LETTER TO THE EDITOR

REMODELING THE NECK AND THE LOWER JAW WITH DEHOXYCHOLATE INJECTIONS

R. RAUSO[1], G. TARTARO[1], L. RUGGE[1], F. CHIRICO[1] and N. ZERBINATI[2]

[1]Maxillo-Facial Department, University of Campania "Luigi Vanvitelli", Naples, Italy;
[2]Dermatology Department, University of Insubria, Varese, Italy

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Nonsurgical cosmetic facial procedures have gained popularity in recent decades. These procedures are commonly referred to as facial rejuvenation, and only a few are performed in the neck region. Herein, the authors describe their experience with off-label use of deoxycholic acid (DC) injections on 18 patients for remodeling of the neck and lower jaw. The injection protocol was personalized for each patient, and lidocaine was always premixed with the DC. After the initial injection visit, at least 3 months passed before further injections were considered. All documented side effects, including swelling and dysesthesia, resolved spontaneously. All patients received follow-up for at least 3 months, and only 2 patients required a second session of injections. By personalizing the injection protocol for each patient, good outcomes were achieved, including aesthetic enhancement of the shape and contour of the jaw and neck. Although the study is limited by the relatively small sample size, the results are promising and warrant additional investigations.

To the Editor,

Statistics released by the American Society for Aesthetic Plastic Surgery in 2016 show the dramatic increase of surgical and nonsurgical cosmetic procedures throughout the preceding 20 years; the number of plastic surgery procedures doubled in that period, and the quantity of nonsurgical cosmetic procedures increased by 12-fold (1). This demonstrates that an increasing number of subjects are seeking cosmetic improvements and that nonsurgical procedures are preferred to surgical interventions. Reasons for this preference vary and may include fear of surgery and the operating room, and concerns about lengthy convalescence time causing interference with social and/or professional aspects of life (2).

Various tools are available for nonsurgical rejuvenation of the face, including dermal fillers, botulinum toxin, energy-based devices (EBDs). However, until recent years, cosmetic injectables for use in the neck were lacking. Although rejuvenation of the neck can be achieved successfully with several EBDs (such as radiofrequency and high-intensity focused ultrasonography), moving an EBD can be difficult and cumbersome; therefore, these systems may not be practical for physicians who work in multiple locations. Injectable treatments do not have this disadvantage and can be performed on demand. Moreover, EBDs must be purchased upfront, whereas a supply of injectables can be purchased as needed, when needed.

Since 2015 in the United States and Canada, and

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Mailing address:
Prof. Raffaele Rauso,
Maxillo-Facial Department,
University of Campania "Luigi Vanvitelli",
Piazza Miraglia,
Naples, Italy
e-mail: dr.raffaele.rauso@gmail.com

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2 years later in parts of Europe (eg, Italy, Poland, Check Republic), a DC-based product specifically indicated for reduction of submental fullness has been available (3). The product is used according to a specific injection protocol, which includes a grid specifying proper placement. Injection sites are spaced 1 cm apart, and 0.2 mL of the product is injected into each site. Moreover, the product information suggests that injections be performed every 4 to 6 weeks, until the desired outcome is achieved, up to a maximum of 6 sessions. (4)

The authors of the present study have extensive experience with adipocitolitic DC-based solutions. Herein, they describe their own protocol for a DCA-based product, which entails personalizing the timing and sites of injection on a case-by-case basis.

MATERIALS AND METHODS

This is a retrospective clinical study of a cohort of patients (N = 18) treated consecutively between May 2017 and January 2018. The cohort included 12 females and 6 males, aged 24 to 57 years. All patients received 1% DC injections (Belkyra 10 mg/mL, Allergan S.p.A., Rome, Italy). Exclusion criteria were an excess of neck skin ptosis, unelastic skin excess, unrealistic patient expectations, breastfeeding, pregnancy, liver disease, kidney disease, and all medical conditions for which this treatment is contraindicated.

