of a thin shell, or flap that is then closed over.[7,8] Despite the various terms used to describe these methods, the principle is the same: debulk the lesion and leave behind a small portion of the keloid tissue, avoiding trauma to the unaffected skin. The success of this procedure has been demonstrated on a small scale in literature published outside the United States. A Japanese Scar Workshop consensus document in 2018 describes CE as a treatment option.[9]

There are no randomized control trials (RCTs) on KILE, and there are no retrospective studies that include more than 100 cases. This study compiles the current literature and provides a meta-analysis demonstrating the efficacy of KILE as a treatment modality for keloid disease.

METHODS

A search of PubMed, Scopus, and Web of Science was conducted for all papers published before January 2022, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[10] The search was conducted to find all investigations looking at intralesional excision of keloids. Initial keywords were "keloid," and "intralesional excision" or "core excision"; the search was further expanded in PubMed to include "keloid" and "excision." The following inclusion criteria were used: full-length articles that described methods and results sufficiently for analysis, studies that employed a true method of KILE, studies reporting recurrence rates, and articles with more than five cases. The following exclusion criteria were used: full articles that were not available in English and articles not using human subjects. There were no exclusions made based on characteristics of study populations,

Takeaways

Question: What is the likelihood of keloid recurrence after intralesional excision, based on a meta-analysis of the existing literature?

Findings: Data from 23 studies evaluating 608 keloids treated with intralesional excision showed a recurrence rate of 13% versus 45%–100% recurrence occurring after complete excision. Additional therapies did not have an effect on keloid recurrence.

Meaning: This meta-analysis demonstrates that intralesional keloid excision may have much lower rates of recurrence than previously reported techniques, indicating that intralesional keloid excision could be a promising method for recurrence reduction.

