The Safety and Efficacy of Cryolipolysis: A Systematic Review of Available Literature

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Review Article

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Abstract

Background: In the past decade, the practice of body contouring using cryolipolysis has increased tremendously. While numerous anecdotal reports extol the efficacy of this product, the majority of these studies are small, retrospective case-series that lack control groups.

Objective: The authors aim to systematically review available literature to better illustrate the efficacy and safety of this new procedure.

Methods: A systematic literature review performed using MEDLINE, Embase, PubMed, and Cochrane databases identified all published studies evaluating cryolipolysis for body contouring.

Results: A total of 34 articles up to February 2015 were identified. Nineteen articles matched the selection criteria and were included in the analysis. Sixteen were evaluated in the final analysis. A total of 1445 patients had reportable data for analysis of the safety profile. Twelve patients (0.82%) reported complications with the most common being diminished sensation lasting greater than 4 weeks. An aggregate total of 295 patients had objective data for evaluation of tissue reduction. The mean time from procedure to objective outcome evaluation was 3.83 months. The mean reduction of subcutaneous tissue was 19.55% with respect to a designated control site.

Conclusions: Selective cryolipolysis appears, at short-term follow-up, to reliably decrease subcutaneous tissue deposits. Reported complications are uncommon and appear to resolve without intervention. Future studies should aim to optimize patient selection and treatment characteristics while obtaining long-term follow-up data.

Level of Evidence: 4

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The desire to remove or reshape undesirable focal fat deposits has increased the popularity of body sculpting procedures. Liposuction is considered to be the most effective procedure to reduce such deposits. However, it is not without significant risks and necessary recovery time. Abnormal body contours, infection, nerve damage, seroma, hematoma, and risks associated with general anesthetic or intravenous sedation are all potential complications of liposuction.[1] Therefore, options that reduce invasiveness, risks, and recovery time while still being effective are an appealing alternative. One such procedure is cryolipolysis, which has received FDA clearance for treatment of the focal fat deposits in the flanks (2010, K080521), abdomen (2012, K120023), and thighs (2014, K133212).[2] The practice of body contouring using cryolipolysis (CoolSculpting, Zeltiq Aesthetics, Pleasanton, CA) has increased tremendously.[3]

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In cryolipolysis, fat cells are preferentially destroyed by a controlled thermal reduction. Exposure to below normal, but above freezing, temperatures induces apoptosis-mediated cell death.[4] The adipocytes are more sensitive to the cooling process than other cells, resulting in minimal collateral damage to surrounding tissues.[5] A subsequent inflammatory response beginning on day 3 and peaking around day 14 removes the damaged adipocytes.[1] The resolution of inflammation and lipid metabolism is thought to be completed by 3 months after treatment.[6] Authors of previous studies in porcine models and in humans have demonstrated this process results in a reduction of the treated area's fat layer.[4]

The procedure is easily performed in a clinical setting without anesthetics or analgesics. The tissue containing the focal fat deposit is drawn into an applicator with the assistance of a vacuum after coupling gel has been applied. Cooling panels on either side then begin a controlled thermal reduction that is maintained for a time period between 45 and 60 minutes. The cooling intensity factor (CIF) is a modifiable variable measured in mW/cm^2 that determines the rate of cooling. A larger CIF corresponds to an increased average energy extraction per cm^2 during treatment.[4] The treatment lasts for a preset time, the device then shuts off and is removed. Sasaki et al inserted a temperature probe into the treated area and revealed that tissues reached as low as 9°C. The lowest temperatures were at the 60-minute mark, or completion of treatment, and temperatures returned to baseline within 60 minutes after device removal.[7] The patient is able to immediately return to regular daily activities with no restrictions and minimal discomfort.

While numerous anecdotal reports extol the efficacy of this product, the majority of these studies are small, retrospective case series that lack control groups. The authors aim to systematically review available literature in an effort to fully understand the indications and efficacy of the procedure while focusing only on studies with objective evidence on safety and outcomes.

METHODS

Search Strategy

A literature search was performed by the investigators in February 2015 using the following electronic databases: MEDLINE, Embase, PubMed, and Cochrane. The keywords used were "cryolipolysis" and "CoolSculpting."