Each patient was evaluated, including clinical and photographic assessment. Before treatment, all patients signed a consent form confirming that they had been informed of the off-label protocol to be used for their treatment. Every patient received a personalized injection protocol that did not adhere strictly to the manufacturer's proposed protocol. Each individualized protocol was based on the patient's anatomy and need. The pretreatment evaluation of skin elasticity was helpful for the patient to have a clear understanding of the result that would likely be achievable, which was explained to the patient in advance.

The injection grid designed by the manufacturer was used only for the submental area. For each patient, a specific marking was made based on pretreatment clinical evaluation. If overall improvement of the neck area was desired, a "neck collar–like" marking was drawn (Fig. 1). If the aesthetic goal was a more acute cervico-mental angle, pre- and retro-platismatic fat injections were planned.

All patients received injections to the neck area and/or pre-jaw line. Injection sites were spaced 1 cm apart. The contents of each 2-mL vial of DC were premixed

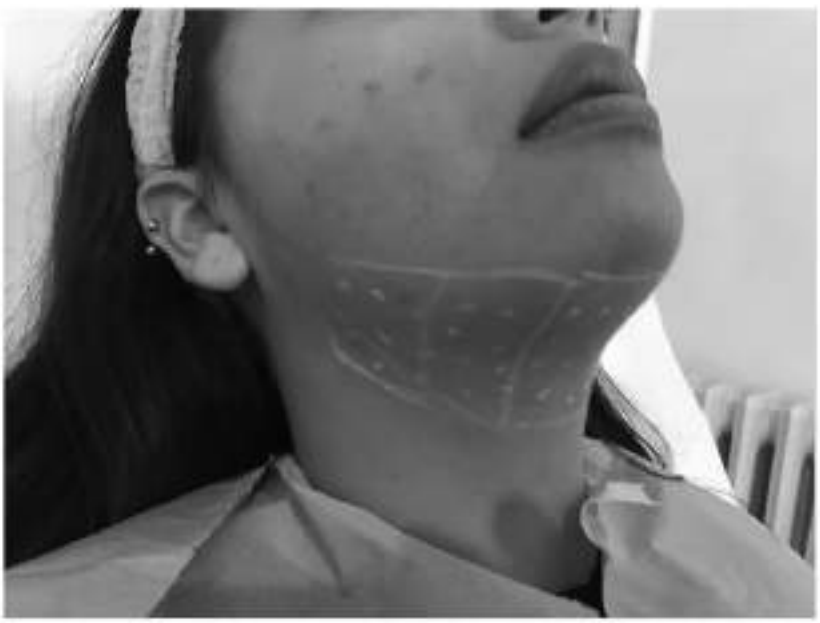

Fig. 1. *The pre-operative marking of "neck collar" injections.*

with 0.5 mL of 2% lidocaine (lidocaina cloridrato 20 mg/mL; Bioindustria L.I.M.; Novi Ligure, Italy). Each site was injected with 0.25 mL of solution, and no more than 4 vials were used during each session.

Following the first session of injections, a waiting period of at least 3 months ensued, after which the result was evaluated and a decision made as to whether to perform a second series of injections.

All patients were followed-up for at least 6 months after the final session of injections.

RESULTS

No patient complained of pain during the procedure. All patients experienced progressive swelling, as expected, which lasted 25 days on average. For 3 patients, ecchymosis was observed, which self-resolved within 1 week. Four patients experienced dysesthesia of the treated area, which lasted for 2 months after the injections and also self-resolved. One patient vomited within 6 hours of the injection session (data presented in Table I). No other complications were recorded.

Only 2 patients required a second session of injections. All patients returned for clinical control 1 and 3 months after the injection session(s) and were followed-up for 6 at least months after the final injections. Each patient affirmed to be happy with his or her result. (Fig. 2 shows clinical photographs of a female patient).

DISCUSSION

In humans, DC is derived from cholic acid produced by the liver and is then metabolized by intestinal bacteria; in the small intestine, DC determines the emulsification and absorption of fat.