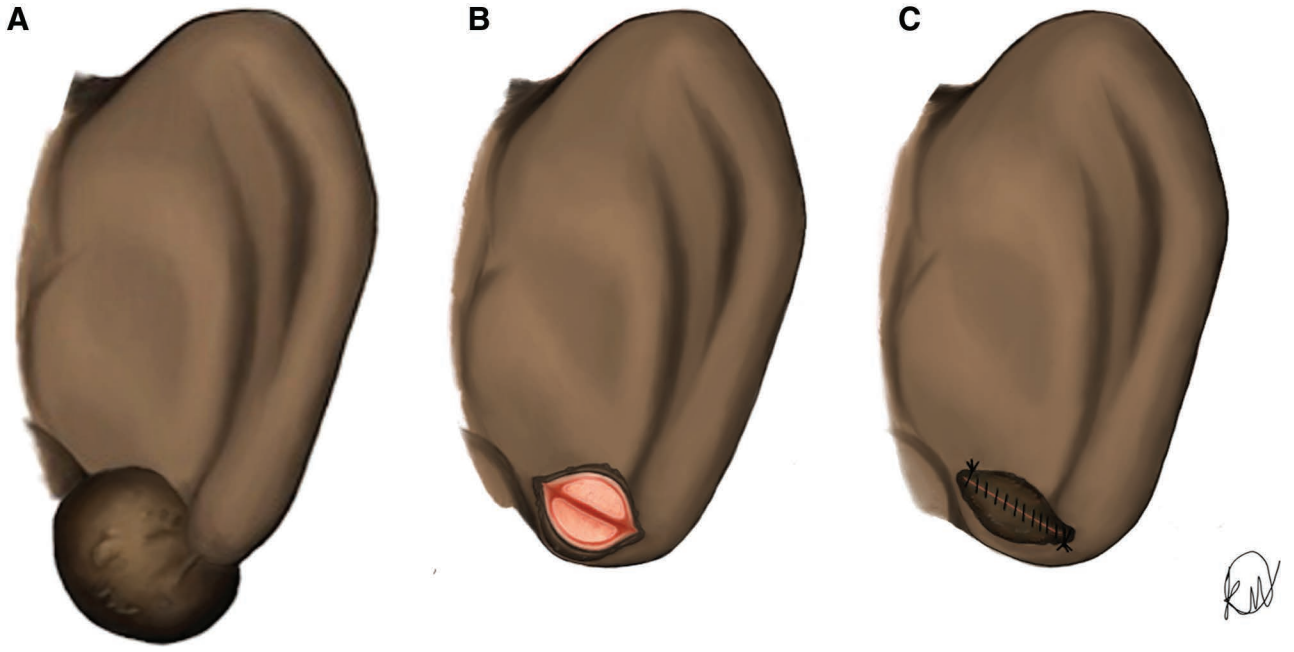

Fig. 1. Illustration of intralesional excision technique. Preoperative illustration of posterior auricle width auricular keloid (A). Intraoperative illustration of postexcision of wedge-shaped bulk of keloid and skin, leaving a symmetric margin of keloid tissue and skin flaps to approximate (B). Postoperative closure (C).

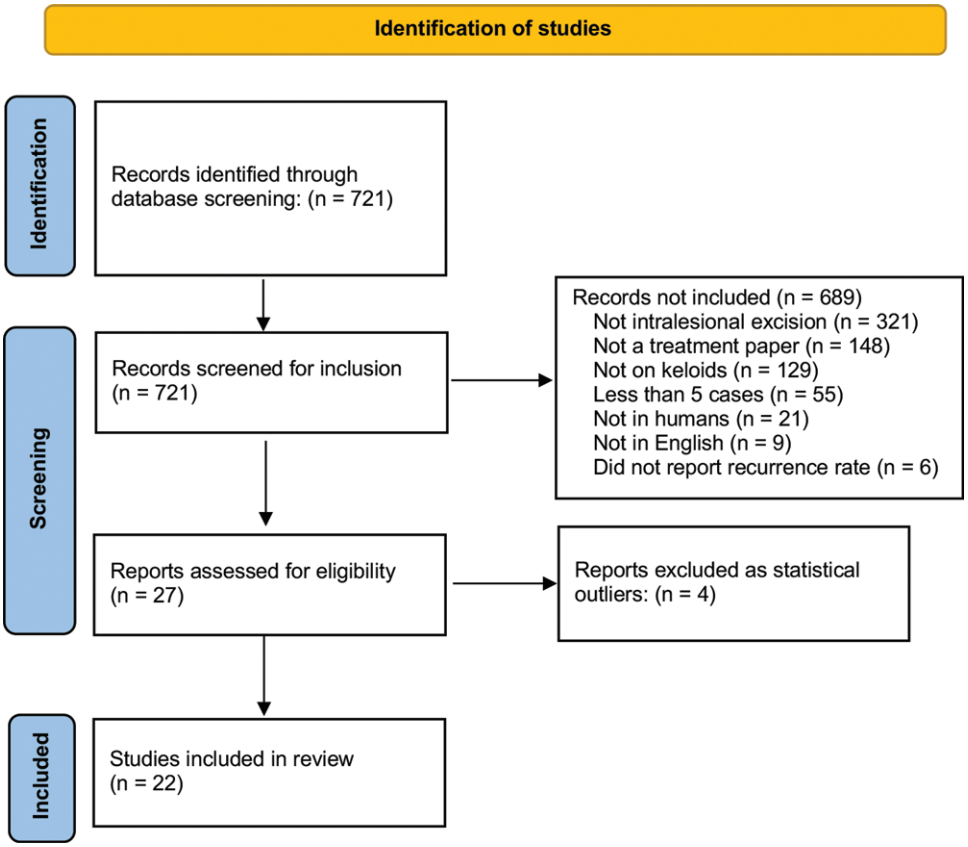

Fig. 2. PRISMA flow diagram of the study selection process.

use of adjuvant therapies, or time to follow-up. Two authors independently evaluated studies for eligibility using the predetermined criteria. Articles were initially screened by title and abstract. A summary of the review process can be found in Figure 2. Articles meeting criteria for inclusion in the study, and articles where further information was needed to determine eligibility were reviewed in full. Data were recorded from the studies by one reviewer and confirmed by another review. No automation tools were used in the selection process or data collection.

