Noninvasive approach to treatment of submental fullness

Geeta M Shah, MD;[1,2] Judah N Greenberg, MD;[3] Elizabeth L Tanzi, MD;[1,2] and Gary D Monheit, MD[3,4]

Abstract

A recent survey done by the American Society for Dermatologic Surgery indicated that 67% of respondents were bothered by "excess fat under the chin/neck." Accumulation of fat in the preplatysmal compartment of the neck is a common cause for fullness in the submental area. In the past, surgical liposuction was the only option to remove fat in the submental area. Although effective, liposuction does have risks and downtime. Recently, noninvasive options for treatment of submental fat have been introduced. These include treatment with deoxycholic acid, known as Kybella®, and cryolipolysis using the CoolMini™ handpiece. Both of these treatments offer less downtime fewer potential risks than the surgical counterpart. This article summarizes these two procedures and describes noninvasive approaches to treatment of submental fat.

Semin Cutan Med Surg 36:164-169 © 2017 Frontline Medical Communications

The contours of the chin and neck play a significant role in the aesthetics of the aging face. While the ideal youthful face shape involves fullness of the midface tapering toward the chin, submental fullness or convexity contributes to a loss of definition of the lower face and so-called "double chin," resulting in an older or overweight appearance.[1] Among the most common causes of submental fullness is accumulation of fat in the preplatysmal submental compartment. The 2015 American Society for Dermatologic Surgery Consumer Survey on Cosmetic Dermatologic Procedures indicated that 67% of respondents were bothered by "excess fat under the chin/neck."[2] In a similar survey, 77% of patients reported that they noticed extra fat under their chin, and 61% expressed interest in having that excess fat reduced.[3]

Until recently, the primary modality for reduction of submental fat has been surgical liposuction. While surgical liposuction of the submental region is an effective treatment for submental fullness, it carries the risks associated with an invasive surgical procedure, including postoperative bleeding/bruising, infection, scarring, and neurologic or vascular compromise.[4] Patients may also be reluctant to pursue liposuction due to its cost and postoperative recovery time. Accordingly, noninvasive modalities for the reduction of submental fat have been developed.

ATX-101 (deoxycholic acid injection; Kybella in the United States and Belkyra in Canada; Kythera Biopharmaceuticals, Inc, Westlake Village, CA) is a synthetic chemical compound homologous to an endogenous bile acid secreted in the small intestine for the digestion of dietary fats. When injected into the submental fat compartment, ATX-101 results in adipocyte lysis and consequent reduction in submental fat. Cryolipolysis has also been employed for the treatment of submental fat. Already approved for the treatment of excess fat on the abdomen, flanks, thighs, and most recently the submental area, cryolipolysis utilizes the application of controlled cooling to the skin surface to cause noninvasive lysis of subcutaneous adipocytes in the target area. The safety and efficacy of these nonsurgical techniques has led to their rapid integration into clinical practice for the reduction of submental fat.

ATX-101 (Kybella)

Deoxycholic acid was initially utilized as an emulsifying agent in compounded preparations of injectable phosphatidylcholine/sodium deoxycholate used for the reduction of subcutaneous fat.[5] Rotunda et al ultimately identified deoxycholic acid as the primary adipolytic constituent of such compounded products.[6] Subsequent investigation confirmed that protein-rich tissues such as skin and muscle are relatively resistant to the adipolytic effects of deoxycholic acid,[7] enhancing its clinical utility in selectively destroying fat cells while sparing surrounding tissues. Injectable deoxycholic acid acts as a deterrent to solubilize and disrupt the cell membranes of target adipocytes, resulting in cell lysis. After an initial neutrophilic inflammatory response, adipocyte contents and debris are removed by lipid-laden macrophages with consequent atrophy of the fat lobules.[8] Subsequent thickening of fibrous septae suggests neocollagenesis also takes place,[8] with clinical tightening of the submental skin.

Injectable deoxycholic acid (hereinafter referred to as ATX-101) has been studied extensively for the reduction of submental fat. Initial phase 3 clinical trials were conducted in Europe. Two large, multicenter, double-blind, placebo-controlled trials demonstrated significant improvement in both observer-rated and patient-reported endpoints pertaining to reduction of subcutaneous fat after injection of ATX-101.[9,10] Subsequently, 2 additional phase 3 clinical trials (REFINE-1 and REFINE-2) of similar design were conducted in the United States and Canada. Like the European trials, the REFINE