When DC is injected into fat, it alters the permeability of fat cell membranes, causing progressive cellular swelling that ultimately results

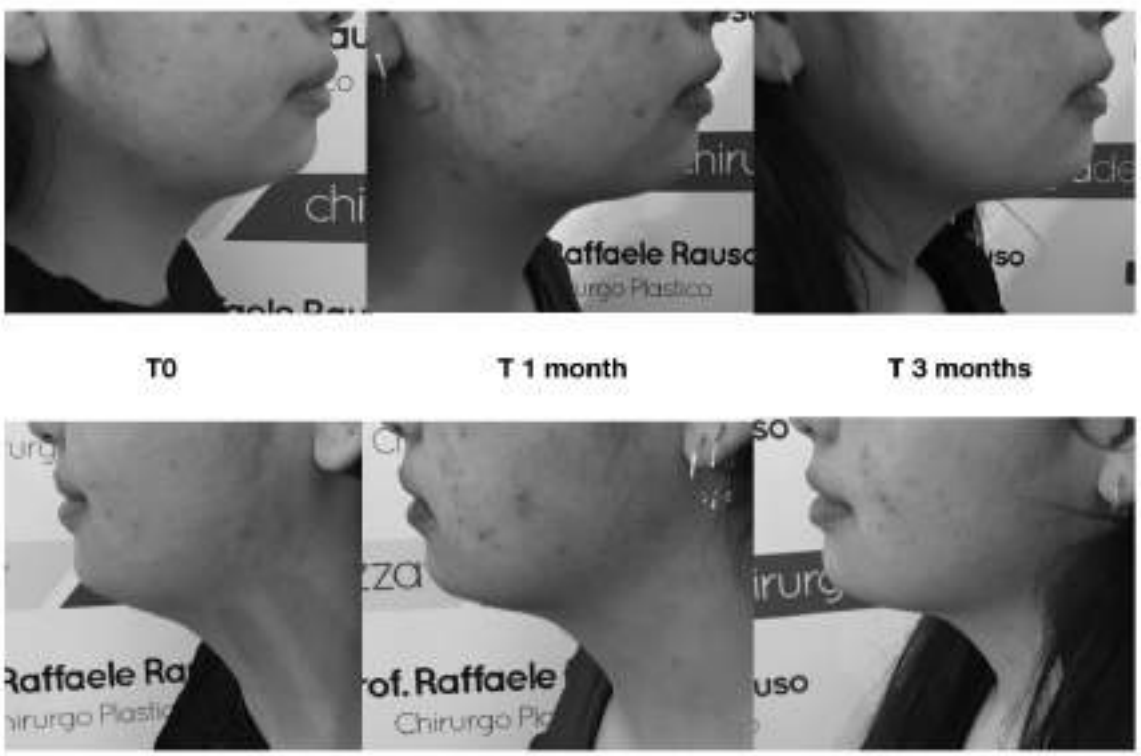

Fig. 2. *In this figure it is possible to see the progressive improvements of the neck appearance of a 26-year-old woman 1 and 3 months after injection of 4 vials of ATX 101, injected in a single session.*

in the breakup of fat cells. This process can take several days to several weeks. After cellular breakup, macrophages enter the site and eliminate cytoplasm and cell membranes, while the healing process is carried out by the development of fibrotic tissue. The entire process, including healing, usually takes several months. These processes have been described in scientific literature (5, 6). Based on this knowledge and on previous experience with DC compounds, in the present study Belkyra was injected to reduce fat in the neck and pre-jawline and to achieve tightening of the overlying skin.

The use of DC as an injectable for fat reduction has been debated for years, since the discovery by Rotunda and Duncan regarding its role in injection lipolysis that refuted the findings of Dr. Rittes from early in the 21st century (7-10). Over the years, DC injections have been largely performed to reduce body fat, despite the lack of information on posology, timing of injections, and safe use of DC. A major safety concern, namely skin necrosis after subcutaneous injection of DC, has been reported (11).

