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REVIEW ARTICLE

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Deoxycholic acid in the submental fat reduction: A review of properties, adverse effects, and complications

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Abstract

Background: Deoxycholic acid (DCA) was developed by the pharmaceutical industry for aesthetical use in submental fat reduction. It represents the first lipolytic substance approved by the Food and Drug Administration (FDA) for fat reduction in that area.

Aims: This study presents an update of properties and the use of DCA, as well as adverse events and possible complications.

Methods: A search in MEDLINE/PubMed, Cochrane, and Bireme/LILACS databases was performed using the terms: "deoxycholic acid" OR "ATX-101" AND "injection" NOT "amphotericin" NOT "biliary" NOT "bile." Experimental studies developed in animals, clinical trials, literature reviews, case reports, and letters to the editor that included the DCA mechanism of action, dose, manner of use, adverse effects, and complications were selected.

Results: The most frequent adverse events are edema, local pain, bruise, and numbness, which usually spontaneously regress. However, complications, including, skin necrosis, nerve injury, alopecia, and vascular events, can occur, demanding complex management without specific protocols.

Conclusion: Although DCA is beneficial for lysis of adipose tissue, clinicians should be aware about the adverse effects and risks involved with the use of this substance. The knowledge of local anatomy, properties, and adverse effects are fundamental to treatment with DCA.

KEYWORDS

adipose tissue, adverse effects, deoxycholic acid, submental fat

1 | INTRODUCTION

Face and neck aesthetical procedures are sought for beauty and facial renewal. The main compounds used in these procedures are botox, hyaluronic acid, poly-L-lactic acid, calcium hydroxyapatite, and deoxycholic acid (DCA). Each of these substances has a specific function and application. The modification of facial structure by reduction of volume and fat has increased in popularity in recent years.[1,2] The shape and contour of the chin and neck play fundamental roles in personal aesthetics, and fat accumulation deforms the shape and definition of this area.[3,4] In light of this, use of DCA began in 2007 as a non-surgical alternative to submental fat reduction procedures; however, its use was only approved by the Food and Drug Administration (FDA) in 2015.[5] When applied in the subcutaneous fat localized within the preplatysmal (supraplatysmal) compartment of the submental region, DCA causes the lysis of local adipocytes to improve the appearance of the convexity of the region.[3–6]

TABLE 1 Controlled clinical trials involving DCA injection

Article	Design/ Duration	Objectives	Sample/Sex	Mean age	Outcome
Rotunda et al[14]	• Exploratory study • Randomized • Double-blind • Single-center Duration: • 4 weeks	• Injection of pure DCA vs. phosphatidylcholine with DCA in the submental region • Safety and effectiveness assessment	n = 42 36/F 6/M	52	• 5 sessions with DCA • 4 sessions with the association • Profile improvement was superior with DCA • No differences in the incidence, duration, or severity of adverse effects between groups
Shridharani[15]	• Observational prospective study • Single-arm • Single center Duration: • 24 to 172 days	• DCA injection • Single vs. multiple sessions • 1-month interval for submental injections • Evaluation of efficacy, safety, and adverse effects	n = 100 39/M 61/F	45.4	• 58, 33, 8, and 1 patient participated in 1, 2, 3, and 4 sessions, respectively • DCA was effective and well-tolerated • Effects such as edema, numbness, and pain were reported with an average duration of 7.7, 28.5 and 3.5 days, respectively • Paresthesia in the marginal mandibular nerve occurred in two patients
Walker & Lee[10]	• Phase I study • Single-center • Open-label Duration: • 24.5 hours	• AD injection • Abdominal fat • Safety, pharmacokinetic, and pharmacodynamic assessment	n = 10 5/F 5/M	22.9	• Plasma concentration of endogenous DCA showed a transient increase; • Plasma concentration of DCA reached the maximum plasma level quickly • They returned to normal concentrations in 12 h • No significant systemic changes in:- cholesterol - triglycerides totals - free fatty acids - C-reactive protein - interleukin-6
Goodman et al[17]	• Phase II study Duration: • 16 weeks	• Comparison of different doses of DCA • 1 mg/cm^2, 2 mg/cm^2, or 4 mg/cm^2 vs placebo • Assessment of submental fat reduction and skin laxity • CR-SMFRS, SLRS, and SSRS scales were used	n = 155 -	46	• All DCA groups showed significant improvement in fat reduction • Skin laxity unchanged throughout evaluation • Most common adverse effects were: pain, edema, anesthesia, bruising, induration • Spontaneous regression within 28 days • No systemic adverse effects was identified
Jones et al[18]	• Phase III study • Randomized, double-blind, placebo-controlled Duration: • 12 or 24 weeks	• Injection of DCA vs. placebo on submental fat • Evaluation of effectiveness and safety • CR-SMFRS, PR-SMFRS scales were used with magnetic resonance	n = 506 421/F 85/M	49.5	• DCA was effective in reducing submental fat • Adverse events were mild/moderate and transient