[1]Capital Laser and Skin Care, Chevy Chase, Maryland.
[2]Department of Dermatology, George Washington University Medical Center, Washington, DC.
[3]Total Skin and Beauty Dermatology Center, Birmingham, Alabama.
[4]Departments of Dermatology and Ophthalmology, University of Alabama at Birmingham, Birmingham, Alabama.
Disclosures: Dr. Shah has no disclosures. Dr. Greenberg has nothing to disclose. Dr. Tanzi is on the Scientific Advisory Board for Zeltiq/Allergan, Scientific Advisory Board of Sciton, Consultant for Allergan, Galderma, Syneron/Candela, Valeant/Solta, and Merz. Dr. Monheit reports grants and personal fees from Allergan, grants from Galderma, grants from Teoxane, grants from CROMA, outside the submitted work; and Revance-consultant, Galderma-consultant, Kythera-consultant and clinical investigator, Merz-consultant, Suneva-consultant and clinical investigator, Alphaeon-clinical investigator.
Correspondence: Geeta M Shah, MD; gshah@capitalskinlaser.com

1085-5629/13$-see front matter © 2017 Frontline Medical Communications
https://doi.org/10.12788/j.sder.2017.040

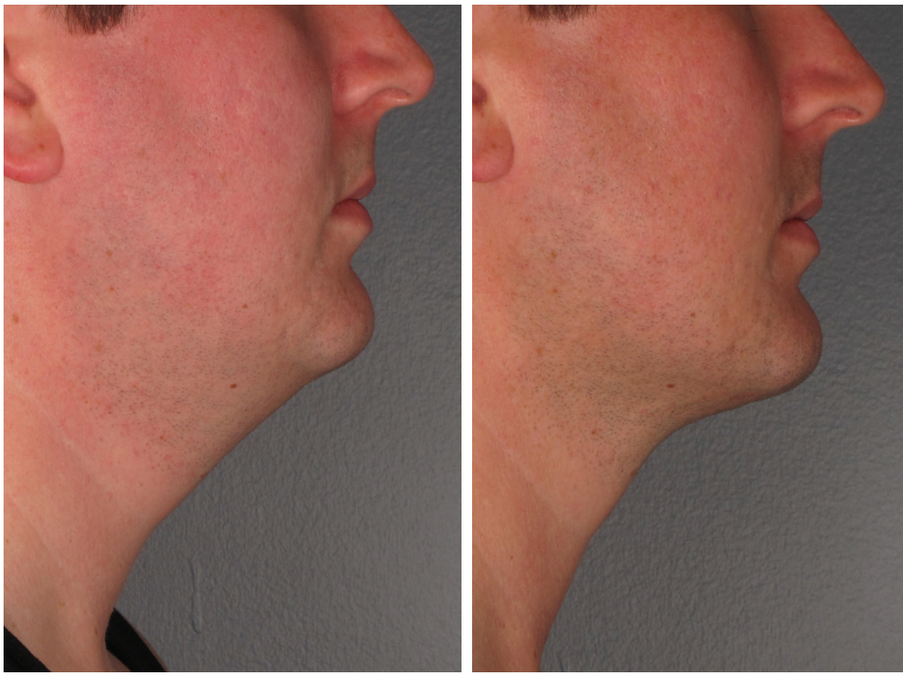

FIGURE 1. (**A**) Submental area before and (**B**)12 weeks after four 4 mL treatments of ATX-101 (16 ml total)

trials demonstrated the efficacy of ATX-101 for the reduction of submental fat compared to placebo, as assessed by multiple observer-rated and patient-reported outcome measures, as well as objective reduction of submental fat, as measured by magnetic resonance imaging. In these studies, ATX-101 was injected at 28-day intervals for up to 6 treatments, and efficacy was assessed at 12 weeks after the final treatment. Results of these studies showed that the primary efficacy endpoint was met in 70% and 66.5% of ATX-101-treated patients versus 18.6% and 22.2% of patients treated with placebo, respectively.[11,12] The durability of response to treatment with ATX-101 has also been established by long-term follow-up of patients treated in the clinical trials (Figures 1 and 2).[13]

Patient selection and consultation

Proper patient selection is essential to successful treatment with ATX-101. A focused history and physical examination should be conducted to identify suitable candidates for treatment. Patients should be screened for previous surgeries (or other cosmetic procedures) in the submental region, as well as a history of dysphagia or facial nerve dysfunction. Physical examination will evaluate the amount of submental fat, degree of skin laxity, and the presence of complicating factors in the treatment area (including submental inflammation, infection, or scarring). The ideal candidate for treatment with ATX-101 will have a moderate to large amount of preplatysmal submental fat and no more than moderate laxity of submental skin. Patients must be instructed to tense the platysma (to isolate the preplatysmal fat compartment), swallow (to rule out dysfunction), and smile (to identify asymmetry of the lower face). Medical conditions causing submental fullness (such as thyromegaly, thyroglossal duct cysts, or submental/cervical lymphadenopathy) should also be ruled out.[14]

Treatment expectations should be discussed with patients in detail. Patients must be advised that injection of ATX-101 results in gradual reduction of submental fat; results may not be fully visible until 1-2 months after each treatment, and multiple treatments may be required (depending upon the amount of submental fat). Realistic treatment goals and expectations should be emphasized at the outset in order to promote both patient and provider satisfaction with treatment outcomes. Patients should also be informed of the possible adverse effects of ATX-101 injection (discussed below) and expected recovery time.

