Advances in Minimally Invasive and Noninvasive Treatments for Submental Fat

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PRACTICE **POINTS**

- New developments in minimally invasive techniques for treating submental adiposity include laser-assisted and radiofrequency-assisted lipoplasty with demonstrated clinical benefit and acceptable safety.
- Noninvasive treatments for submental adiposity include radiofrequency-assisted contouring devices, deoxycholic acid, and cryolipolysis, which offer an alternative to more invasive procedures such as lipoplasty.
- There are no comparative studies to date to suggest noninferiority of these noninvasive treatments compared to lipoplasty.

Submental fat (SMF) accumulation is a cosmetically distressing concern for which there have been recent advances in minimally invasive and noninvasive therapeutic options. In this article, we review the newest treatments available for SMF, including laser-assisted lipolysis (LAL), radiofrequency (RF)–assisted lipolysis, deoxycholic acid (DCA), and noninvasive devices. These treatments provide additional options for patients seeking nonsurgical approaches to treatment of SMF.

Cutis. 2017;99:20-23.

Submental fat (SMF) accumulation within the subcutaneous (preplatysmal) or subplatysmal fat compartment of the cervical anatomy results in an obtuse cervicomental angle and loss of mandibular and cervical contours. It is a common cosmetic concern due to its aesthetic association with weight gain and aging.[1] Minimally invasive or noninvasive submental lipolytic agents and techniques are sought for patients who are not candidates for surgery or prefer more conservative cosmetic treatments. These methods typically are only effective in addressing preplatysmal SMF, as subplatysmal SMF requires more surgical methods due to its less-accessible location. The pathology of SMF should initially be assessed by clinical examination or ultrasonography. In this article, we review the most relevant clinical and safety data on minimally invasive and noninvasive treatments for SMF, including laser-assisted lipolysis (LAL), radiofrequency (RF)–assisted lipolysis, deoxycholic acid (DCA), and cryolipolysis.

MINIMALLY INVASIVE MODALITIES

Traditional, or tumescent, liposuction is still widely considered the most effective method for removal of large masses of adiposity. Laser- and RF-assisted adjuncts have been more recently developed to improve patient side effects and recovery time and reduce the manual effort of surgeons. Of note, these adjuncts, with some exceptions, still require the

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Ms. Dong and Ms. Amir report no conflicts of interest.
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same invasiveness as traditional liposuction, involving submental stab incisions of up to 2.4 mm.

Laser-Assisted Lipolysis

Laser-assisted lipolysis produces a similar effect as suction-assisted lipoplasty by focusing pulses of laser energy through a 1-mm wide fiber optic cannula and inducing thermally mediated adipolysis. The directed laser results in adipocyte rupturing with added benefits of skin retraction and small vessel coagulation, thus lessening intraoperative blood loss.[2] This technique typically requires smaller incisions than traditional liposuction. The most common laser lipolysis systems used in cosmetic dermatology are the 920- to 980-nm diode lasers and 1064- to 1440-nm Nd:YAG lasers. The 924-nm diode, 1064-nm Nd:YAG, and 1064/1320-nm Nd:YAG have been best characterized in clinical trials, as reviewed by Fakhouri et al,[3] with demonstrated efficacy in reducing SMF density.

The first randomized prospective trial comparing LAL (using 1064-nm Nd:YAG) and traditional liposuction in various anatomical areas on 25 patients showed no difference in cosmetic results, ecchymoses, edema, or retraction, and significantly lower postoperative pain ratings ($P<.0001$) in LAL.[4] A more recent prospective randomized comparison of LAL (980-nm diode laser; 6–8 W) and traditional liposuction of the submental area in 40 female patients showed greater reduction in SMF thickness in the LAL group compared to the liposuction group at 2-month follow-up (6.2 vs 8.22 unspecified units; $P<.001$) with significant improvement from baseline in both groups ($P<.001$).[5] However, the cosmetic benefit of LAL over traditional liposuction remains controversial and has not been unequivocally established in the literature.

Common adverse events (AEs) are postoperative swelling, ecchymoses, and pain, and complications of interest are nodularity, skin infections, burns, and nerve damage.[6] In one retrospective investigation (N=537), these complications occurred at a rate of less than 1% (4 burns and 1 skin infection).[6] Patients treated with LAL may report fewer AEs, especially pain and bleeding, compared to liposuction-treated patients.[3]

RF-Assisted Lipolysis

Radiofrequency-assisted lipolysis is one of the newest technologies in lipocontouring. NeckTite (Invasix Aesthetic Solutions) is effective for treatment of preplatysmal adiposity and cervicomental lipocontouring; a 2.4-mm bipolar probe that is inserted into the subdermal space and connected with an external electrode emits RF energy and simultaneously coagulates and aspirates adipose tissue. NeckTite also may be used in conjunction with FaceTite (Invasix Aesthetic Solutions), which promotes fibroseptal network remodeling and dermal contraction.[2]

