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SAFE DEOXYCHOLIC ACID INJECTION TECHNIQUE FOR SUBMENTAL FAT REDUCTION

Introduction

Body contouring is gaining popularity in the aesthetic world, as many patients are opting for non-surgical treatments to reduce fat and to improve their appearance. Prior to 2015, patients seeking cosmetic enhancement to reduce submental fat (SMF) typically underwent submental liposuction. Health Canada and the United States Food and Drug Administration approved deoxycholic acid for the reduction of moderate-to-severe SMF in 2015. Deoxycholic acid (BELKYRA™, Allergan, Madison, NJ) is a minimally invasive injectable treatment for the non-surgical reduction of submental adipose tissue. It is a synthetic bile acid that acts on adipocytes by emulsifying fats. Upon injection in the submental fat, it disrupts plasma membranes and ultimately induces adipocyte cell lysis. This is followed by an inflammatory reaction, with a subsequent reduction in fat.[1] The swelling takes up to a week to resolve, and then tissue remodelling takes place over months. In one of the early randomized controlled trials (RCT) comparing deoxycholic acid to placebo, between 64 – 69% of patients (n=360) were highly satisfied with the appearance of their face and chin using the Subject Self-Rating Scale (SSRS score ≥4) after up to 4 treatments compared to 29% in the placebo group ($P < 0.001$).[2] Deoxycholic acid injection can be a safe and effective addition to a dermatologist's cosmetic practice, with a high rate of patient satisfaction.

The first portion of this article will address the safety concerns of deoxycholic acid treatment, outlining not only the common adverse effects (AEs) but also highlighting rare side effects that have been reported in case reports and case series. The second portion of the article will review patient selection, anatomic considerations, and injection techniques to achieve a safe outcome.

Adverse events associated with deoxycholic acid injection

Multiple phase III clinical trials have established the safety profile of deoxycholic acid and have reported the most common AEs'.[2-5] Since coming to market, a growing body of literature regarding real-world AEs after injection have come to light.

The pivotal randomised controlled trials, REFINE-1, authored by Jones et al. and REFINE-2, authored by Humphrey et al., reported the common adverse events observed after deoxycholic acid injeciton.[4,5] They reported that AEs were common, mostly transient, and for the most part, mild-to-moderate in nature. The four most common reported AEs were swelling (87%), bruising (72%), pain (70%), and numbness (67%). These common effects lasted for an average of about four days. Somewhat less common were erythema (27%), induration (23%), paresthesia (14%), nodule formation (13%), and pruritus (12%). Notably, dysphagia was observed in 2% of patients, with a median duration of 3 days. Marginal mandibular nerve injury was reported in 4% of treated subjects, with a median duration of about 44 days (ranging from 1-298 days to resolution). Other less common side effects included site warmth, skin tightness, nausea, and headache. Most of the reported adverse events occurred around the injection site and were easily managed by using ice packs and oral analgesics.

Post-marketing studies and case series described uncommon AEs that were not originally reported in the phase III randomised controlled trials. Shridharani (2017) was one of the first to report mild transient alopecia at the injection sites in 8 of 39 male patients; 5 of 21 [23.8%] who underwent multiple sessions versus 3 of 18 [16.7%] who underwent a single session (p = .702).[6,7] In this series, all the cases of alopecia resolved within six weeks of the last treatment session. Five additional cases of localized non-scarring alopecia at injection sites were subsequently reported.[8-11] Some of the affected patients experienced re-growth, while others did not. One male developed patchy alopecia in the treatment area one week after injection, which eventually resolved at the seven month mark.[8] Another patient with beard alopecia reported only a 60% improvement in the alopecia fourteen months after his first treatment.[8] Sebaratnam et al. (2019) performed a biopsy on a patient with post-treatment beard alopecia which was suggestive of a localized telogen effluvium as the likely responsible mechanism.[11]