(Continues)

TABLE 1 (Continued)

Article	Design/ Duration	Objectives	Sample/Sex	Mean age	Outcome
Humphrey et al[13]	• Phase III study • Randomized, double-blind Duration: • 44 weeks	• DCA injection compared to placebo • Evaluation of effectiveness and safety • PR-SMFIS and CR-SMFRS scales were used and magnetic resonance	n = 516 445/F 71/M	47.9	• DCA was more effective in reducing submental fat in all assessment methods • 85.7% of local adverse effects were recorded with DCA and 76.9% with placebo • DCA was more likely to achieve submental volume reduction confirmed by magnetic resonance imaging

Abbreviations: CR-SMFRS, Clinician-Reported Submental Fat Rating Scale; DCA, deoxycholic acid; PR-SMFIS, Patient-Reported Submental Fat Impact Scale; PR-SMFRS, Patient-Reported Submental Fat Rating Scale; SLRS Skin Laxity Rating Scale; SSRS Subject Satisfaction Rating Scale.

In view of the increasing use of DCA by health professionals, and considering that this substance is relatively new to the market, it is necessary for professionals to better understand the substance, its specificities, and potential adverse effects. Therefore, this study presents an update of properties and applications of DCA, reported adverse events, and possible complications of its use.

2 | MATERIALS AND METHODS

A review of the literature was performed in Medline/PubMed, Cochrane, and Bireme/LILACS databases using the terms: "deoxycholic acid" OR "ATX-101" AND "injection" NOT "amphotericin" NOT "biliary" NOT "bile." Papers written in English without date stipulation, in vivo studies (humans and animals), clinical trials, and literature reviews were selected. In addition, case reports and letters to the editor regarding the adverse effects of DCA application were included.

3 | RESULTS

A total of 751 papers were found in the databases. After exclusion of duplicated papers, the title and abstracts of the papers were reviewed. The papers which fulfill the inclusion criteria of the present study were included, as well as the references within them. Additional information made available by the manufacturer of DCA was also used.

4 | DEOXYCHOLIC ACID: COMPOSITION AND MECHANISM OF ACTION

Deoxycholic acid is a secondary bile acid endogenously produced inside human intestines and stored inside the gallbladder.[3,7] It functions to emulsify and solubilize dietary fats, assisting in their breakdown, and absorption by the gastrointestinal tract. The majority of endogenous DCA is resorbed by small intestine and recycled by enterohepatic circulation, while a smaller fraction is released in the feces without alteration. The pharmaceutical industry developed synthetic DCA, with a chemical structure identical to endogenous acid, but without contaminants of human or animal origin.[2,3]