A power analysis conducted a priori demonstrated that the required number of studies to achieve 80% power for detecting a medium effect size was n = 6, assuming moderate heterogeneity and an average within-study sample size of 25. Meta-analyses of rates of recurrence were calculated using R studio (version 2021.09.0) package Metafor and Meta software.[11,12] A random effects model was used in anticipation of heterogeneity. Weighted average proportions were calculated to estimate effect sizes for each study. Proportions were logit-transformed to account for observed recurrence rates that were close to 0. Individual effect sizes were then pooled to calculate a logit-transformed summary proportion. These proportions were then converted back to the nontransformed proportion, yielding true summary proportions of recurrence and their 95% confidence intervals (CIs). We screened all studies for externally studentized residuals (calculated by dividing the residual by an estimate of its SD) to identify studies with outlying effect sizes using the R package Metafor, and excluded studies with residuals larger than 2.0. Proportions were converted to percentages to increase ease of interpretation.

Heterogeneity was expressed using the I^2 statistic, with 0%–40% considered low, 30%–60% as moderate, 50%–90% as substantial, and 75%–100% as considerable heterogeneity.[13] A forest plot was created to visualize point estimates of study effects and their CIs. A funnel plot was used to graphically assess publication bias, and Egger regression test was used to quantify the likelihood of publication bias. To determine whether therapies given simultaneously with KILE (preoperative steroids, intraoperative steroids, postoperative steroids, cryotherapy, radiation, pressure therapy, laser, 5-FU, skin graft, silicone sheet, mitomycin, and PRP) contributed to significantly different effect sizes, a meta-regression was run to estimate how the effect of additional interventions in each subgroup differed from the reference group receiving only KILE. This meta-regression model also included time to follow-up for each study to assess whether this contributed significantly to different effect sizes. Adjunctive treatments were treated as dichotomous variables, and time to follow-up was treated as a continuous variable measured in

Table 1. Additional Therapies [Number of Keloids (Percentage)] Used in Each Study

Authors, Year	Preoperative Steroids	Intraoperative Steroids	Postoperative Steroids	Radiation	Pressure Therapy	Cryotherapy	5-Fluorouracil	Laser	Calcium Channel Blocker	Skin Graft	Silicone Sheet	Mitomycin C	Platelet-rich Plasma
Madura et al[14]		32 (71.1)	40 (88.89)			8 (17.8)	1 (2.22)	Unclear					
Choi et al[25]			20 (100)										
Jun et al[28]					22 (100)								
Lee et al[8]													
Al Aradi et al[29]		21 (100)	21 (100)										
Cerejeira et al[30]			16 (100)										
Donkor et al[31]			18 (100)										
De Sousa et al[32]		22 (100)	22 (100)								22 (100)		
Kim et al[33]			4 (44.4)										
Hao et al.,2019[34]			98 (100)		98 (100)								
Azzam et al[15]			unclear			37 (100)							37 (100)
Zhang et al[16]				74 (100)									
Walliczek et al[17]			42 (100)		42 (100)								
Sun et al[18]			43 (100)	43 (100)									
Stewart et al[19]			2 (20)									10 (100)	
Park et al[20]					40 (100)								
Park et al[21]					40 (100)								
Jung et al[22]	18 (100)		18 (100)										
Rasheed et al[23]			6 (100)							6 (100)			
Mohammadi et al[24]			22 (100)										
Ogawa et al[26]			Unclear	108 (100)									
El-Kamel et al[27]									19 (100)				
Total	1	3	16	3	5	2	1	1	1	1	1	1	1

months. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

The literature search resulted in 721 articles, of which 27 met the inclusion criteria. No randomized controlled trials were found. After excluding statistical outliers by assessing studentized residuals, a total of 22 studies were included in the meta-analysis, totaling 608 keloids.[8,14–34] (In cases where one patient had multiple keloids treated, each keloid was considered a unique case.) Additional therapies used are summarized in Table 1. The most common additional therapy was postoperative steroids (n = 16 studies), followed by pressure therapy (n = 5), intraoperative steroid use (n = 3), and radiation (n = 3). The mean age of patients in the 22 studies was 24.9 years; mean age was not reported in seven studies. Of all patients studied, 79% were women and 21% were men; sex was not included in three studies. Only four studies included information on patients' race/ethnicity.[19–21,25] Average time to follow-up was 19.2 months (range 6–35 months). Shorter time to follow-up was not associated with lower recurrence rate ($P = 0.63$). Demographic data and keloid recurrence rates for the studied patients are summarized in Supplemental Digital Content 1. [**See table, Supplemental Digital Content 1,** which displays the demographics of patients and keloid recurrence rates reported in the twenty-three studies of intralesional keloid excision efficacy. (NR = not reported.) **http://links.lww.com/PRSGO/D96**.]

