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REVIEW ARTICLE

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Cryolipolysis for the treatment of submental fat: Review of the literature

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Summary

Background: Submental fat accumulation is a common cosmetic concern. Cryolipolysis utilizes noninvasive cooling to lyse adipocytes. A cryolipolysis device was recently approved for treatment of submental fat.

Objective: This manuscript provides a review of the preclinical work and clinical trials related to cryolipolysis for the treatment of submental fat. Settings, efficacy, and side effects are also discussed.

Materials and Methods: A literature search was performed through Pubmed, EMBASE, Web of Science, and CINAHL, using the search terms "cryolipolysis," "submental," and "paradoxical adipose hyperplasia". Additional sources from the original source bibliographies were used to further supplement this review.

Results: There are 4 clinical trials and one case series (total 101 patients) that evaluated the use of cryolipolysis for treatment of submental fat. In these studies, there was a statistically significant reduction in submental fat and patients expressed high satisfaction with the treatment. Adverse effects were mild and transient.

Conclusions: Cryolipolysis is a noninvasive cooling technique that is safe and effective for treatment of submental fat. To date, there are no reports of marginal mandibular nerve injury or paradoxical adipose hyperplasia following treatment with this device.

KEYWORDS
cryolipolysis, marginal mandibular nerve, paradoxical adipose hyperplasia, submental fat

1 | INTRODUCTION

Submental fat excess is common esthetic concern because it results in a distortion of the anterior cervicomental triangle.[1] Many patients report that they are unhappy with their "double chin" or that it makes them look older. Etiologies include genetic predisposition, age, lifestyle, and diet.[2,3] In two separate patient surveys on cosmetic procedures, fat accumulation was one of the top concerns reported by 67% and 77% of patients, respectively.[4,5] At one time, liposuction and surgery were the only options for removal of submental adipose tissue and are still considered first line for removal of large collections of fat or deeper postplatysmal fat. However, these techniques are fraught with long recovery times, risk of contour irregularities, lax skin, vascular and neurologic compromise, and infections.[6] Therefore, patients often desire minimally invasive or noninvasive options. In fact, nonsurgical cosmetic procedures have increased 508% since 1997.[7] In recent years, more conservative alternatives for the treatment of submental fat have been developed including laser-assisted lipolysis,[8] radiofrequency-assisted lipolysis,[9] radiofrequency-assisted contouring,[10] injection adipolysis,[11] and cryolipolysis.[12] While the efficacy of injection adipolysis for submental fat has been shown in clinical trials, up to 4-6 treatments sessions were required in order to achieve the desired effect, prolonged bruising was common, and injury to the marginal mandibular nerve was reported in a number of cases.[13-16] Cryolipolysis utilizes noninvasive cooling applied to the skin surface to lyse

preplatysmal adipocytes. The adipose cells are destroyed, but the surrounding skin and other tissue are unaffected because adipose cells are more susceptible to cold-induced injury than water-rich cells.[12] Cryolipolysis was approved by the United States Food and Drug Administration (FDA) in 2015 for treatment of adipose tissue in the submental area. The review summarizes the preclinical data, clinical trials, settings, efficacy, and adverse effects for cryolipolysis applied to the submental area.

2 | METHODS

A review of the literature was performed through Pubmed, EMBASE, Web of Science, and CINAHL on May 22, 2017, using the search terms "cryolipolysis" and/or "submental." An additional search was performed using the search term "paradoxical adipose hyperplasia." The relevant records that met the following criteria were selected for inclusion: preclinical data on cryolipolysis, clinical trials of cryolipolysis on the submental area, and clinical reports of paradoxical adipose hyperplasia postcryolipolysis. Exclusion criteria included non-English articles. Additional sources from the original source bibliographies were used to further supplement this review.