Procedure

Careful identification of topographic landmarks of the submentum and anterior neck is necessary to facilitate injection of ATX-101 into the target preplatysmal fat compartment and to avoid adjacent anatomic structures.[15] These landmarks include the inferior border of the mandible, the anterior border of the sternocleidomastoid muscles bilaterally, and the superior notch of the thyroid cartilage. The preplatysmal fat compartment is delineated by the submental crease anteriorly and the hyoid bone (at the cervicomental junction) posteriorly. The lateral borders of the fat compartment are best appreciated by palpation but can be approximated as imaginary caudal continuations of the labiomandibular folds.[16] These landmarks are marked prior to injection. Additionally, it is recommended that the probable location of the marginal mandibular nerve should be marked as a "no treatment zone." Posterior to the facial artery, the marginal mandibular branch of the facial nerve commonly courses 1 to 2 cm below the inferior border of the mandible.[17]

After marking the necessary anatomic landmarks, the skin of the anterior neck and submentum is cleansed with a topical antiseptic. The treatment area may then be anesthetized via local injection of lidocaine with epinephrine (the inclusion of epinephrine may help to reduce bruising). Application of a cold pack may also enhance patient comfort. The 1-cm injection grid (supplied with the injection kit) should then be applied to the treatment area (Figure 3). When injecting ATX-101, the needle must pass adjacent to, but not directly through, grid markings in order to avoid foreign body deposition. The preplatysmal fat should be pinched between the thumb and forefinger to elevate it and ensure injection of ATX-101 into the fat compartment rather than overlying skin or underlying platysma muscle. ATX-101 aliquots of 0.2 mL are placed via perpendicular injection midway into the preplatysmal fat compartment at 1-cm intervals (as defined by the injection grid). This will ensure uniform infiltration of the fat compartment based upon the diffusion characteristics of ATX-101 and its radius of effect.[14] Cold packs may be applied immediately upon completion of treatment. Treatment can be repeated as soon as 1 month later.

Side effects and complications

The majority of adverse effects associated with ATX-101 are predictable injection site reactions.[9-12] Patients must be advised that pain

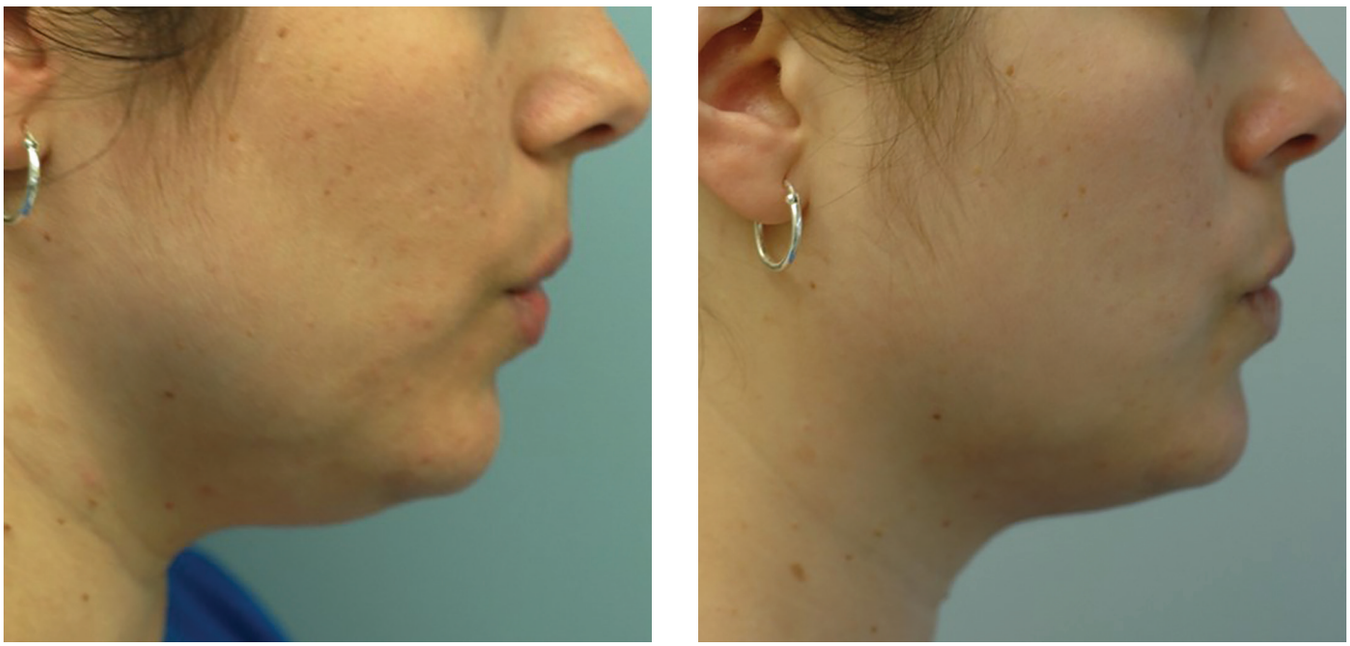

FIGURE 2. (**A**) Submental area before and (**B**) 6 weeks after two 4 mL treatments of ATX-101 (8ml total)