Article Eligibility

Inclusion criteria included studies containing objective data on safety or efficacy of cryolipolysis. Exclusion criteria were nonEnglish articles, case reports, and studies not involving humans. For safety profile analysis, only studies that specifically described complications and/or safety data were included for analysis. For efficacy analysis, only studies that specifically described objective measurements of tissue loss and compared this to a designated control site were included for analysis. Objective measurement analysis included tissue caliper measurements, ultrasound-assisted measurement of tissue thickness, and 3-dimensional (3D) volume analysis.

Data Extraction

The following data were extracted from each primary article and used for comparison: sample size, age, gender, body mass index (BMI), treatment variables, outcome measures, results, and complications.

RESULTS

Articles up to February 2015 were included. A diagram of the selection of articles is shown in Figure 1. The initial search yielded 59 articles, 25 of which were duplicate manuscripts. Inclusion and exclusion criteria were then applied to a review of the abstracts of the remaining 34 articles; 15 were eliminated based on this review. The remaining 19 articles were fully examined. Sixteen articles matched the selection criteria and were included in the analysis. Characteristics of the included studies are presented in Table 1.

A total of 1445 patients underwent cryolipolysis in the included studies. Of the studies that reported descriptive data, 76.2% of the patients were women (n = 1067) and 23.8% were men (n = 333). The mean age at treatment was 39.7 years with a range of 18 to 79 years. The mean reported BMI was 25.1 kg/m^2 with a range from 19.5 to 31.8 kg/m^2. The range of CIF for treatments was 33 to 42 mW/cm^2. Treatment time ranged from 30 to 120 minutes per cycle with a range of 1 to 2 cycles per treated area. Mean time to follow-up was 3.8 months with a range from 2 to 60 months.

A cumulative total of 1445 patients had reportable data for analysis of the safety profile. Complications were defined as altered sensation lasting longer than 4 weeks, persistent pain lasting longer than 14 days, or any other averse outcome attributable to the procedure. There were a total of 12 reported complications in 0.82% of patients treated with cryolipolysis. The most common complication was decreased sensation of the treated area lasting greater than 4 weeks (0.34%, n = 5) with the longest time to return to normal sensation being 4.5 months. Other reported complications were: 2 patients (0.14%) with paradoxical adipose hyperplasia (PAH), 2 patients (0.14%) with visible contour irregularities, 1 patient (0.07%) with pain sufficient enough to abort the procedure, 1 patient (0.07%) who had a vasovagal reaction, and 1 patient (0.07%) had post-treatment anxiety, bloating, nausea, and pruritis.

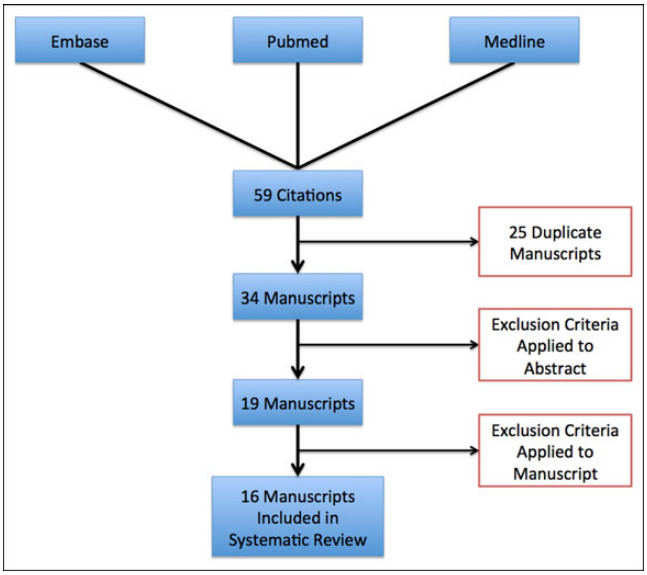

Figure 1. Systematic review study design.

An aggregate total of 295 patients had objective data for evaluation of tissue reduction. Only patients who had data for one treatment with cryolipolysis were included for analysis. The mean time from procedure to objective outcome evaluation was 3.8 months. The mean reduction of subcutaneous tissue as measured by ultrasound evaluation or caliper thickness was 19.55% with respect to a designated control site. One study included 3D volumetric analysis showing an average reduction of 39.5 mL in the treated area compared with a contralateral control.[8]

DISCUSSION

Cryolipolysis is one of many newly approved noninvasive treatments to reduce focal lipodystrophy. Researchers of new technology should focus initially on safety and efficacy. As in many new-to-market products, the safety of cryolipolysis was studied first in an animal model. These initial experiments were performed in a swine model to determine whether cold application could result in selective damage to adipocytes. An initial exploratory study resulted in mild increased pigmentation for a week but otherwise no skin damage. There was visible fat loss in the shape of the applicator and they recorded a 40% total fat loss from the procedure.[9]