2.1 | Initial observations

The theory that cold could destroy fat cells was developed after two observations in newborns. In one patient, surface cooling was applied to the skin for 24 hours as part of treatment for birth asphyxia. Red-purple skin nodules were observed on the 6th day, and a biopsy was performed. Histopathological analysis showed findings consistent with subcutaneous fat necrosis of the newborn.[17] In another case, a baby experienced supraventricular tachycardia on the first day of life, the patient. During the initial attempt at cardioversion, an ice pack was applied to the bilateral cheeks. On the next day, the baby developed indurated erythematous plaques on the cheeks. A biopsy with histological analysis again showed findings consistent with subcutaneous fat necrosis of the newborn.[18]

Further data on the response of adipocytes to cold were derived from a study designed to assess whether adipocytes were of best quality for autologous fat transfer when they were fresh, refrigerated, or frozen. Fat was harvested from Sprague-Dawley rats and either implanted immediately into the animals or stored at −16°C or 1°C for 1-2 weeks. Histological analysis indicated that inflammation and fat cell necrosis occurred when the animals received stored fat, thus indicating that the cold was toxic to the adipocytes.[19]

The effect of cold on adipose tissue was also derived from a study analyzing fat cells harvested from patients undergoing elective plastic surgery procedures. The study's purpose was to evaluate the viability of autologous fat cells at −20°C without additional additives and to investigate whether cell survival was affected by decreasing the storage temperature from −20°C to −80°C. Freezing resulted in a 92.7% loss of metabolic activity, and cell destruction was more pronounced at lower temperatures.[20]

2.2 | Preclinical data

To test the theory that cold treatment would selectively destroy fats cells while sparing surrounding tissue, three Yucatan pigs and one Yorkshire pig underwent treatment with three-section cooling applicators connected to a prototype cooling control device. Using photography, the authors noted inward contour changes on the surface of the treated areas compared to the nontreated areas. Using ultrasound, the contour alterations were consistent with decreased thickness of the fat layer, with a greater change correlating with more intense and longer treatments. The decrease in fat layer thickness was evident in the gross pathology photographs. In two of the pigs, ultrasound and gross pathology were used to quantitate the reduction in superficial fat. Using ultrasound, there was a 33% reduction in fat in both pigs, and a 53% and 50% reduction in fat analyzed by gross pathology.[21]

Using histopathology, the authors demonstrated that cryolipolysis resulted in adipocyte apoptosis by day 3, with an inflammatory response days 3-14, and phagocytosis by macrophages days 14-30. During days 60-90, interlobular septa became thickened and a substantial loss of fat cells was evident. There was no evidence of necrosis in the epidermis, dermis, hair follicles, or sweat glands.[21] Erythema was noted following treatment, but resolved within 30 minutes. No edema, bruising, purpura, or scarring was observed. Lipids fluctuated but remained within the bounds of normal for pigs.[21]

2.3 | Clinical trials using cryolipolysis on fat on areas excluding the face/neck

The first clinical trials demonstrating safety and efficacy of cryolipolysis in humans were performed on the abdomen, flanks, and thighs.[22-28] Further studies also established that cryolipolysis was safe and effective for fat reduction in the back, arms, and chest.[29-34]

To evaluate whether rapid lysis of adipocytes would lead to fluctuations in lipids or liver damage, two clinical trials were performed on patients undergoing cryolipolysis to their lower abdomen and flanks.[35,36] In the first trial, 40 subjects were treated with a cooling device to their bilateral flanks and blood tests were performed prior to treatment and on post-treatments day 1, and then 1, 4, 8, and 12 weeks after treatment.[35] In the second trial, 35 patients underwent cryolipolysis to their lower abdomen, followed by simultaneous cryolipolysis to their bilateral flanks. Blood tests were performed prior to treatment and at 1, 4, and 12 weeks following treatment.[36] In both trials, no significant changes in lipids levels or liver functions tests were seen at any of the time points.[35,36]

2.4 | Another study was designed to evaluate whether cryolipolysis was associated with injury to nerve fibers

Ten patients were treated with cryolipolysis, and in addition to measurement of reduction in fat, sensory function was assessed by

neurologic evaluation in nine patients, and one patient underwent a biopsy for nerve staining. Six of nine patients experienced an alteration in sensation, but baseline sensation returned after a mean of 3.6 weeks following treatment. Biopsy with histopathology demonstrated no enduring nerve fiber structure alteration.[37]