and edema are expected reactions to injection of ATX-101, but they are generally mild and self-limited. These may be managed by the intraprocedural measures detailed above, as well as continued application of cold packs at home and treatments with acetaminophen and/or nonsteroidal anti-inflammatory agents (NSAIDs). Although there is some concern that the use of NSAIDs could increase the risk of bruising (and NSAIDs should therefore be discontinued 7-10 days prior to treatment), resumption of NSAIDs within 1 hour of treatment has not been associated with increased bruising.[18] Continuous compression and antihistamine administration have not been shown to significantly improve pain or swelling.[19]

Patients may also experience numbness/tingling, erythema, induration, or itching as a result of the inflammatory effects of ATX-101. These side effects are typically tolerable to patients, peak within the first several hours after treatment, and subside within 7 days.[19] Rarely, marginal mandibular nerve paresis can also result from injection of ATX-101, given the proximity of the marginal mandibular nerve to the intended treatment area. The marginal mandibular nerve can be avoided by proper anatomic localization of the preplatysmal fat compartment prior to injection. All instances of marginal mandibular nerve paresis reported in the clinical trials resolved spontaneously without lasting sequelae.[20] Patients should be counseled that those with more submental fat prior to initial treatment may experience more local side effects (ie, swelling and discomfort) than those with less fat, but these are expected to lessen with subsequent treatments as the amount submental fat is reduced.

Clinical pearls: ATX-101

- Appropriate patients should have a moderate to large amount of submental fat and minimal skin laxity.
- Topographic landmarks bounding the submental fat compartment must be carefully identified and marked to prevent complications and undesirable outcomes.
- Pinch submental fat between thumb and forefinger upon injection to isolate the preplatysmal compartment and elevate it from deeper structures.
- Side effects are generally local, mild, and easily managed with measures common to other facial injectable treatments.
- Injectable submental fat reduction may be included as part of a face and neck contouring regimen for facial rejuvenation.

Cryolipolysis

Cryolipolysis (Coolsculpting™ ZELTIQ Aesthetics, Pleasanton, CA) is a noninvasive method that uses localized, controlled cooling to selectively lyse fat cells.[21] First described by Manstein and Anderson in 2008, cryolipolysis is based on reports of "popsicle panniculitis" and "equestrian panniculitis" that suggested that human adipose tissue is preferentially damaged by cold exposure.[21-23] Initial animal studies demonstrated a 33% fat layer reduction with cryolipolysis by ultrasound measurement and by pathology evaluation. The inflammatory response in the subcutaneous fat begins approximately 24 hours after cold exposure and continues to intensify with eventual rupture of the adipocytes.[24] No changes in lipid profiles or hepatotoxicity have been observed.[25,26]

CoolSculpting™ was approved by the United States Food and Drug Administration (FDA) for treatment of excess fat in the flanks in 2010, followed by indications for the abdomen and thighs. The original cryolipolysis applicator uses 2 cooling plates, into which a fold of adipose tissue is suctioned by negative pressure and cooled to −10ºC.

In 2016, Kilmer et al performed a study on treatment of submental fat in which 60 patients were enrolled for treatment with cryolipolysis using a prototype small volume vacuum applicator (CoolMini™). Subjects underwent 1 or 2 treatments in the submental area spaced 6 weeks apart, with an efficacy endpoint of at least 80% correct identification of the pretreatment images by 3 blinded reviewers, as well as ultrasound measurement of reduction

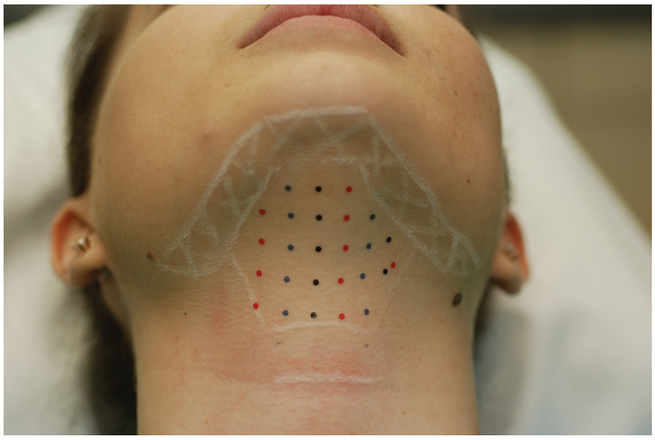

FIGURE 3. Pretreatment markings for Kybella® injections in the submental area

in fat layer thickness at the end of 12 weeks. Of the 60 patients treated, 59 had 2 cycles of treatment, and 1 patient had only 1 treatment. At the end of the study, there was an over 80% correct identification of pretreatment images and a mean fat layer reduction of 2.0 mm, as measured by ultrasound. Patients were surveyed, and 83% of patients treated were satisfied and 77% reported visible fat reduction. The most commonly reported side effects were erythema, edema, numbness, and tingling, all of which resolved by the end of the 12-week study period.[27]