There was concern that adipocyte damage would lead to abnormal lipid levels or liver function studies. Both animal and human studies have shown that there are no significant changes in these measurements.[9,10] Klein et al treated bilateral flanks and measured serum lipid levels and liver function tests. Measurements were taken pretreatment, 1 day, and 1, 4, 8, and 12 weeks posttreatment. The only statistically significant change for lipids or serum liver tests was a decrease in mean high-density lipoprotein (HDL) from 67.0 to 66.7 mg/dL. This is likely the result of the very slow process of phagocytosis and removal of the lipids over the course of days to weeks.[10]

Coleman et al compared 10 flank treatment sites with contralateral controls. Ultrasound measurements were obtained for 9 patients pretreatment, 2 months posttreatment, and 4 months posttreatment for comparison and measuring fat-layer reduction. The average reduction of fat was 20.4% at 2 months and 25.5% at 6 months. Independent blinded reviewers were able to correctly identify the treated side from a photograph in 93% of cases.[4] Nine patients had weekly evaluations by a neurologist; 3 had no sensory changes and 6 had transient reductions in sensation.

Kotlus and Mok evaluated cryolipolysis in 67 patients with 192 treatments.[11] Treatment areas included abdomen (n = 50), flank (n = 23), outer thigh (n = 6), inner thigh (n = 2), and medial upper arm (n = 2). One treatment cycle was performed for 60 minutes at each area. Ultrasound measurements were taken before and 2 months after treatment. There was a mean reduction of 25.2% for all treatment areas. Data for treatments outside of the abdomen and flanks were not presented. There was a mean reduction of 25% for abdomen and 21% for love handles. These were the only researchers to analyze fat-layer reduction by percent body fat and initial fat layer thickness. The greatest percentage reduction was noted to be 34.5% in the 41% to 45% group. For the 15% to 40% groups mean reductions ranged from 20.4% to 28.8%. The mean reduction in the 46% to 50% group was 16.0%. There was a 45% mean reduction in the initial thickness of 46 to 55 mm. Many researchers note that cryolipolysis is ideal for fit persons with focal lipodystrophy. However, there may be beneficial fat-layer reduction in a wider range of body habitus than initially recommended.

Shek et al evaluated a Chinese population for efficacy of a single treatment compared with 2 treatments to determine if multiple treatments showed additional benefit.[12] Twenty-one patients had a single treatment and 12 patients had 2 treatments 3 months apart. BMI for both groups were measured and remained unchanged. Each site was treated at a CIF of 41.6 mW/cm^2 for 60 minutes. In the single treatment group, there was a statistically significant 14.67% fat-layer reduction. Also, 81% rated moderate to good improvement on photographic evaluation. In the abdomen 2-treatment group there was a 14% fat-layer reduction after the first treatment and a 7.2% reduction after the second treatment. For the flank 2-treatment group, there was a 13.4% mean reduction after the first treatment and a 4.3% reduction after the second treatment.

Bernstein has the longest recorded follow-up after treatment.[5] Two subjects were followed for up to 5 years after treatment of 1 flank with a contralateral control. Patient 1 was treated with a CIF 42 mW/cm^2 for 60 minutes. At 2 years posttreatment, there was still a visible reduction at the