2.5 | Clinical trials using cryolipolysis on submental fat

Based on prior clinical trials on cryolipolysis treatment for fat reduction on the body, a multicenter, prospective, open-label, nonrandomized interventional cohort study was performed using a cryolipolysis device to treat 60 patients in the submental area. The subjects were treated one to two times, 6 weeks apart, at −10°C for 60 minutes with a small volume vacuum cup applicator. The primary endpoints were safety and a greater than 80% correct identification of the baseline photographs by three blinded independent reviewers. The secondary endpoints were a decrease in fat layer thickness measured by ultrasound and subject satisfaction at 12 weeks after the final treatment. All 60 patients completed the trial and 58 patients were included in the final photograph analysis, due to incomplete cooling cycles in 2 patients. The overall correct identification rate was 91.4%, which was statistically significant ($P < .0001$), meeting the primary efficacy endpoint. For the 57 patients analyzed by ultrasound, there was a mean fat layer reduction of 2.0 mm or 20% (standard deviation of 2.0 mm, range + 2.0 mm to −5.9 mm), which was statistically significant ($P < .0001$). Out of the 60 patients, 83% of subjects were satisfied with the treatment, 77% reported noticeable fat reduction, and 76% felt that the treatment was comfortable. The most common side effects immediately post-treatment and for up to 6 weeks were erythema, edema, bruising, and numbness, which resolved by week 12. Other adverse events included prolonged erythema in two subjects, hyperpigmentation in one patient, and sensation of fullness in the back of the throat in one participant. These four treatment-related adverse events resolved within 40 days without treatment, indicating that the primary safety endpoint of safety was met.[38]

In a prospective, nonrandomized interventional cohort study using cryolipolysis on submental fat, the investigators utilized two overlapping applications on different treatment visits to examine whether this approach would be more effective than a single central treatment. Fourteen participants were enrolled in the trial and were treated with the cooling device for two cycles of 45 minutes using a 20% overlap, with a second set of sessions repeated 6 weeks later. Study endpoints were tolerability and treatment satisfaction at 12 weeks after the second treatment. Adverse events were recorded, calipers were used to measure fat reduction, and treatment efficacy was quantitated using 2-dimensional (2-D) and 3-dimensional (3-D) imaging. Three blinded independent reviewers correctly identified the pretreatment vs. post-treatment photographs 81.0% of the time (95% CI, 65.9%-91.4%; $P = .02$). Using 3-D imaging, the mean fat volume reduction was 4.82 (SD, 11.42) cm3 (95% CI, −1.39 to 11.02 cm3, $P = .13$), the mean central submental fat thickness reduction was 3.77 (SD, 3.59) mm (95% CI, 1.82-5.72 mm; $P < .001$), and the mean (SD) skin surface area reduction was 1.29 (SD, 1.42) cm2 (95% CI, 0.51-2.06 cm2; $P < .001$). Using skinfold calipers, the mean fat layer reduction was 2.3 (SD, 0.8) mm (95% CI, 1.9-2.7 mm; $P < .001$). Using patient surveys, 93% of subjects were satisfied with the procedure, and 86% expressed that they felt the treatment enhanced their chin and neck contour. Utilizing a pain scale of 0-10, the mean pain score during the first treatment visit was 2.6 and 1.4 for the first and second cycles, respectively. The mean pain score for the second treatment visit was 2.7 and 1.8 for the first and second cycles, respectively. The mean pain score was 1.5 at 1 day and decreased to 0 at 6 weeks after treatment. The most common adverse effects were erythema, swelling, tingling, and numbness, which resolved by follow-up visits. Two other adverse events occurred, namely sharp ear pain and tongue tingling. These side effects resolved by days 5 and 7 post-treatment, respectively, indicating that the study met the endpoint of safety.[39]