Table 2. Summarized Results and Network Meta-analyses of Pooled Recurrence Rates with 95% CI

Pooled Recurrence Rate (95% CI)	Recurrence Range	Heterogeneity (95% CI)
13% (9%–16%)	6%–98%	19% (0%–65%)

Heterogeneity is reported in terms of the I^2 statistic along with its 95% CI.

Summarized results and meta-analyses of recurrence are shown in Table 2. The pooled recurrence rate was 13% (95% CI, 9%–16%). Statistical heterogeneity was determined to be low ($I^2 = 19\%$, 95% CI, 0%–65%). A forest plot demonstrating point estimates and 95% CIs of weighted average proportions for all KILE studies included in the meta-analysis is shown in Figure 3. Meta-regression estimating the effect of treating keloids with additional therapies including intraoperative steroids, postoperative steroids, radiation, and cryotherapy indicated no evidence that these adjunctive treatments had a significant effect on the overall pooled effect size (Table 3). Further, meta-regression estimating the effect of length of time to follow-up indicated no evidence that differences in time to follow-up significantly affected the overall effect size ($P = 0.47$). All but three studies were within the 95% CI in

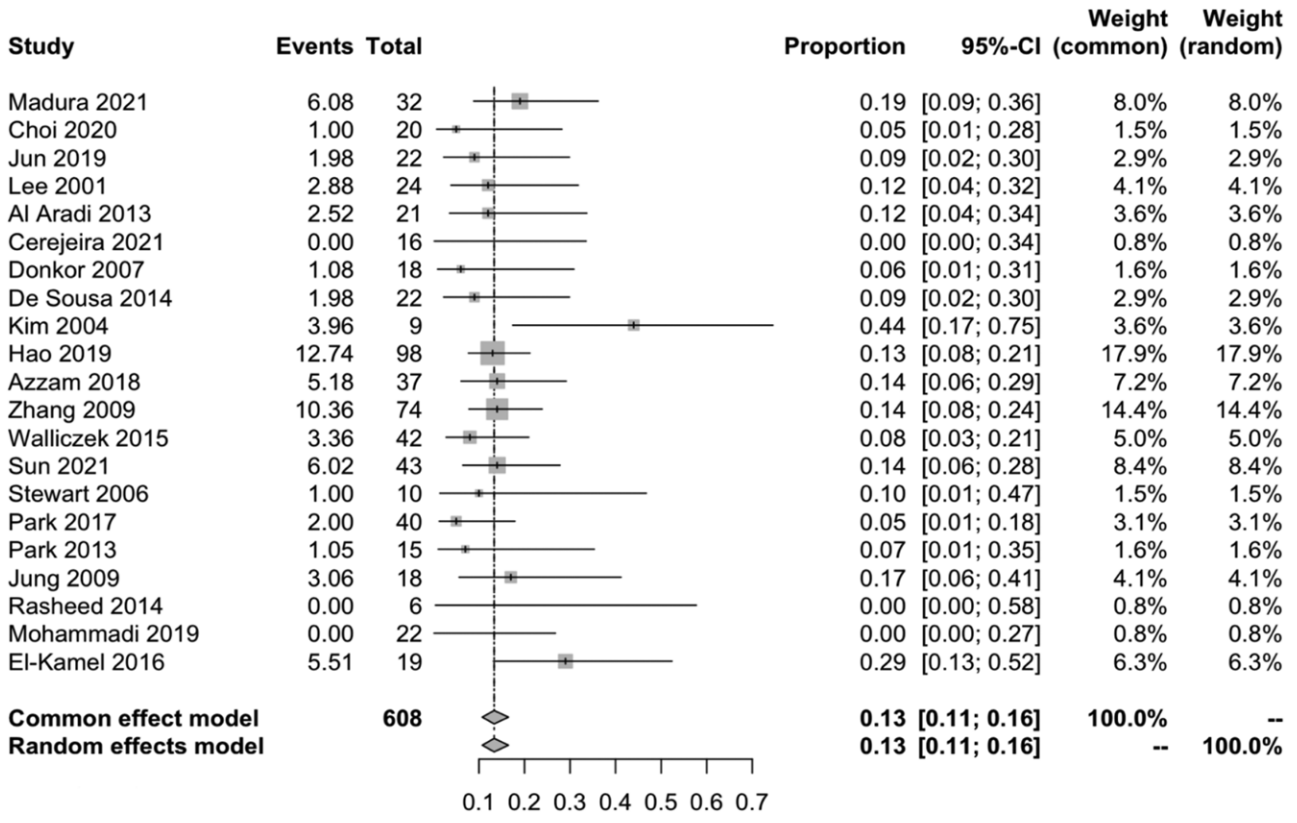

Fig. 3. Forest plot showing the pooled proportions for recurrence in all intralesional keloid excisions using logit transformation and a random effects model with a 95% CI. Each square represents the effect size for a particular study, with the size of the square being proportional to the study size.

Table 3. Results of a Meta-regression Estimating How the Effect of Additional Interventions in Each Subgroup Differs from the Reference Group (Intralesional Excision Only)

Additional Therapy	No. Keloids Treated	Coefficient	*P*
Preoperative steroids	18	0.35	0.70
Postoperative steroids	329	0.37	0.42
Intraoperative steroids	75	0.32	0.75
Cryotherapy	45	0.50	0.57
Radiation	225	0.03	0.96
Pressure therapy	242	-0.22	0.69
Laser	Unclear	0.49	0.55
Calcium channel blockers	19	1.41	0.11
Skin graft	6	-0.62	0.70
Silicone sheet	22	-0.69	0.60
Mitomycin C	10	0.12	0.93
PRP	37	0.50	0.57

a funnel plot, indicating that the significance of publication bias is low (Fig. 4). Egger regression test resulted in a *P* value of 0.07, further indicating no statistical evidence of publication bias.