Table 1. Summary of Articles Included for Analysis

Study	Study Design	Level of Evidence	Location	Number of Patients	Age of Patients (Years)	Gender of Patients	BMI (kg/m^2)	Treatment CIF (mW/cm^2) and Time (Minutes)	Follow-up Time (Months)	Outcomes	Safety/ Complications
Bernstein, 2013[5]	Case series	IV	United States	2	Avg: 45 Range: 44-45	0% female 100% male	Avg: 25.4 Range: 23.7-27	CIF: 34-42 Time: 60-120	Avg: 42 Range: 24-60	Visible reduction	None reported
Bernstein et al, 2014[14]	Case Series	IV	United States	10	Avg: 42.2 Range: 33-56	100% female 0% male	Avg: 24.3 Range: 21.1-28.8	CIF: 41.6 60 minutes × 2 with 50% overlap	Avg: 3 Range: NR	94.4% correct ID Avg 4.3 on 10 point scale	No complications
Boey and Wasilenchuk, 2013[18]	Cohort	III	Canada	17	Avg: NR Range 30-50	100% female 0% male	Range: 30-50	CIF: 42 Time: 60	Avg: 4 Range: NR	44% greater fat reduction on massaged side at 4 months	1 patient had decreased sensation for 2 months. No necrosis on histological analysis of massaged side
Coleman et al, 2009[4]	Case control	III	United States	10	Avg: NR Range: NR	NR	NR	CIF: 33-37 Time: 45-60	Avg: 6 Range: NR	Avg. reduction 25.5% at 6 months; No nerve damage on histology	1 patient aborted the procedure due to pain; Nerve biopsy showed no signs of subdermal plexus damage
Dierieckx et al, 2013[13]	Case series	IV	Belgium and France	518	Avg: 42.7 Range: NR	73% female 27% male	NR	NR	Avg: 3 Range: NR	Avg. reduction 23%	1 patient had a vasovagal reaction
Friedmann et al, 2013[6]	Cohort	III	United States	8	Avg: NR Range: NR	100% female 0% male	NR	CIF: 41.6 Time: 60	Avg: 4 Range: NR	On a visual improvement scale from −2 to 2, mean 0.56	No complications
Garibyan et al, 2014[11]	Cohort	II	United States	11	Avg: NR Range: NR	55% female 45% male	Avg: 27.1 Range: 22.5-29.1	CIF: 41.6 Time: 60	Avg: 2 Range: NR	39.5 mL reduction; 14.9% reduction	2 patients had decreased sensation for 2 months
Jalian et al, 2014[17]	Case report	V	United States	2	Avg: NR Range: 40-50	50% female 50% male	NR	NR	Avg: 7 Range: 5-9	Increased adipose tissue at treated site	2 patients with paradoxical adipose hyperplasia
Kim et al, 2014[16]	Cohort	III	South Korea	15	Avg: 30.1 Range: 22-41	73% female, 27% male	NR	CIF: 33 Time: 60	Avg: 3 Range: NR	1.7 on scale implying good to excellent	No complications
Klein et al, 2009[10]	Case series	IV	United States	40	Avg: 42 Range: 21-66	80% female 20% male	Avg: 26.7	CIF: 42 Time: 30	Avg: 3 Range: NR	No statistically significant change in blood lipid or liver function tests	1 patient had transient anxiety, nausea, bloating, and pruritis
Kotlus and Mok, 2013[11]	Case series	IV	United States	57	Avg: 47 Range: 23-67	88% female 12% male	NR	CIF: NR Time: 60	Avg: 2 Range: NR	Mean reduction of 25.2%	2 patients had visible contour irregularities
Sasaki et al, 2014[7]	Case series	IV	United States	112	Avg: 34.2 Range: 26-51	71% female 29% male	Avg: 24.7 Range: 19.5-31.8	CIF: 42 Time: 60	Avg: 6 Range: NR	Avg. reduction of 21.5%	No complications

(*Continued*)

Table 1. (Continued)

Study	Study Design	Level of Evidence	Location	Number of Patients	Age of Patients (Years)	Gender of Patients	BMI (kg/m^2)	Treatment CIF (mW/cm^2) and Time (Minutes)	Follow-up Time (Months)	Outcomes	Safety/ Complications
Shek et al, 2012[12]	Case control	III	China	33	Avg: 46.5 Range: 27-72	76% female 24% male	Avg: 23.2	CIF: 41.6 Time: 60	Avg: 2 Range: 2-5	Avg. reduction of 14.3% after 1st treatment and 7.2% after 2nd	No complications
Stevens et al, 2013[3]	Case series	IV	United States	528	Avg: 46.5 Range: 18-79	76% female 24% male	NR	CIF: not reported Time: 60	Avg: 3 Range: 2-3	No statistical data reported for fat reduction	No complications
Stevens and Bachelor, 2015[2]	Cohort	III	United States	37	Avg: 43.2 Range: 22-65	100% female 0% male	Avg: 25.3 Range: 20.7-30.4	CIF: default Time: 120	Avg: 4 Range: NR	87% correct ID; 2.8 mm mean fat reduction	1 patient had decreased sensation for 2 months
Zelickson et al, 2015[15]	Case series	IV	United States	45	Avg: 48.1 Range: 35-60	NR	Avg: 24.6 Range: 20.9-30	CIF:41.6 Time:60	Avg: 4 Range: NR	91% correct ID; 2.6 mm mean fat reduction	Mild numbness lasting 4.5 months

Avg, average; BMI, body mass index; CIF, cooling intensity factor; ID, identification; NR, not reported.

treated side despite gaining 10 pounds. Patient 2 was treated with CIF 34 mW/cm^2 for 60 minutes and also had visible reduction of the treated flank at 5 years posttreatment. Patient 2 lost 10 pounds from time of treatment to follow-up. Although it is a very small sample size, these cases show that there are persistent reductions in the treated fat deposits despite weight fluctuations either up or down.