Initially, DCA was used in the pharmaceutical market in association with other substances such as phosphatidylcholine (Lipostabil®, Aventis Pharma) and amphotericin B (Fungizone®, Bristol-Myers Squibb Canada). It was also used in the treatment of lipomas[8] and the manufacturing of influenza vaccines, such as Fluarix® (GlaxoSmithKline Australia Pty Ltd) and Fluviral® (GlaxoSmithKline Inc).[2]

Rotunda et al[9] found that DCA was the primary mediator of adipocyte lysis in the formulation of phosphatidylcholine with DCA commercially called Lipostabil®, which was later banned. Research continued, and in 2007, an extensive program of pre-clinical and

clinical studies was initiated with pure DCA, without association, for submental fat reduction. The substance was named ATX-101 (commercial name Kybella®) (Kythera Biopharmaceuticals, Inc). It was approved by the FDA in the United States and Canada in 2015 and became the first injectable drug indicated for submental fat reduction.[2,7,10–12] In Brazil, the National Agency for Sanitary Surveillance (ANVISA) approved the use of ATX-101 in 2018 with the commercial name of Belkyra (Allergan Produtos Farmacêuticos LTDA.).

In the available commercial formulations, each 2-mL bottle contains 20 mg of synthetic DCA as the active ingredient, and benzyl alcohol, dibasic sodium phosphate, sodium chloride, and sodium hydroxide in water as inactive ingredients. Hydrochloric acid and additional sodium hydroxide are added as necessary to adjust the formulation to pH 8.3.[12] When injected into the subcutaneous adipose tissue, DCA causes lysis of adipocytes.[10,13] On the first day post-injection, there is induction of pores in the cell membrane, leading to leaking of the cytoplasmic content of the cell, destabilizing it, with subsequent lysis.[14] The process of membrane rupture of the adipocyte is irreversible[15] and causes an inflammatory tissue response dominated by neutrophils. On the seventh day after DCA application, a macrophage infiltrate is present to scavenge cell debris and lipids. On the 28th day, the recruitment of fibroblasts and inflammation remission is observed.[7,10,11,13,16] The observation of those histological features helped recommend a one-month interval between DCA injections. A dose of 2 mg/cm^2 of DCA was more effective than 1 mg/cm^2 and, yet, a dose of 4 mg/cm^2 increased the severity and frequency of adverse effects without an increase in effectiveness.[7,9,11,17]

The safety, pharmacokinetics, and pharmacodynamics of DCA injection have been investigated, as well as the local effects. The substance has a high affinity for adipose tissue but low affinity by protein-rich tissues such as muscle tissue, blood vessels, and skin.[7,10,15,16] Besides local mechanisms, after injection, DCA is rapidly absorbed by the human body, accompanied by an increase of plasmatic concentration which returns to normal 12–24 hours after administration. In addition, an increase in plasmatic levels of lipids is observed, similar to what occurs after eating.[3,7,10] The plasmatic levels of C-reactive protein, free fatty acids, total cholesterol, triglycerides, and interleukin-6 were analyzed pre- and post-injection of DCA in the abdominal region without significant changes.[10,11]

After those initial observations, scales were developed to measure the amount of submental fat reduction due to DCA therapy, including the Clinician-reported Submental Fat Rating Scale (CR-SMFRS), Patient-Reported Submental Fat Rating Scale (PR-SMFRS), Subject Satisfaction Rating Scale (SSRS), Skin Laxity Rating Scale (SLRS) and the Patient-Reported SMF Impact Scale (PR-SMFIS). Also, magnetic resonance images have been used to accompany the evaluation of DCA effects on local fat.[7,11,13,18]

Table 1 presents the clinical trials testing the effects of DCA application on the submental region.