DISCUSSION

Current literature suggests that recurrence rates after surgical excision of keloids are as high as 45%–100%, and that there are currently no standardized guidelines for keloid treatment.[35] This meta-analysis examined keloid recurrence rates after intralesional keloid excision and demonstrated a pooled recurrence rate of 13% from a sample size of 608 lesions, whereas the largest individual study to date included only 85 patients. Meta-analysis validity was confirmed by the statistical between-study heterogeneity ranging from low to moderate. Both qualitative and quantitative assessments of publication bias demonstrate little to no evidence of the presence of publication bias.

The vast majority of the literature describing partial excision techniques for keloid treatment is written outside of the United States, namely Asia and Africa. The propensity to form keloids is increased with people of African, Asian, and Hispanic descent. It would stand to reason that practitioners in populations rich in these demographics have greater experience in treating keloid disease with remarkably low recurrence. We believe that our medical community may benefit from bringing these treatment techniques into practice in the United States.

The current evidence highlights intralesional excision as an effective technique for keloid treatment, with recurrence rates that are significantly lower than those typically reported in the literature for complete excision. While some individual studies show benefit of adjuncts to complete excision, the use of additional therapies such as intraoperative steroids, postoperative steroids, radiation, and cryotherapy in addition to KILE did not have a significant effect on the likelihood of keloid recurrence in this analysis. Unfortunately, due to differences in reporting, it is difficult to assess complication rates and patient satisfaction in KILE.

This study has several important limitations that should be noted. First, there were no RCTs examining keloid recurrence rates after KILE. As a result, we used meta-analysis of proportions instead of meta-analysis of treatment comparisons, which is the gold standard for meta-analytic studies. Meta-analysis of proportions has been described as an acceptable alternative method of synthesizing data when