A prospective, single-center, interventional cohort study was performed to treat 10 Korean patients with a cryolipolysis device in the submental area. The cryolipolysis device was applied to the submental area twice for 45 minutes each with a 30% overlap. Study endpoints were safety and efficacy assessed by digital photography, caliper, and ultrasound measurements 8 weeks following the procedure. Nine of ten patients had a reduction in submental thickness (mean reduction 4 mm, range 0-13 mm) when measured by calipers. Using ultrasound, all patients had a reduction in the median diameter of the subcutaneous fatty layer (mean reduction 2.8 mm, range 0-6 mm). Subjectively, 1 patient reported some, 5 reported moderate, and 4 reported marked improvement. Side effects were mild and included mild erythema and swelling which resolved by 1-week post-treatment.[40]

A prospective, single-center, nonrandomized, and open-label interventional cohort study was performed on 15 Hispanic subjects using cryolipolysis to the submental area. Two treatments were performed 10 weeks apart. The first was at −12°C for 45 minutes and the second was at −15°C for 30 minutes, which was colder than in previous studies. The primary endpoint of the study was safety and assessed by recording adverse events. The secondary endpoint, efficacy, was evaluated using digital photography, caliper measurements, and magnetic resonance imaging (MRI). The mean reduction in submental fat, measured by calipers, was 33% (3.2 mm [standard deviation, 1.7 mm]). Using a t test comparison between the two treatment types measured by calipers, there was no statistically significant difference between the two treatments ($P = .1782$). MRI measurements were performed before treatment and after the last treatment in 13 of 15 patients. The mean fat layer reduction was 1.78 mm (SD, 1.157 mm). A blinded panel of physicians correctly identified pre- and post-treatment photographs 60% of the time. Using a patient survey, 80% of the subjects reported that they were satisfied or very satisfied with the esthetic improvement of the procedure. Twelve subjects preferred the shorter treatment session, one preferred the first cycle, and one patient had no preference. Thirteen of 15 patients reported no pain during treatment 1, with two

patients reporting scores of 1 and 4 on a scale of 0-10. All patients reported no pain during the second treatment. Erythema, edema, and numbness were the most common adverse affects immediately following the first treatment and resolved by the 2nd treatment. Tingling and pruritus were also reported after immediately after treatment 2 and side effects resolved 12 weeks after the second treatment. There was one patient who developed petechiae and hyperpigmentation due to a malfunction of the device which resolved by 12 weeks post-treatment.[41]

A retrospective chart review was performed on two patients that underwent submental cryolipolysis and reduction and fat and skin laxity were analyzed by 3-D imaging. The first patient was a 57-year-old woman who underwent 1 treatment of submental cryolipolysis (60 minutes). At 4 months following treatment, 3D imaging showed a calculated 5.0 ml reduction in volume and 2.0 mm decreased in submental skin laxity. However, at 9 months following treatment, this volume returned to near baseline levels. The second patient was a 51-year-old woman who underwent 1 treatment of 2 overlapping cycles of submental cryolipolysis (60 minutes each). One week following treatment, 3D imaging showed a calculated 12.1 mL reduction in volume and 2.5 mm decreased in submental skin laxity. Three months following treatment, the volume reduction was 11.9 mL and skin laxity reduction was 3.3 mm.[42]

2.6 | Food and drug administration approval for cryolipolysis

Based on the efficacy and safety of cryolipolysis in clinical trials, a cryolipolysis device (CoolSculpting®; ZELTIQ Aesthetics, Inc., Pleasanton, CA, USA) received U.S. Food and Drug Administration (FDA) clearance for the flanks (K080521) in 2010, abdomen (K120023) in 2012, thighs (K133212) in 2014, submental area (K151179) in 2015, and arms (K162050), bra bulge, back, and underneath the buttock (K160259) in 2016.[43,44]