In 2009, without any preclinical study, a product containing DC was sold in Europe (Aqualyx; Marllor International; San Giovanni in Marignano, Italy) and was classified as a medical compound. However, in 2013, Duncan et al. compared the cytolytic index of this medical compound with that of a phosphatidylcholine/DC compound and noted that Aqualyx had a higher cytolytic effect; in order of effectiveness, the cells most sensitive to cytolysis were dermal, endothelial, muscular, fat, and neural (12). These findings emphasized the lack of safety of the medical compound. In fact, in 2016, the Italian Ministry of Health blocked the merchantability of Aqualyx (5, 11-13). In 2014, McDiarmid compared DC volumes of 1 mg/cm^2 and 2 mg/cm^2, and observed that 1 mg/cm^2 was associated with a better safety profile, including a lower incidence of side effects (14). That study represents the first investigation of optimal posology for injection of DC. Several months later, in 2015, the product debuted in the United States (as Kybella) and Canada (as Belkyra) as the first DCA-based drug specifically indicated for reduction of submental fat.

The DC present in Belkyra/Kybella is a nonanimal, nonhuman, purified version that appears to be partially selective because cells with a high percentage of membrane proteins (such as those in the dermis, muscles, nerves, and vessels) seem to be less sensitive to its action. Investigators have demonstrated that albumin neutralizes or binds DC in nonadipose tissue, given the lack of tissue damage seen by endogenous DC (3, 4).

The injection protocol used in the present study was in part concordant with the manufacturer's guidelines. However, in addition to injecting into the area indicated in the manufacturer's protocol, injections were performed elsewhere to achieve neck and jaw recontouring secondary to fat cell lysis. To accomplish this, it was necessary to vary the injection sites and to customize them for each patient.

Moreover, DC was premixed with lidocaine in the present study because it is well known that DC injection is painful for the patient. For the same reason, it has been suggested to use ice packs immediately prior to injections or to administer local anesthesia before DC injections. However, ice packs are often not helpful in reducing pain during injection, and local anesthesia may alter the anatomy of the area to be injected. These potential problems can be avoided by mixing DC with lidocaine, effectively minimizing pain during injection.

In respect to the quantity of lidocaine added to the contents of each vial of DC, we aimed for the minimum amount required to reduce pain whilst still allowing the physician to easily inject the appropriate volume of DC into each site. Considering the posology of 0.2 mL of DC per site (as prescribed by the manufacturer) and that each vial contains 2 mL of product (from each vial, it is possible to fill two 1-mL syringes to inject 10 points), adding 0.5 mL of lidocaine permitted the filling of two 1-mL syringes plus another half syringe, enabling 10 individual placements of 0.25 mL of DC per site.

The buffer system present in the injectable DC product, represented by anhydrous disodium phosphate, is able to avoid pH modification if another drug is added, which explains why the effectiveness of DC is maintained after mixing with lidocaine. Another favorable feature of this mixture is the total absence of precipitation of the solution.

In the present study, the interval between injection sessions was substantially longer than usual. In general, DC is injected every 4 to 6 weeks; in the present study, it was injected every 3 months (if a subsequent session was required). This protocol was successful because of the authors' previous experience with DC injections (5). In 2015, Dr Salti and the senior author of the current study (R.R.) described their own protocol, derived from analyzing an abdominal specimen harvested 3 weeks after injections: different phases of progressive cellular swelling were apparent, including the breakup of cells. Areas of cytoplasmic homogenization and cell membrane dissolution also were present (5). These findings demonstrate that, even after several weeks, an inflammatory component is still present in the injected area; therefore, a period of more than 4 to 6 weeks is needed to allow for sufficient healing and for objective evaluation of fat reduction and skin tightening. Therefore, our protocol is to wait at least 3 months between injection sessions.

In the present study, a relatively new DC-based product was injected to improve the appearance of the neck and/or lower jawline, according to a novel protocol characterized by premixing lidocaine, performing "on-demand" injections, and waiting at least 3 months between injection sessions. Good results were achieved in all patients, and side effects were minimal, with a lower incidence than reported previously by others. (3) Larger and longer-term studies of the present protocol are warranted to confirm its safety and effectiveness.

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