Application of cryolipolysis in an overlapping fashion on the flanks was first described in 2014.[28] More recently, Bernstein and Bloom reported significant fat layer reduction using bilateral, overlapping small-cup applicator treatment cycles for submental fullness in 14 patients. Patients received bilateral treatment with approximately 20% treatment area overlap. Three-dimensional imaging found a mean reduction in fat volume of 4.82 cm^3, skin surface area of 1.29 cm^2, and fat thickness of 3.77 mm. Side effects of the procedure were typically mild, including numbness and tingling, which resolved without intervention at the 12-week follow-up visit. This study demonstrated the safety and efficacy of overlapping cryolipolysis treatment in the submental area, with 93% of study participants reporting satisfaction with this treatment.[29]

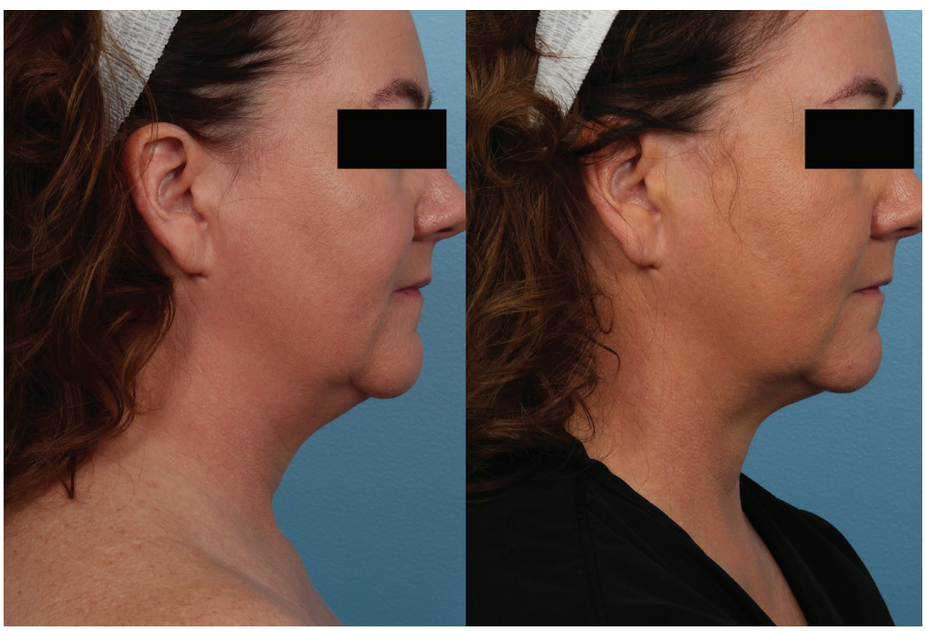

FIGURE 4. Results 3 months after single treatment of cryolipolysis using 2 overlapping applications in submental area

Patient selection and consultation

Careful patient selection is the crucial first step to ensure a successful outcome with cryolipolysis. The ideal candidate for submental cryolipolysis will have a moderate amount of preplatysmal submental fat. As prominent, hyperdynamic platysmal bands may be "unmasked" with a reduction of submental fat, evaluation, documentation, and a discussion of treatment options is appropriate during the consultation. Patients should be informed that CoolSculpting™ is not meant to treat skin laxity, although studies have demonstrated modest skin tightening after cryolipolysis.[30,31] As the cosmetic appearance of skin laxity may worsen once fat is removed under slack skin, a discussion including subsequent nonsurgical skin tightening techniques may be introduced during the initial consultation for submental contouring.

A thorough discussion about realistic expectations is important prior to treatment initiation with cryolipolysis. An improved submental contour is expected after a single treatment; however, a second session may be required for the best cosmetic outcome (Figures 4 and 5). Patients should be counseled that full effects of each treatment may not be noted until 3 to 4 months postprocedure.

Procedure

Baseline clinical photos are essential when treating patients with cryolipolysis. Frontal, 45-degree, and 90-degree angle photos are best to fully capture all the subtleties of the submental area. To ensure consistency with photos, it is best to instruct the patient to look at a fixed focal point on the wall with body turned toward the focal point while standing or sitting in a standardized position. Remove jewelry and clothing to expose the entire neck and lower face area. A single-color, blue or black background is helpful to easily delineate clinical changes.

Patient positioning prior to cryolipolysis application facilitates a smooth treatment. It is imperative to minimize movement during treatment cycles to reduce the risk of applicator loss of contact with the skin. In our experience, having the patient watch a properly placed TV during treatment helps to keep the chin stationary and at a slight upward angle. Use of a laptop or cell phone during treatment is discouraged, as this could result in downward movement of the chin, causing loss of full contact with the applicator.