Friedmann et al evaluated 8 patients with cryolipolysis compared with high-intensity focused ultrasound for treatment of the flanks.[6] Each patient had 1 flank treated with each method. For cryolipolysis a CIF of 41.6 mW/cm^2 was used for 60 minutes. Photographs were assessed at 4 months posttreatment based on a 5 point scale. The mean improvement score for the cryolipolysis treated flank was 0.56, which fell between unchanged and improved on the scale. There was no significant difference between the treatments.

Stevens et al performed a retrospective chart review of 528 patients.[3] The group reportedly treated 1785 sites with 2729 cycles. Two cycles of 60 minutes spaced 8 weeks apart were usually recommended. They do not report the CIF used to treat nor were data regarding percentage fat reduction, clinical photograph assessments, or patient surveys available for comparison. However, patient data regarding practice growth were evaluated and the authors noted 66% of patients were new to the practice and 62% had not had any previous cosmetic procedures. Furthermore, 40% later underwent additional procedures.

Dierickx et al performed a retrospective study on 518 patients with 891 cryolipolysis treatment sites.[13] A subset of 49 patients underwent caliper measurement and photograph analysis. However, the method for determining the subset was not explained. CIF and treatment times were not stated, although they report 77% felt treatment time was "about right." At 3 months posttreatment, 73% of patients stated they were either "extremely satisfied" or "satisfied," and 82% would recommend the treatment to a friend. Of the patients evaluated with caliper measurements, 94% had fat-layer reduction, with a mean of 23%. On photograph assessment 85.5% showed improvement at the abdomen and flanks. The number dropped to 73% when other treatment sites were included.

Bernstein et al treated 10 patients' flanks with a sharply contoured vacuum applicator (CoolCurve+, Zeltiq Aesthetics, Pleasanton, CA).[14] Two cycles of 60 minutes with 50% overlap were delivered at CIF 41.6 mW/cm^2. Blinded reviewers were able to correctly identify treatment photos in 94.4%. Treated sites also scored 4.3 on a 10-point scale of improvement. There were no significant complications. The authors felt the newer applicator was able to increase tissue draw into the vacuum and improve the fit for treatment of the flanks.

Garibyan et al performed the first known volumetric analysis after cryolipolysis treatment on 11 patients using 3D photography.[8] One flank was treated with a single cycle at CIF 41.6 mW/cm^2 for 60 minutes with a contralateral control. At 2 months post-treatment, they found an average reduction of 39.5 mL when corrected for the control site. Caliper measurements were also performed showing a 14.9% average reduction. Blinded evaluators were able to correctly identify the treated side in 79% of patients. They reported 2 patients that had decreased sensation at 2 months post-treatment which resolved spontaneously.

Stevens and Bachelor treated 40 women's lateral thighs with cryolipolysis at a default CIF for 120 minutes using a

nonvacuum conformable-surface applicator.[2] One thigh with a more distinct bulge was treated with the contralateral thigh serving as the control. Of the 37 patients completing the study, blinded reviewers were able to correctly identify baseline images in 87% of cases. On a patient questionnaire, 86% felt the treatment met or exceeded their expectations, 89% would recommend lateral thigh cryolipolysis to a friend, and 97% were likely to undergo a second procedure. Ultrasound measurements revealed a significant mean normalized fat-layer reduction of 2.6 mm. They reported 1 patient that had prolonged numbness that resolved spontaneously 63 days posttreatment.

Zelickson et al reported a series of 45 patients treated with a flat-cup applicator (Coolfit, Zeltiq Aesthetics, Pleasanton, CA) for cryolipolysis of the inner thighs.[15] The inner thighs were treated with a CIF of 41.6 mW/cm^2 for 60 minutes. Blinded reviewers were able to correctly identify the baseline image in 91% of cases. They also demonstrated a significant reduction in mean thigh circumference of 0.9 cm at 16 weeks posttreatment. In addition, ultrasound measurements showed a significant mean normalized fat-layer reduction of 2.6 mm. Eighty-four percent of patients reported they noticed a visible fat reduction in their inner thighs after a single treatment. Additionally, the authors reported 1 case of mild numbness lasting 132 days posttreatment.