Four cases of skin necrosis or vascular injury have been reported after deoxycholic acid treatment.[12-15] Most cases presented with pain upon injection and immediate visible skin blanching, followed by the development of retiform purpura, papular or vesicular lesions following the procedure. Some of the cases of skin necrosis resolved without sequelae, while others resulted in scarring. One case of skin necrosis and ulceration along the mandible healed with an indurated red plaque, which was improved using pulsed dye laser and fractionated CO2 laser.[14] There was one reported case of hypertophic scar formation after resolution of a vascular event and another case of atrophic, depressed scars on the neck which persisted at a follow up visit one month after injection.[15]

Most of the AE's of deoxycholic acid treatment are expected, tolerable, transient, and easily managed. Although rare, skin necrosis and beard alopecia have been reported in post-marketing reports. An understanding of the possible side effects of the procedure are needed for informed consent to take place and may help set expectations for post-procedure discomfort.

Patient selection

Proper patient selection is the first step to achieving a safe and aesthetically desirable outcome. Deoxycholic acid injection is indicated for improvement in the appearance of moderate-to-severe convexity or fullness associated with SMF in adults via the reduction of pre-platysmal fat, which is located between the platysma and the dermis. Patients with excess adipose or soft tissue in the post-platysmal area will not benefit from treatment. Excessive skin laxity in the submental area is another sign that the patient may not be an ideal candidate for treatment. Further reduction of SMF in these patients may accentuate the skin laxity and result in an aesthetically undesirable outcome. It is important to palpate the submental area to assess the location and amount of adipose tissue, as well as to assess for the presence or absence of excessive skin laxity.

Safe injection technique

When delineating a safe treatment area, it may be useful to visualize or draw a treatment zone that is bordered superiorly by the submental crease, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone (at the cervicomental angle). The injection points should be 1.5 cm away from the inferior border of the mandible to avoid injecting near

the marginal mandibular branch of the facial nerve (Figure 1). Doing so can lead to neuropraxia or transient asymmetrical smile.

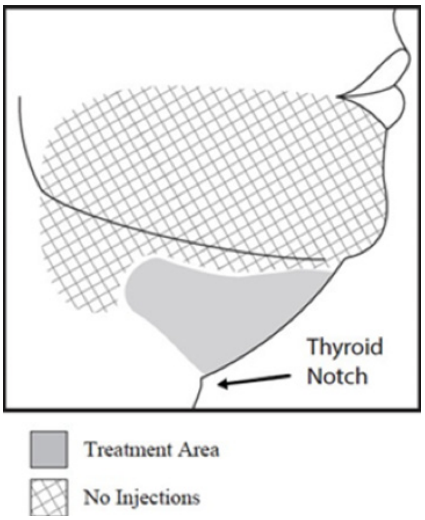

Figure 1. Avoid the Marginal Mandibular Nerve Area; BELKYRA™ product monograph, March 2016

A 1x1 cm grid is marked on the area to be treated, so that each injection point is 1 cm apart. As per the product monograph, 0.2 ml is injected next to each grid marking, spaced 1 cm apart, with a 30G (or smaller) 0.5-inch needle. Pinch the subcutaneous tissue between two fingers to isolate the fat prior to injection. Consider aspirating prior to injecting the product to avoid intravascular injection. Up to 50 injection points or a maximum of 10 mL of product is advisable in one session. Repeat treatments should be spaced at least 1 month apart for a maximum of 6 sessions.[16]

In addition to avoiding injecting near the mandible and near the course of the marginal mandibular nerve, try to visualize the approximate locations of other important anatomical structures. These include the mental and submental arteries, the submandibular glands (these lie close to the mandible and are the second largest salivary glands after the parotid gland), as well as

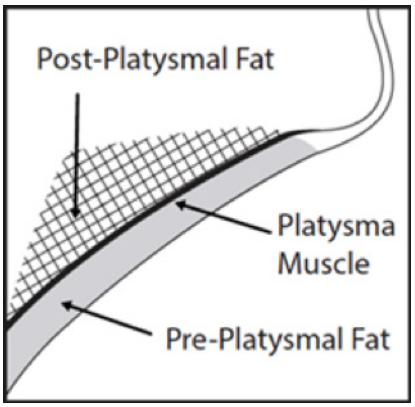

Figure 2. Sagittal View of Platysma Area; BELKYRA™ product monograph, March 2016

the digastric, sternocleidomastoid and platysma muscles. Try to be mindful of the most likely locations of the lymph nodes in the submental, submandibular, and cervical areas. If you meet resistance with your needle, withdraw and reposition. Inserting your needle into adipose tissue should not give a feeling of resistance.