When treating with CoolMini™, the treatment area should first be cleansed with alcohol to remove oils that may be on the skin. Mark out the treatment area

FIGURE 5. Results 3 months after 2 treatments of cryolipolysis performed 3 months apart. The submental area was treated with 2 overlapping applications at both treatment sessions.

using the applicator template, ensuring that there is overlap in the center just under the chin, if pursuing a bilateral treatment (Figure 6). Seat the patient in a comfortable reclined position, massage the pretreatment skin wipe onto the treatment area for 60 seconds, and apply the CoolMini™ Gel onto the treatment area. Once the liner and gel trap have been placed in the applicator and the applicator is in proper position on the securement arm, the CoolMini™ applicator can be applied straight onto the treatment marking. Ensure that the patient does not feel compression on the throat and can swallow comfortably prior to starting the 45-minute treatment cycle. The applicator should be secured into place. Once the cycle is complete, there will be a butter-stick appearance to the treated skin, which should be massaged for a 2-minute cycle. During this time, watch for any vasovagal response that may occur. This procedure should be repeated on the other side of the submental area if attempting a bilateral treatment.

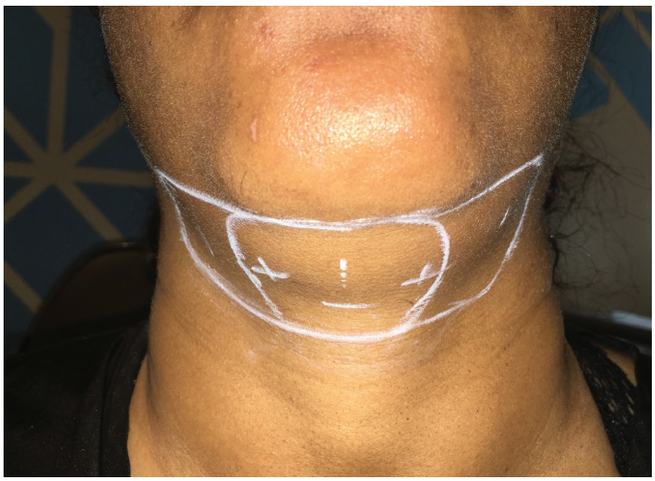

FIGURE 6. Pretreatment markings for overlapping application of CoolMini™ in the submental area

Side effects and complications

Cryolipolysis is generally a well-tolerated procedure. Discomfort during the initial few minutes of the cooling cycle and during the posttreatment massage is expected. In the FDA-approval study for the submental application of the small cup applicator, erythema and edema were the most common side effects, and most symptoms resolved within 1 week. Numbness, bruising, sensitivity, itching, and tenderness were reported and resolved by week 12. There were 2 reports of persistent erythema, 1 report of hyperpigmentation in the treated area, and 1 report of a full feeling at the back of the throat. These side effects resolved by day 20, 27, and 40, respectively.[27]

Late-onset pain has been reported with cryolipolysis, occurring on average 3 days after treatment. This has been defined as having 2 of the 3 following characteristics: (1) neuropathic qualities such as stabbing, burning, or shooting pains in the treatment area; (2) prominent nightly pain that disrupts sleep; and (3) pain unresponsive to nonsteroidal anti-inflammatory medications and analgesics. In a study done by Keaney et al, it was found that 15.2% of patients developed delayed-onset pain after cryolipolysis treatment. All patients were women with a mean age of 39. The treatment area in the majority of cases was the abdomen; however, there were 2 cases of pain in the flanks and 1 case in the inner thigh. The pain resolved after an average duration of 11 days. It has been thought that variations in sensory nerve anatomy or an enhanced inflammatory response could contribute to the development of this symptom.[32] To date, no cases of delayed-onset pain have been reported after treatment of submental fat with cryolipolysis.

Reports of paradoxical adipocyte hyperplasia (PAH), which is a delayed increase in adipose tissue at the treatment site, have been reported after cryolipolysis. The incidence of PAH is about 1 in 20,000 treated patients or 0.0051% of patients. No single, common characteristic has been identified among affected individuals; however, the incidence of PAH seems to be higher in men. Various anatomic locations have been reported, including flanks, abdomen, and upper back. PAH onset is delayed 2 to 3 months after treatment, and is treated with liposuction or abdominoplasty.[33,34] To date, no instances of PAH have been reported after treatment of submental fat with cryolipolysis.

Combining ATX-101 and cryolipolysis

Both ATX-101 and cryolipolysis can be used safely and effectively to minimize submental fullness and improve the contour of the chin and upper neck. In some cases, a combination of the treatments may be preferred. As side effects with ATX-101 are dose related, a patient with a larger double chin may benefit from an initial treatment with cryolipolysis to debulk the area then addi-

tional sculpting with several sessions of smaller-volume ATX-101 placement. As the full clinical effect of either treatment may take 2-3 months to appreciate, patients are advised to allow adequate time between treatment sessions.