In the first published investigation of the efficacy and safety of NeckTite, 47 of 55 patients received treatment of slight to moderate SMF (average body mass index [BMI], 25 kg/m^2) with NeckTite and FaceTite or NeckTite alone.[7] At 6-month follow-up, 87% (48/55) of patients subjectively rated treatment efficacy as satisfactory, and 2 independent physicians rated the improvement between before-and-after frontal and lateral photographs of the submental area as moderate to excellent in 95% (52/55) of all cases. Reported complications in this study were full-thickness burns resulting in minor scarring (2/55 [4%]), neck tissue hardness that resolved with daily massage after 3 months (5/55 [9%]), and transient facial nerve paresis of the mandibular branch that resolved after 2 months (1/55 [2%]).[7]

NONINVASIVE MODALITIES

RF-Assisted Contouring

Another exciting development in RF technology is truSculpt (Cutera), a noninvasive contouring device that is placed over the epidermis and emits RF energy that preferentially heats fat more than other tissue types. In a single-center prospective trial of efficacy and safety in the treatment of SMF, 17 patients received 2 treatments with truSculpt administered 1 month apart.[8] At 1- and 6-month follow-up, 82.3% (14/17) and 52.9% (9/17) of patients showed improvement on physician assessment. Submental circumference and ultrasonographic fat thickness reductions at 1-month follow-up were 1.4 cm (5.7% of pretreatment circumference [$P<.001$]) and 5.4 mm (9.7% of pretreatment fat thickness [$P=.005$]), respectively. At further longer-term follow-up to 6 months, submental circumference was 0.9 cm (3.8% of pretreatment circumference [$P<.001$]) and ultrasonographic fat reduction was 6.8 mm (10.5% of pretreatment fat thickness [$P=.006$]). Commonly reported AEs were pain (rate not given), erythema (8/17 [47%]), edema (1/17 [6%]), and vesicle formation (1/17 [6%]); all were self-resolving. Erythema usually subsided within 6 hours posttreatment. No other AEs or complications were reported.[8]

Deoxycholic Acid

Deoxycholic acid (DCA)(formerly ATX-101) is an injectable liquid formulation of synthetic DCA that was approved by the US Food and Drug Administration (FDA) in 2015 for moderate to severe SMF. Deoxycholic acid exists endogenously as a bile salt emulsifier and has been shown to cause dose-dependent adipocyte lysis, necrosis, disruption and dissolution of fat architecture, and inflammatory

targeting of adipocytes by immune cells.[9,10] Thus, DCA causes targeted adipocytolysis and is a novel medical agent in the treatment of SMF. Supplied in 2-mL vials, clinicians may inject 10 mL at each treatment for up to 6 treatments administered 1 month apart.[11]

Efficacy—REFINE-1, a pivotal North American–based phase 3 trial, investigated the efficacy and safety of DCA.[12] A total of 506 participants with scores of 2 (moderate) or 3 (severe) on the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) and a mean BMI of 29 kg/m^2 were randomized to receive preplatysmal fat injections of 2 mg/cm^2 of DCA (n=256) or placebo (n=250). Participants received up to 10 mL of product (mean total of 25 mL of DCA across all visits) at each treatment session for up to 6 sessions depending on individual efficacy, with approximately 28 days between sessions. Sixty-four percent of the treatment group received all 6 treatments. At 12-week follow-up after the last treatment session, 70% of DCA-treated participants versus 18.6% of placebo-treated participants ($P<.001$) improved by 1 grade or more on the CR-SMFRS and 13.4% versus 0% ($P<.001$) improved by 2 grades or more. Skin laxity was unchanged or improved in 92.7% of the DCA group and 87.6% of the placebo group.[12]

REFINE-2, the second of the North American phase 3 trials, had parallel inclusionary criteria and study design and established efficacy of 2 mg/cm^2 DCA over placebo in 516 participants (randomized 1:1).[13] At 12 weeks posttreatment, 66.5% of DCA-treated participants versus 22.2% of placebo-treated participants improved by 1 grade or more according to the CR-SMFRS ($P<.001$) and 18.6% versus 3% improved by 2 grades or more in SMF ($P<.001$). Magnetic resonance imaging analysis of participants in the DCA (n=113) and placebo groups (n=112) showed that 40.2% versus 5.2% ($P<.001$) exhibited 10% or more reduction in submental volume, with similar comparative rates of SMF thickness reduction via caliper measurements.[13]