Safe injection techniques for deoxycholic acid injections of the submental region

- Inject at least 1.5 cm away from important structures i.e. the mandible, the marginal mandibular branch of the facial nerve, arteries, and salivary glands
- Do not exceed 0.2 ml per injection site
- Avoid intradermal injections to avoid skin necrosis
- Consider aspiration prior to injection to avoid intravascular injection
- Pinch the adipose tissue between your fingers to isolate it prior to injection

Table 1. Safe injection techniques for deoxycholic acid; courtesy of Dorota Kadlubowska, MD

Conclusion

Dermatologists are sought out in the aesthetic world for their expertise, their regard for safety, as well as their ability to manage complications associated with cosmetic treatments. Accordingly, it is important to have a solid understanding of not only the common, but also the rare complications of the cosmetic treatments they provide. In order to achieve a desirable outcome, the understanding of adverse events, proper patient selection, knowledge of anatomy and safe injection techniques are of utmost importance.

References:

1. Kirk DS. Deoxycholic acid injection for the reduction of submental fat in adults. AAOMS. 2016;e-53.

2. Ascher B, Hoffman K, Lippert S, Wollina U, Havliickova. 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 Venerol. 2014;28:1707-15.

3. Rzany B, Griffiths T, Walker P, Lippert J, McDiarmid J, Havlickova B. Reduction of unwanted subdermal fat with ATX-101 (deoxycholic acid), an adipocytolytic injectable treatment: results from a phase III, randomized, placebo-controlled study. Br J Dermatol. 2014;170:445-53.

4. 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.

5. Humphrey M, Sykes J, Kantor J et al. ATX-101 for reduction of submental fat: A phase III randomized controlled trial. Dermatol Surg. 2016;75:4.

6. hridharani SM. Early experience in 100 consecutive patients with injection adipocytolysis for neck contouring with ATX-101 (deoxycholic acid). Dermatol Surg. 2017;43(7):950-8.

7. Shridharani SM. Real-world experience with 100 consecutive patients undergoing neck contouring with ATX-101 (deoxycholic acid): An updated report with a 2-year analysis. Dermatol Surg. 2019;45(10):1285-93.

8. Grady B, Porphirio F, Rokhsar C. Submental alopecia at deoxycholic acid injection site. Dermatol Surg. 2017;43(8):1105-8.

9. Souyoul S, Gioe O, Emerson A, Hooper DO. Alopecia after injection of ATX-101 for reduction of submental fat. JAAD Case Reports. 2017;3:250-2.

10. Wambier CG. Alopeica em barba causada por desoxicolato para tratamento de gordura submentoniana. Surg Cosmet Dermatol. 2017;9(3):259-60.

11. Sebaratnam DF, Wong XL, Kim L, Cheung K. Alopecia following deoxycholic acid treatment for submental adiposity. JAMA Facial Plast Surg. 2019;21(6):571-2.

12. Riswold K, Flynn V. A cautionary tale: A vascular event with deoxycholic acid injection. Dermatol Surg. 2018;44(6):887-9.

13. McKay C, Price C, Pruett L. Vascular injury after deoxycholic acid injection. Dermatol Surg. 2019;45(2):306-9.

14. Sachdev D, Fabi SG. Deoxycholic acid-induced skin necrosis: Prevention and management. Dermatol Surg. 2018;44(7):1037-9.

15. Ramirez MR, Marinaro RE, Warthan ML, Burton CS. Permanent cutaneous adverse events after injection with deoxycholic acid. Dermatol Surg. 2019;45(11):1432-4.

16. BELKYRA™ deoxycholic acid injection product monograph, Kythera Biopharmaceuticals, Inc. Accessed [April 10, 2020].