5 | APPLICATION METHODS AND ADVERSE REACTIONS

The use of DCA requires an understanding of the anatomy submental region to maximize the effectiveness and minimize risks and potential complications.[1,6,11] The submental region has a complex anatomy, the facial artery and vein cross the inferior border of the mandible. Also, caution must be paid in this region to the submandibular glands, which are located bilaterally and may be mistaken for fat deposits.[6] The mandibular facial nerve, a branch of the facial nerve, is situated close to the injection zone and innervates facial expression muscles, including the depressor anguli oris, depressor labii inferioris, orbicularis oris, and mentalis. The mandibular nerve course can present one to two centimeters below the inferior border of the mandible, varying by patient.[6,19,20] The nerve can suffer damage resulting in paresthesia and an asymmetric smile by muscle paralysis.[12] The authors rule out the hypothesis that damage to the marginal mandibular nerve is secondary to intraneural injection.[15,18] There seems to be damage to the myelin sheath that covers the nerve, with temporary demyelination and inflammation. Therefore, in most cases paresthesia is transient and varies from mild to moderate.[18,21]

The use of DCA in patients using anticoagulants or antiplatelet therapy, or patients with coagulation disorders requires caution.[12] The use of DCA is contraindicated in patients presenting infection at the site of injection, pregnant women or below the age of 18 years.[12] The safety and effectiveness of the applications depend on the correct use of DCA. In order to reduce the risk of complications, a maximum of six sessions can be performed, with a minimum interval of one month between sessions.[5,11,12] The applications must be made using a 1 mL syringe and a 30-gauge needle (or smaller), perpendicularly inserted into the tissue of preplatysmal region. The patient must be guided to tense the platysma muscle, so the local fat can be pinched by the professional to insert the needle.[14] If resistance is met as the needle is inserted, the needle must be immediately withdrawn.[14]

Local adverse events from the application of DCA can be classified as more frequent and less frequent. The most common adverse effects are edema (87%), bruise (72%), pain (70%), numbness (66%), and induration (23%). Local pruritus and nodules also may appear.[3,8,12,20] These events generally range from mild to moderate in severity and are transient in nature. For the management of these adverse reactions, measures such as using ice packs for five minutes prior to and/or after the injection, analgesics 60 minutes before, or topical or injectable anesthetics, must be taken.[12,22] Among the adverse reactions that may occur less frequently, but of greater severity, are damage to the marginal mandibular nerve, dysphagia, damage to lymph nodes, salivary glands and muscles, alopecia at the injection site, and ulceration/necrosis.[12] Table 2 presents case reports of important adverse events and their management after DCA use. Events such as neutrophilic dermatosis, submental abscess, vascular events, skin necrosis, nerve injury, and alopecia are described.

TABLE 2 Case reports of adverse effects after DCA injection

Article	Cases	Sex	Age (years)	Adverse effects	Outcome
Mogle et al[32]	• Case report • Severe neutrophilic dermatosis following submental DCA injection	1/F	44	After 1 week: • Edema, pain, and erythema • Progressed to a deep ulcerative wound • TC—no evidence of abnormal fluid collection • Cultures grew *Pseudomonas aeruginosa*	• No response to antibiotic therapy, local debridement, and hyperbaric oxygenation • Anatomopathological examination revealed neutrophilic infiltrates, a severe skin reaction, compatible with neutrophilic dermatosis • Treatment with methylprednisolone, topical tacrolimus and infliximab
Bhatti et al[33]	• Case report • Submental abscess after DCA injection	1/F	44	Two days after application: • Swelling, erythema, and pain in the submental region • TC—thickening and subcutaneous stranding in the submental area with extensive inflammatory changes within the fat tissue and reactive lymph nodes	• Broad-spectrum intravenous antibiotics, with no result • Surgical drainage and debridement performed to resolve the complication
McKay et al[25]	• Two case reports • Immediate vascular event after injection of DCA	2/F	20, 40	Case 1: • Pain during injection • Change in skin and lower lip color • Region became ischemic Case 2: • Pain in the left side of neck, lower lip, and teeth • Change in skin color • Three days later: retiform purple, hemorrhagic vesicles, and asymmetry in the smile.	Case 1: • Local massage and warm compresses • Oral Prednisone • The situation regressed in a few days Case 2: • Warm compresses and nitroglycerin paste with methylprednisolone, doxycycline and aspirin; • Three days later, fluocinolone ointment was used • The condition regressed in 2 weeks
Lindgren & Welsh[26]	• Case report • Inadvertent injection of DCA intra-arterial	1/F	42	• Pain in the gums and teeth during the injection (interrupted) • Right jaw pain and right-sided headache, and felt faint	• Attempt to recannulate the artery and wash the area with hyaluronidase and serum to limit the injury • Local massage and warm compresses • AAS, prednisone and hyperbaric oxygen • In the following days, intraoral ecchymosis, edema, and ulcer in the injection area
Sachdev, Mohammadi & Fabi[27]	• Case report • Inadvertent injection of DCA on facial artery • Consequent skin necrosis	1/M	NI	• Ischemia of the facial artery path • Pain at time of the injection	• Wash with saline • The region became violet/ with a dark center after 5 days • AAS and dimethicone ointment • After 12 days, two shallow ulcers in the injection area • Hydrocolloid dressing • 4 weeks after initial injection, the patient presented with a slightly indurated erythematous linear plaque along the mandible • Laser therapy performed

