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Reconstructive

Evaluation of Safe and Effectiveness of an Injectable Solution Acid Deoxycholic Based for Reduction of Localized Adiposities

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Background: The use of deoxycholic acid to reduce localized fat deposits is a procedure that has been in use for about 30 years. Its effectiveness as treatment is due to emulsification of phospholipids and therefore, solubilization of the biological membranes with resulting fat necrosis. The purpose of the study was to assess the effectiveness and the safety of an injectable solution containing sodium deoxycholtate 1.25% (DB125), used as intralipotherapy.
Methods: The effectiveness and safety of DB125 solution have been assessed with a multicentre observational prospective study carried out between February and October 2017. The 221 selected patients presented with various forms and degrees of localized fat in several areas. Intralipotherapy treatments were performed 6 weeks apart and until the clinical result was obtained. Aesthetic outcomes were evaluated by the authors using preoperative and postoperative photographic documentation and by the patients with their level of satisfaction by filling out an anonymous form. Major adverse events were reported by each doctor who performed the treatment.
Results: Two hundred twenty-one patients treated in 273 cases of different localized fat deposits. One hundred eighty-five patients who could be assessed for final results gave the effectiveness of the treatment an average score of 7.4. The failure percentage of the treatment was 3.8%. The medical evaluation showed treatment success in 93.5% of cases. Adverse events can be divided into 2 groups: minor adverse events, which are very frequent and major ones, which are extremely rare. For both groups, the adverse events can be ascribed to localized problems in the treatment area.
Conclusion: Studies have shown that the second-generation solution containing sodium deoxycholate 1.25% is effective and safe to treat different localized fat deposits. The high degree of effectiveness shown in the study was not associated with a lesser degree of handling because, at the doses indicated and with the use of intralipotherapy, the occurrence of adverse events was minimal. *(Plast Reconstr Surg Glob Open 2018;6:e1794; doi: 10.1097/GOX.0000000000001794; Published online 11 June 2018.)*

BACKGROUND

The use of solutions containing sodium deoxycholate to reduce unwanted fatty deposits is a procedure that has been used in aesthetic medicine for about 30 years.[1–4] Over the years, there have been numerous adipocytic solutions characterized by different chemical compounds but which however show deoxycholic acid as the sole agent able to bring about effective treatment[5–7] by means of cell damage through the emulsification of the phospholipids and therefore, solubilization of biological membranes (citoplasmic, nuclear, of the organelles)[8] with resulting unprogrammed cell death (adipocyte necrosis).[9] From the first solutions referring to the so-called Natterman formula,[10] containing also phosphatidylcholine, incorrectly considered as the active ingredient in reducing fat deposits under the skin,[5–7] we have passed to those of the second generation, which are more effective, where phosphatidylcholine has been eliminated and the concentration of deoxycholate acid has been reduced to mitigate the aggressiveness of its action[11,12] (Table 1). Today, it is universally accepted that second-generation solutions are far more effective but more aggressive.[13,14]

The purpose of the study was to assess the effectiveness and the safety of an injectable solution containing sodium

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Table 1. Classification of Adipocytolytic Solutions

Adipocytolytic Solution
First generation
FC + DC (Natterman Formula)
Second generation
FC + DC

deoxycholate 1.25% for the treatment of localized fat deposits on the body (125 mg/10 ml - DB125), second generation (free from phosphatidylcholine), used with intralipotherapy.

MATERIALS AND METHODS

Study Outline

The effectiveness and safety of the DB125 solution have been assessed with a multicentre observational prospective study carried out in Italy between February and October 2017. Written informed consent was obtained from each patient.

Patient Selection

The patients presented with various forms and degrees of localized fat in the following areas: buffalo hump, pseudogynecomastia, back rolls, flanks, arm, abdomen, saddlebag thighs, inner thighs, and inner knee.

They did not present with any exclusion criteria for the treatment: psychological (indecisive or immature personalities, anxiety, dismorphophobia, with fictitious disorders, or family members disapproving the treatment), minors, over 60 years old, pregnancy, women who are lactating, obesity, severe allergic reactions, known allergies to the device or to the local anesthetics, severe autoimmune diseases, acute infections in progress, immunosuppressive diseases with weakened immune systems, organ diseases uncompensated, with functional deficits or in acute phase (diabetes, kidney failure, liver disease, severe dyslipidemia, dysthyroidism, and so on), using anticoagulants, with hemorrhagic diathesis or platelet disease.

Local contraindications for the treatment were acute skin diseases (wounds, local infection, acute dermatological lesions), previous surgery on the site or with a fatty layer that is scarcely present (pinch test < 1 cm).