Kim et al performed cryolipolysis on 15 patients using Micool (Hironic Co., Seongnam, Korea) and were the first to report efficacy of the device.[16] Numerous sites were treated including love handles, abdomen, upper hip, inner thigh, bra line, and under the buttocks. Treatment lasted 60 minutes per site at a CIF of 33 mW/cm^2. On a 1 to5 scale (1 = excellent, 5 = no reduction), patients scored an average of 1.7. This implied a good to excellent improvement or 50% to 100% fat reduction. Average subjective assessment by patient questionnaire was 2.1, indicating moderately satisfactory results. No significant complications were reported.

Sasaki et al treated 112 patients at a CIF of 41.6 mW/cm^2 for 60 minutes per site. Of the 85 patients with 6-month follow-up data, there was an average fat reduction of 21.5% by caliper measurement.[7] Patients were evaluated by an investigator for subjective signs of improvement at 6 months and noted significant improvements in the abdomen and hip application sites. They did not report any complications.

Jalian et al described 2 cases of paradoxical adipose hyperplasia (PAH), the most significant complication reported to date.[17] They report 33 confirmed cases of PAH had been reported to the device manufacturer with an incidence of 1 in 20,000 treatments. Of the 33 patients, 15 were men and 18 were women, which would be an overrepresentation in males given a significant majority of patients treated are women. The authors hypothesize that PAH is caused by reactive fibrosis from damaged adipocytes that leads to septal thickening and adipose tissue hypoxia resulting in increased vascularity and fat hyperplasia.

Boey and Wasilenchuk performed cryolipolysis on 17 patients with the objective of evaluating subcutaneous tissue loss with and without massage therapy.[18] The authors found that standard cryolipolysis without massage resulted in a mean subcutaneous tissue reduction of 12.9% at 2 months and that the massaged side of the abdomen displayed a 21% reduction. Subsequent histological analysis up to 120 days showed no signs of necrosis or fibrosis in either the treated or untreated side. They hypothesize that posttreatment massage increases reperfusion injury resulting in additional adipose tissue destruction.

Efficacy and safety profiles based on two important treatment variables, CIF and treatment time, have yet to be adequately studied. Treatment times range from 30 to 120 minutes per site in the reviewed studies. It is unknown whether a longer treatment time would result in more significant side effects. In addition, the studies comprised patients treated with a variety of CIFs ranging from 33 to 42 mW/cm^2 without explaining the process by which the setting for the given patients was determined. A prospective randomized study comparing the safety and efficacy at various CIFs for given treatment times would be beneficial to help guide patient-specific guidelines for treatment. It could also help identify any maximum treatment time or CIF to prevent increased complication rates.

One limitation of this systematic review is that there was heterogeneity in treatment CIF and treatment time. There were also differences in the ways efficacy was evaluated, with some studies utilizing objective ultrasound measurements and others using caliper measurements. Another limitation is the potential for selection bias given that 2 of the studies performed objective assessments on a subset of their total population without describing how the subset was selected. There is also the possibility of a publication bias, given that some of the studies included have been funded by Zeltiq Aesthetics or have authors with financial interests with the same company.

In this age of an increasingly economically conscious healthcare environment, it is important that the safety and efficacy of emerging medical technologies be founded in science that is evidence driven.[19] As is evident from some of the studies examined in this review and others, it is possible to generate high-quality, prospective evidence with many of these devices.[20,21] Therefore, future planned studies should strive to contain high-quality evidence with appropriate controls to justify both their expense and their use. Given that much of the information in emerging aesthetic innovations is generated by advertising, it is imperative that surgeons performing aesthetic surgery review available evidence prior to adopting these technologies.[22]

CONCLUSIONS

Selective cryolipolysis appears, at short-term follow-up, to reliably decrease subcutaneous tissue deposits. Although side effects occur, they appear to resolve without intervention within 4 weeks. Furthermore, complications are rare, and in most cases, tend to resolve with time. Future studies should aim to optimize patient selection, treatment time, and CIF settings while obtaining long-term follow-up data.

Disclosures

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