Clinical Pearls: Cryolipolysis for submental fullness

- Assess for platysma bands and skin laxity
- Use bilateral, overlapping application whenever possible
- Optimize patient positioning during treatment
- Follow up at 3 months to review clinical photos for additional treatment
- Can debulk with cryolipolysis then sculpt with ATX-101

Conclusion

Our armamentarium of choices to treat a "double-chin" have increased tremendously in the recent years. With the options of larger areas of fat reduction using cryolipolysis as well as removing smaller pockets of fat with deoxycholic acid, the submental area can effectively be treated with minimal to no downtime. Cryolipolysis is most effective using the double-cross method in the submental area, allowing for a more expansive treatment area and overlap in the central area where the largest amount of fat resides. Deoxycholic acid can then be used to address a pocket of fat under the chin. Due to the safety profile of both of these procedures, patients can be treated with fewer risks than surgical options and more effective results.

References

1. Coleman SR, Grover R. The anatomy of the aging face: volume loss and changes in 3-dimensional topography. *Aesthet Surg J*. 2006;26(1S):S4-S9. https://doi.org/10.1016/j.asj.2005.09.012.
2. American Society for Dermatologic Surgery. Consumer Survey on Cosmetic Dermatologic Procedures. https://asds.net/_Media.aspx?id=8963. Updated August 4, 2015. Accessed March 26, 2017.
3. Schlessinger J, Weiss SR, Jewell M, et al. Perceptions and practices in submental fat treatment: a survey of physicians and patients. *Skinmed*. 2013;11(1):27-31.
4. Koehler J. Complications of neck liposuction and submentoplasty. *Oral Maxillofac Surg Clin North Am*. 2009;21(1):43-52. https://doi.org/10.1016/j.coms.2008.10.008.
5. Duncan D, Rotunda AM. Injectable therapies for localized fat loss: state of the art. *Clin Plast Surg*. 2011;38(3):489-501. https://doi.org/10.1016/j.cps.2011.02.005.
6. Rotunda AM, Suzuki H, Moy RL, Kolodney MS. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. *Dermatol Surg*. 2004;30(7):1001-1008.
7. Thuangtong R, Bentow JJ, Knopp K, Mahmood NA, David NE, Kolodney MS. Tissue-selective effects of injected deoxycholate. *Dermatol Surg*. 2010;36(6):899-908. https://doi.org/10.1111/j.1524-4725.2010.01566.x.
8. Walker P, Lee D, Toth BA. A histological analysis of the effects of single doses of ATX-101 on subcutaneous fat: results from a phase 1 open-label safety study of ATX-101. Presented at: Annual Meeting of the American Society for Dermatologic Surgery; October 3-6, 2013; Chicago, IL.
9. Ascher B, Hoffmann K, Walker P, Lippert S, Wollina U, Havlickova B. Efficacy, patient-reported outcomes and safety profile of ATX-101 (deoxycholic acid), an injectable drug for the reduction of unwanted submental fat: results from a phase III, randomized, placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2014;28(12):1707-1715. https://doi.org/10.1111/jdv.12377.
10. Rzany B, Griffiths T, Walker P, Lippert S, McDiarmid J, Havlickova B. Reduction of unwanted submental fat with ATX-101 (deoxycholic acid), an adipocytolytic injectable treatment: results from a phase III, randomized, placebo-controlled study. *Br J Dermatol*. 2014;170(2):445-453. https://doi.org/10.1111/bjd.12695.
11. Jones DH, Carruthers J, Joseph JH, et al. REFINE-1, a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial With ATX-101, an Injectable Drug for Submental Fat Reduction. *Dermatol Surg*. 2016;42(1):38-49. https://doi.org/10.1097/DSS.0000000000000578.
12. Humphrey S, Sykes J, Kantor J, et al. ATX-101 for reduction of submental fat: A phase III randomized controlled trial. *J Am Acad Dermatol*. 2016;75(4):788-797. https://doi.org/10.1016/j.jaad.2016.04.028.
13. Bhatia AC, Dayan SH, Hoffmann K, et al. Reductions in submental fat achieved with deoxycholic acid injection (ATX-101) are maintained over time: results from long-term, follow-up studies. Presented at: Annual Meeting of the American Society for Dermatologic Surgery; October 15-18, 2015; Chicago, IL.