(Continues)

TABLE 2 (Continued)

Article	Cases	Sex	Age (years)	Adverse effects	Outcome
Ramirez et al[29]	• Two case reports • Cutaneous adverse effects after DCA injection	2/F	45, 30	Case 1: • Severe pain after the second DCA injection. Redness and induration at the injection site, followed by a wound and eschar. Case 2: • One month after the second session, multiple depressed scars on the anterior neck.	Case 1: • The wound was treated with petrolatum an hydrocolloid dressing. After that, topical steroids and intralesional triamcinolone, followed by pulsed dye laser. A hypertrophic scar remained. Case 2: • No treatment was performed. The dimple scars have no improved in 2.5 years of follow-up.
Sorenson & Chesnut[30]	• Two cases report • Marginal mandibular nerve injury	2/F	37, 31	• Asymmetry of the mouth when smiling. Deficits of inferior lip depression.	Case 1: • Full resolution 4 weeks after injection. Case 2: • Full resolution 4 days after onset.
Grady, Porphirio & Rokhsar[31]	• Two case reports • Alopecia after DCA injection	2/M	38, 36	Case 1: • Hair loss in the application region 1 week later Case 2: • Hair loss in the application region 3 weeks later	Case 1: • Alopecia regressed after 7 months Case 2: • After 14 months there was an improvement of 60% of the condition • No complete regression
Souyoul et al[23]	• Case report • Alopecia after DCA injection	1/M	37	• Hair loss in the application region observed in the 1-month follow-up evaluation (after the first session)	• Treatment with 0.03% bimatoprost, solution daily was performed. • Eleven months after DCA injection, the patient still had persistent alopecia.
Sebaratnam et al[24]	• Case report • Alopecia after DCA injection	1/M	NI	• Hair loss in the application region two weeks later	• A punch biopsy was completed of lesional skin. • Treatment and outcome have not been informed.

Abbreviations: AAS, acetylsalicylic acid; CT, Computed Tomography; DCA, deoxycholic acid; NI, not informed.

Alopecia is becoming an increasingly recognized adverse effect of DCA in male patients. Areas of alopecia, affecting the beard in the submental region, were first described by Souyoul et al.[23] The mechanism of hair loss induced by deoxycholic acid is yet to be elucidated. It is not yet known because in some cases this adverse reaction is transient while in other cases it is a permanent phenomenon. Sebaratnam et al[24] performed a biopsy of lesional skin from the anterior neck in a patient with alopecia. Overall, the histological changes were consistent with a nonscarring alopecia with an increased telogen-catagen count of 75%. The authors suggested that inflammatory response induced by the deoxycholic acid could lead to perturbations in the hair cycle. However, this does not account for the clinical observation of persisting alopecia in some reports. Alopecia is an important adverse effect to discuss with patients, particularly given the possibility of incomplete resolution.