3 | DISCUSSION

Cryolipolysis has been studied extensively for its safety and efficacy to reduce nonfacial focal lipodystrophy.[45] There have been no changes in lipid levels or liver function tests and no peripheral nerve damage.[35-37] A systemic literature review evaluating the safety and efficacy of cryolipolysis for body contouring showed that only 0.82% reported adverse effects last greater than 4 weeks, with decreased sensation being most common. At 4 months, the mean reduction in subcutaneous fat was 19.6% compared to the control site.[45] To date, four clinical trials and one case series have demonstrated the safety and efficacy of cryolipolysis for treatment of the submental region. A comparison of the trials is shown in Table 1. Mean age, weight, and body mass index were similar between the trials, but there are certain key differences in design and endpoints. In the trial by Kilmer et al,[38] treatments were 60 minutes long, with a single cycle per session. Using ultrasound, there was mean fat layer reduction of 2.0 mm. In the trial by Bernstein et al., treatments were 45 minutes long, with 2 overlapping treatments per cycle and caliper measured mean fat layer reduction was 2.3 (standard deviation, 0.8) mm and the mean fat thickness reduction with 3D imaging was 3.77 (standard deviation, 3.59) mm.[39] In the study by Suh et al,[40] two 45-minute overlapping treatments were also performed, with a mean 4 mm and 2.8 mm reduction in fat thickness as measured by ultrasound and calipers, respectively. Finally, in trial by Leal Silva et al,[41] 2 treatment sessions resulted in a mean reduction in fat of 1.8 mm when measured with MRI and 3.2 mm when measured using calipers. As device settings, number of cycles and treatment sessions, and methods to quantitate fat reduction varied between studies, the ideal treatment protocol to maximize fat reduction and minimize adverse effects is currently unclear. Based on the available data, longer and overlapping treatment cycles, and additional treatment sessions do not seem to result in greater fat reduction. Patient satisfaction surveys at the final follow-up visit in all trials clarify that overall, patients were content with the procedure and results of the treatment. The satisfaction rate was greater than 80% in all 4 trials.[38-41]

The marginal mandibular nerve is a branch of the facial nerve that passes over the mandible at the antegonial notch to innervate the lower lip depressors. The course is variable posterior to this notch and may course 1 or more centimeters below the inferior mandibular border.[46] When performing procedures in the submental region, knowledge of cervicomental anatomy is essential to avoid injury to the marginal mandibular nerve. Injury to this nerve will cause paresis to the lip depressor and muscle and result in an asymmetric smile. No injury to the marginal mandibular nerve was reported in any of the submental cryolipolysis studies or case series.[38-42] Nevertheless, patients should be asked to smile before and after treatment and caution should be taken when applying the cryolipolysis applicators to avoid injury to the marginal mandibular nerve.

The most common side effects in the submental cryolipolysis studies were bruising, erythema, edema, numbness, and tingling which resolved by the end of the study. Pain was assessed in only 2 of 4 of the clinical trials.[39] In the study by Bernstein et al,[39] pain was tolerable and rapidly decreased to baseline shortly after the procedure. In the study by Leal Silva et al,[41] only two patients experienced pain during treatment 1 and there was no pain during treatment 2.

Paradoxical adipose hyperplasia has been reported in patients who underwent cryolipolysis to the flanks abdomen, and upper back. The estimated incidence is reported as 0.0051%, or about 1 in 20 000 treated patients,[47] and men are affected more often than women.[48] However, other studies have reported higher incidences, namely 0.47% or 2 in 422 cryolipolysis treatments in one report,[49] and 0.78% or 4 in 510 patients in another report.[50] These patients developed large, painless, demarcated, tender fat masses at the treated sites 2 to 3 months following cryolipolysis treatment. Spontaneous resolution has not been reported, further cryolipolysis worsens the condition, and the treatment of choice is liposuction.[44] There is one report of a patient with paradoxical adipose hyperplasia