Safety—Safety data from REFINE-1 showed higher rates of treatment-related AEs in DCA-treated participants compared to placebo, including hematoma (70% vs 67.3%), anesthesia (66.9% vs 4.4%), pain (65.4% vs 23.4%), edema (52.9% vs 21.8%), induration (18.3% vs 1.6%), paresthesia (12.8% vs 3.2%), nodule formation (12.5% vs 0.8%), and pruritus (8.6% vs 3.6%).[12] In this trial, 11 of 258 cases (4.3%) of marginal mandibular nerve paresis and asymmetric smile occurred, all in DCA-treated participants and with a median duration of 31 days. Dysphagia resolving in a median duration of 4 days occurred in 1.6% (4/258) of DCA-treated participants.[12] REFINE-2 exhibited similar rates of common AEs. Complications of note were 14 cases of marginal mandibular nerve paresis (11 in DCA group, 3 in placebo group) attributed to injection technique, 1 case of skin ulceration possibly related to accidental injection into dermis, and 6 cases of dysphagia in DCA participants attributed to higher volume treatment sessions and postinjection swelling. Dysphagia lasted a median of 2.5 days and resolved without sequelae.[13]

Overall, DCA demonstrated high rates of minor injection-site AEs that resolved without sequelae and could be mitigated by comfort therapies (eg, lidocaine, nonsteroidal anti-inflammatory drugs) as well as understanding the anatomy of the submental region. Adverse effects of particular interest included marginal mandibular nerve palsy, skin ulceration, and dysphagia.[12,13]

Cryolipolysis

Cryolipolysis is an advancement that utilizes the application of noninvasive cooling temperatures to the skin's surface to destroy underlying adipocytes based on the concept that lipid-filled cells are more susceptible to cold-induced injury than water-filled cells. Thus, cryolipolysis selectively targets adipose tissue, leading to cell death without harm to surrounding cells and without the need for surgery or injections.[14]

Cryolipolysis typically is delivered via a vacuum applicator (CoolMini, Zeltiq Aesthetics Inc), which applies temperatures of −10°C (14°F) to the skin in cycles of 60 minutes each. Initially approved by the FDA for treatment of flank adiposity in 2010, cryolipolysis has since been approved for treatment of the abdomen, thighs, and submental area.[14] An advantage of cryolipolysis is that it does not require frequent treatment sessions for maximal efficacy.

Efficacy—The efficacy of cryolipolysis in the treatment of SMF was established in a multicenter device investigation resulting in its FDA approval for the submental region.[15] Sixty participants with a mean BMI of 31.8 kg/m^2 received 1 (1/60) or 2 (59/60) treatment sessions of the submental area administered 6 weeks apart. Primary efficacy assessments included analysis by 3 blinded reviewers who viewed photographs of each participant at baseline, immediately posttreatment, 6 weeks posttreatment, and 12 weeks posttreatment; ultrasonographic measurements of SMF thickness; and a 12-point patient satisfaction questionnaire. Blinded reviewers correctly identified baseline images in 91.4% (55/60) of cases. Ultrasonography confirmed a mean reduction in SMF of 2 mm ($P<.0001$) or 20% of fat thickness at 12 weeks posttreatment. On subjective patient satisfaction surveys, 83% (50/60) of participants were satisfied with the procedure and

77% (46/60) reported a visible reduction in fat and perceived an improvement in appearance.[15]

Safety—The most common immediate posttreatment AEs were erythema/purpura (100%), numbness (90%), edema (62%), tingling (30%), blanching (25%), and bruising (3%) at the site of cryolipolysis with resolution within 1 week posttreatment, except for numbness.[15] At 6-week follow-up, all AEs had resolved, except continued numbness in 4 participants that resolved by 12-week follow-up. A further event of note was fullness in the throat in 1 participant that was attributed to swelling and resolved at 40 days posttreatment without incident. No serious AEs were reported in this trial.[15]

A particularly concerning but rare complication that is increasing in awareness is paradoxical adipose hyperplasia following cryolipolysis. Patients may develop firm painless areas of soft tissue enlargements in the area of cryolipolysis typically 3 to 6 months posttreatment.[16] The largest published report recorded an incidence rate of 0.46% (n=2, all males) at a single-center institution of 422 cryolipolysis treatments.[16] Other incidence rates reported are 0.0051% and 0.78%.[17] Causes and associations are not known, though male gender is speculated to increase risk.

CONCLUSION

This article highlights the available information on advances in minimally invasive and noninvasive treatments for SMF accumulation. The efficacy and safety trials varied in quality and in different methods of end point analysis of SMF reduction. Further, few trials have featured head-to-head comparisons of treatments.

Although liposuction and adjuncts remain the gold standard in large-mass lipid removal, these procedures are invasive and exhibit typical risks of surgery. Given its sensitive location, the submental area may require the use of more delicate therapeutic methods, including completely noninvasive devices such as truSculpt and cryolipolysis. Regardless of the chosen treatment, the most important factors in yielding patient satisfaction and SMF improvement are proper patient selection and an understanding of the anatomical source of adiposity to be addressed with the therapeutic modalities.

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