14. Jones DH, Kenkel JM, Fagien S, et al. Proper Technique for Administration of ATX-101 (Deoxycholic Acid Injection): Insights From an Injection Practicum and Roundtable Discussion. *Dermatol Surg*. 2016;42 Suppl 1:S275-S281.
15. Kenkel JM, Jones DH, Fagien S, et al. Anatomy of the Cervicomental Region: Insights From an Anatomy Laboratory and Roundtable Discussion. *Dermatol Surg*. 2016;42 Suppl 1:S282-S287.
16. Hatef DA, Koshy JC, Sandoval SE, Echo AP, Izaddoost SA, Hollier LH. The submental fat compartment of the neck. *Semin Plast Surg*. 2009;23(4):288-291. https://doi.org/10.1055/s-0029-1242180.
17. Batra AP, Mahajan A, Gupta K. Marginal mandibular branch of the facial nerve: An anatomical study. *Indian J Plast Surg*. 2010;43(1):60-64. https://doi.org/10.4103/0970-0358.63968.
18. Fagien S, McChesney P, Subramanian M, Jones DH. Prevention and Management of Injection-Related Adverse Effects in Facial Aesthetics: Considerations for ATX-101 (Deoxycholic Acid Injection) Treatment. *Dermatol Surg*. 2016;42 Suppl 1:S300-S304.
19. Dover JS, Kenkel JM, Carruthers A, et al. Management of Patient Experience With ATX-101 (Deoxycholic Acid Injection) for Reduction of Submental Fat. *Dermatol Surg*. 2016;42 Suppl 1:S288-S299.
20. Kythera Biopharmaceuticals, Inc. KYBELLA (deoxycholic acid injection) prescribing information. https://www.mykybella.com/~/media/Unique%20Sites/MyKybella/Documents/KYBELLA-Combined-FINAL-Labeling.pdf. Accessed April 16, 2017.
21. Manstein D, Laubach H, Watanabe K, Farinelli W, Zurakowski D, Anderson RR. Selective cryolysis: A novel method of non-invasive fat removal. *Lasers Surg Med*. 2008;40(9):595-604. https://doi.org/10.1002/lsm.20719.
22. Epstein EH Jr, Oren ME. Popsicle panniculitis. *N Engl J Med*. 1970;282(17):966-967.
23. Beacham BE, Cooper PH, Buchanan CS, Weary PE. Equestrian cold panniculitis in women. *Arch Dermatol*. 1980;116(9):1025-1027.
24. Avram MM, Harry RS. Cryolipolysis for subcutaneous fat layer reduction. *Lasers Surg Med*. 2009;41(10):703-708. https://doi.org/10.1002/lsm.20864.
25. Zelickson B, Egbert BM, Preciado J, et al. Cryolipolysis for noninvasive fat cell destruction: initial results from a pig model. *Dermatol Surg*. 2009;35(10):1462-1470. https://doi.org/10.1111/j.1524-4725.2009.01259.x.
26. Klein KB, Zelickson B, Riopelle JG, et al. Non-invasive cryolipolysis for subcutaneous fat reduction does not affect serum lipid levels or liver function tests. *Lasers Surg Med*. 2009;41(10):785-790. https://doi.org/10.1002/lsm.20850.
27. Kilmer SL, Burns AJ, Zelickson BD. Safety and efficacy of cryolipolysis for non-invasive reduction of submental fat. *Lasers Surg Med*. 2016;48(1):3-13. https://doi.org/10.1002/lsm.22440.
28. Bernstein EF, Bloom JD, Basilavecchio LD, Plugis JM. Non-invasive fat reduction of the flanks using a new cryolipolysis applicator and overlapping, two-cycle treatments. *Lasers Surg Med*. 2014;46(10):731-735. https://doi.org/10.1002/lsm.22302.
29. Bernstein EF, Bloom JD. Safety and Efficacy of Bilateral Submental Cryolipolysis with Quantified 3-D Imaging of Fat Reduction and Skin Tightening. *JAMA Facial Plast Surg*. https://doi.org/10.1001/jamafacial.2017.0102. [Epub ahead of print].
30. Stevens WG. Does cryolipolysis lead to skin tightening? A first report of cryodermadstringo. *Aesthet Surg J*. 2014;34(6):NP32-NP34. https://doi.org/10.1177/1090820X14539699.
31. Carruthers J, Stevens WG, Carruthers A, Humphrey S. Cryolipolysis and skin tightening. *Dermatol Surg*. 2014;40 Suppl 12:S184-S189. https://doi.org/10.1097/DSS.0000000000000229.
32. Keaney TC, Gudas AT, Alster TS. Delayed onset pain associated with cryolipolysis treatment: a retrospective study with treatment recommendations. *Dermatol Surg*. 2015;41(11):1296-1299. https://doi.org/10.1097/DSS.0000000000000502.
33. Jalian HR, Avram MM, Garibyan L, Mihm MC, Anderson RR. Paradoxical adipose hyperplasia after cryolipolysis. *JAMA Dermatol*. 2014;150(3):317-319. https://doi.org/10.1001/jamadermatol.2013.8071.
34. Ho D, Jagdeo J. A systematic review of paradoxical adipose hyperplasia (PAH) post-cryolipolysis. *J Drugs Dermatol*. 2017;16(1):62-67.