TABLE 1 Comparison of submental cryolipolysis clinical trials

Clinical Trial	Kilmer et al[38]	Bernstein et al[39]	Suh et al[40]	Leal Silva et al[41]
Number of patients	60	14	10	15
Male/Female	12/48	2/12	2/8	13/2
Mean age (yrs)	49.3	50.5	46.6	46.2
Mean weight (lbs)	196.1	206.1	Not reported	178.5
Mean body mass index	31.8	33.1	Not reported	30.5
Number of cycles per treatment session	1	14 patients: 2 cycles, treatment session 1 12 patients: 2 cycles, treatment session 2 2 patients: 1 cycle, treatment session 2	2	1
Number of treatment sessions	59 patients −2 1 patient −1	2	1	2
Length of each cycle (mins)	60	45	45	Treatment 1-45 Treatment 2-30
Temperature (degrees Celsius)	−10	−11	−11	Treatment 1: −12 Treatment 2: −15
Safety endpoint	Met safety endpoint	Met safety endpoint	Met safety endpoint	Met safety endpoint
Correct identification of the baseline photographs by three blinded independent reviewers	91.4% ($P < .0001$)	81.0% (95% CI, 65.9%-91.4%; $P = .02$)	Not performed	60%
Mean fat layer reduction measured by US or MRI	US −2.0 mm or 20% (standard deviation of 2.0 mm, range + 2.0 mm to − 5.9 mm) ($P < .0001$)	Not performed	US −2.8 mm, range 0-6 mm and 35.2%, range 0%-60%	MRI (13/15 patients) − 1.8 mm (standard deviation, 1.157 mm), ($P < .050$)
Mean (SD) fat volume reduction (3D image)	Not performed	4.82 (11.42) cm3 (95% CI, −1.39 to 11.02 cm3; $P = .13$)	Not performed	Not performed
Mean (SD) central submental fat thickness reduction (3D image)	Not performed	3.77 (3.59) mm (95% CI, 1.82-5.72 mm; $P < .001$)	Not performed	Not performed
Mean (SD) skin surface area reduction (3D image)	Not performed	1.29 (1.42) cm2 (95% CI, 0.51-2.06 cm2; $P < .001$)	Not performed	Not performed
Mean (SD) fat layer reduction (caliper measurement)	Not performed	2.3 (0.8) mm (95% CI, 1.9-2.7 mm; $P < .001$)	4 mm, range 0-13 mm and 23.2%, range 0%-54.2%	3.2 mm (1.7 mm), (95% CI, 0.2297-0.4236; $P = .05$)
Patient satisfaction with treatment	83%	93%	90%	80%

following cryolipolysis that was refractory to liposuction.[51] While the mechanism of action is unknown, there have been a number of proposed explanations. For example, recruitment of resident or circulating stem cell population may lead to activation of preexisting adipocytes. In addition, hypoxia resulting from inadequate cooling may lead to rebound adipose hypertrophy and septal thickening.[52] Finally, reduction in sympathetic innervation of adipose tissue may lead to adipocyte proliferation.[53,54]

To date, paradoxical adipose hyperplasia has not been reported following cryolipolysis treatment to the submental region. In the overlapping submental cryolipolysis trial, one patient experienced a 13.85-cm^3 fat volume increase. The authors concluded that since she did not gain weight, did not have increased skinfold caliper measurement, and that photographs showed no evidence of increased volume in the submental area, and that this volume change was not due to paradoxical adipose hyperplasia.[39] However, as this phenomenon has been observed numerous times postcryolipolysis on the body, it is certainly possible that adipose hyperplasia could also occur in the submental area and patients should be warned about this possibility prior to treatment.

Appropriate patient selection and expectations are fundamental before performing cryolipolysis treatments. Patients should be counseled on clinical improvement in the submental contour, number of sessions necessary, side effects, downtime, and cost. Liposuction still remains the gold standard for removal of large fat deposits. In addition, it is important to keep in mind that while cryolipolysis may reduce submental fat, it may also worsen the appearance on the neck by making platysmal banding or skin imperfections more obvious.[55]

4 | CONCLUSIONS

Cryolipolysis is a noninvasive cooling technique that is FDA approved for treatment of submental fat. Clinical trials have demonstrated safety, tolerability, and efficacy using 1-2 treatments sessions. Side effects are mild, with the most common being bruising, erythema, swelling, tingling, and numbness, which resolve within weeks. To date, there have been no reports of injury to the marginal mandibular nerve or paradoxical adipose hyperplasia post-treatment with cryolipolysis.

CONFLICT OF INTERESTS

Dr. Shari R. Lipner has no conflict of interests to disclose.

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