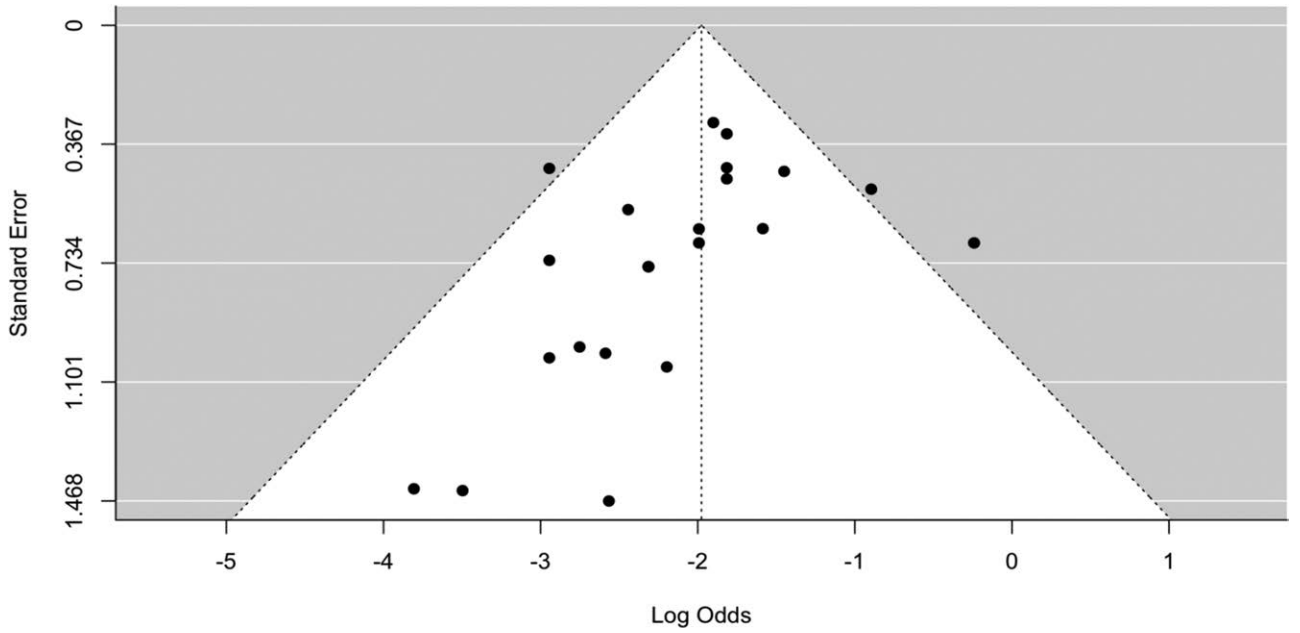

Fig. 4. Funnel plot of keloid recurrence rates graphically assessing for publication bias. The plot represents the standard error for each study plotted against the measured effect size. The vertical line represents the combined effect for all studies, whereas the diagonal lines represent the 95% CI.

RCTs are not available.[36] Additionally, statistical heterogeneity as represented by the I^2 statistic ranged from low to moderate. However, other authors have demonstrated that the I^2 heterogeneity statistic is often biased in small meta-analyses and should therefore be interpreted cautiously.[37] To account for potential bias in the I^2 calculation, we also report the 95% CI of I^2. Further, to account for any heterogeneity contributed by the use of additional therapies, we conducted meta-regression for subgroup effect sizes and found that the simultaneous use of additional therapies did not have a significant effect on recurrence rates. Length of time to follow-up also did not have a significant effect on recurrence rates. The findings regarding effects of additional therapies should be interpreted carefully due to the low power of these analyses given the small number of keloids treated with each additional therapy. Though our review used the best data available, these results reflect only what is reported in the literature and can only give an indication of the true results of intralesional keloid excision.

Future research should involve histological and biochemical studies to elucidate the mechanism behind reduction of keloid recurrence rates with KILE, as the mechanism is not currently well understood.[38] Proposed mechanisms for the effectiveness of KILE include removal of the most proliferative fibroblastic group and preservation of portion of the skin most prone to keloid formation, but results from studies exploring both of these mechanisms have been mixed.[39,40] Additionally, comparative studies assessing keloid recurrence after intralesional versus extralesional excision with matched scar and patient characteristics are needed to better inform guidelines on management of keloids. Overall, our study shows that intralesional excision of keloids provides promising results and should be considered to reduce recurrence in keloid treatment.

Angelo A. Leto Barone, MD
6535 Nemours Parkway
Orlando, FL 32927
E-mail: angelo.letobarone@nemours.org
Instagram: @angelo_leto_baronemd

DISCLOSURES

All authors have no financial interest to declare in relation to the content of this article. Dr. Leto Barone is the Founder and Chief Medical Officer of ReconstratA, LLC and Founder and President of Reconstruct Together, Corp.

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