Inadvertent intra-arterial injection of DCA, with consequent skin necrosis, is a severe complications that have also been described in literature.[25–27] The mechanism of damage from intravascular injection of DCA is unknown; however, DCA has vasoconstrictive properties and cause disruption of the cell membrane with cell lysis, cell death, and tissue inflammation.[26] Reflux should always be performed prior to injection to avoid intravascular injection. Lindgren and Welsh[26] have proposed the following protocol to treat vascular injection: if severe pain occurs, injection must be stopped immediately for evaluation. If there is any sign of vascular compromise, or blanching, bruising, the area should be reaspirated and flooded with normal saline and hyaluronidase. Massage and warm compresses to increase blood flow and the administration of aspirin to inhibit platelet aggregation may be helpful. Prednisone is used to decrease the inflammation that can lead to tissue damage. Wound healing and subsequent skin

compromise may be treated by local wound care. Pulsed dye lasers have been used with good result to reduce redness and accelerate wound healing.[26,27] Riswold and Flynn[28] still stress the risk of vascular occlusive events after DCA injection.

Ulceration and skin necrosis are important adverse effects and may also be due to superficial injection (intradermal) of the substance.[12] Ramirez et al[29] reported two cases of permanent cutaneous adverse effects after injection with DCA. Both patients remained with scars in the site of application.

6 | DISCUSSION

The demand for aesthetic facial harmonization procedures has grown exponentially in recent years. The compound DCA was synthesized to reduce submental fat and, according to a series of studies, this substance is effective in the reduction of local fat by means of adipocyte rupture, with definitive lysis of the cell.[7,9] Several scales were developed to monitor the effects of DCA, fulfilled by the professional and the patient, as well as magnetic resonance images, confirm the reduction of submental fat.[13,17,18]

Still, its approval by control agencies is relatively recent. Even with the confirmation of reduction of submental fat, the DCA presents several limitations due to a variety of adverse events such as edema, pain, local induration, hematomas, numbness, and, less frequently, mandibular nerve paresthesia, ulcerations, skin necrosis, alopecia, and vascular events.[2,20,23–27,29–31] The occurrence of alopecia was inserted in the medicine leaflet after the sales started since it was discovered later, as most of the DCA patients were female.[31] As deoxycholic acid is a relatively new drug for cosmetic submental fat, case reports are useful in the qualitative detection of new reactions which may be caused by the substance and, therefore, be monitored in subsequent studies.

The use of the DCA demands a series of precautions, such as prior assessment of the patient, trans, and post-application care, correct application technique, knowledge of local anatomy, and skin antisepsis, among others. Patients must always be informed of possible adverse reactions. Although the manufacturer advises on the risks of applying deoxycholic acid to anatomical structures such as muscles, salivary glands, and lymph nodes, there are few studies describing the product's effects on these structures. According to Thuangtong et al,[16] DCA presents low affinity for rich protein tissues, including muscle, blood vessels, and skin, and therefore, its use is limited to adipose tissue, which is low in protein.

In the present study, a number of adverse effects and complications of the use of DCA to reduce submental fat were reviewed. The cases of permanent alopecia, severe vascular events, and permanent skin lesions should serve as a warning to clinicians about the risks involved with the use of this substance. Each case must be evaluated individually, seeking to relieve pain and repair the damage caused after the injection. For the management of more severe complications, different alternatives have been reported in the literature, such as antibiotic therapy, corticosteroid therapy, surgical drainage, and debridement, among others.

7 | FINAL CONSIDERATIONS

Even with the promising results of DCA, some aspects have not been satisfactorily clarified, requiring further investigation, among them, permanent alopecia, severe vascular events, and permanent skin lesions. The long date efficiency, late adverse events, and the use in geriatric patients also require additional studies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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