Adipocytolytic Agent

The adipocytolytic agent used was a galenic drug, "Solution for injection based on Sodium Deoxycholated 1.25%, for subcutaneous use only" (manufactured by Industria Farmaceutica Galenica Senese s.r.l. - Via Cassia Nord, 351 - 53014 Monteroni d'Arbia – Italy).

Population

The authors treated 221 patients in different areas of the body in the way and according to the dosages described as follows.

Administration

Treatments were performed 6 weeks apart and until the clinical result was obtained and in any case no more than 5 infiltration sessions.

Dosage

A vial of DB125 (125 mg DC/10 ml) is used for each 100 cm^2 (10 × 10 cm) over the localized fat deposits. The maximum limit per session is the administration of 5 vials.[15]

Posttreatment Management

After the treatment, the use of contenitive elastic sheaths or a pressure bandage was compulsory for the first 72 hours (24 hours per day) and highly recommended during the first week post. These, in addition to reducing the initial pain, which is typical during the first 12 to 24 hours, also reduce edema, the risk of increasing skin laxity and in general, the posttreatment phase. Lymphatic drainage or pressure therapies were also advised to reduce the postoperative phase and accelerate a full recovery (2 sessions per week for 2–3 weeks posttreatment starting from the third day after the treatment). No other therapies or techniques were allowed in the treated area throughout the study. Pain killers were allowed although generally not necessary.

Technique

The technique used was intralipotherapy,[11] that involves the following steps:

- Marking the treatment area and access points (2–3 per area, opposing if possible) when the patient is in an orthostatic position and the calculation for the quantity of the device required.
- In each 10 mL vial, 0.5 mL of local anesthetic 2% was added before starting the injections.
- In a decubitus position, the best position according to the area to be treated, infiltration of the device is performed after first disinfecting the area to be treated.
- From the access point that was marked, the intralipotherapy needle (a long, 23-gauge × 10 cm needle, very similar to the needles used for spinal anesthesia) is inserted into the subcutaneous fat parallel to the cutaneous surface, avoiding contact with the skin and muscle. The total amount of the device previously calculated to be used is distributed using a retrograde release and a fan technique, releasing 0.2–0.4 mL of product during each passage. The fan technique consists of an advancing and retracting movement of the needle, very similar to that used with liposuction.[16] The panniculus adiposus is a 3-dimensional structure with an extension and a thickness that varies. It is well represented centrally (core area) and less graded in the surrounding areas. The aim of the intralipotherapy is to treat localized fat throughout its thickness and extension, releasing the lipoclasic solution in a parceled, controlled manner.

Evaluation of the Results

Aesthetic outcomes were evaluated by the authors using preoperative and postoperative photographic documentation. In some cases, pre- and postultrasound and/or centimetric evaluations were made. In patients who had been treated in different areas simultaneously, each area was evaluated independently. Each case was assessed

by 2 doctors who did not perform the treatment; they did not know the characteristics of the treatment (number of sessions, the quantity infiltrated, and the doctor who performed the treatment). The question put to the 2 doctors was divided into 2 categories: liporeduction change—significant or nonsignificant. The outcome was considered positive only if observed by both doctors. The patients also evaluated the results: their level of satisfaction was rated and the occurrence of minor adverse events (that were very frequent) was evaluated by filling out an anonymous form in the waiting room and given to nonmedical personnel (the results were rated from 0 to 10, where 0 is "no result at all" and 10 is "the best result achievable"). Major adverse events were reported by each doctor who performed the treatment. The postoperative evaluations were not performed before 2 months after the last treatment. Follow-up ranged from a minimum of 2 months to a maximum of 6. Aesthetic outcome was evaluated only in patients who completed the right follow-up. Patients evaluated with variations of 4% of initial body weight were considered in this study from the safety viewpoint but not in terms of results.

RESULTS

The study treated 221 patients, 159 women, and 62 men, for a total of 273 body areas (57 abdomen, 51 flanks, 42 saddlebag thighs, 38 inner knee, 29 inner thighs, 26 back rolls, 17 arm, 8 pseudogynecomastia, 5 buffalo hump) and 857 infiltration sessions (average 3.14 per anatomical area). Thirty-six patients were assessed from a safety point of view and not in terms of effectiveness, because their weight variation was above 4%.

Effectiveness

One hundred eighty-five patients who could be assessed for final results, for a total of 232 cases of localized fat, gave the effectiveness of the treatment an average score of 7.4 (7.51 in men with 90 cases of localized fat treated and 7.33 in women with 142 cases of localized fat deposits treated). The greatest successes were the flanks, abdomen, and inner knee, while the least successful were the inner thigh and arms (Figs. 1–4). The percentage of treatment failures, assessed with a score of less than 6, was 3.8% (9 cases of localized fat). The medical evaluation showed therapeutic success in 217 (93.5%) of the 232 cases of localized fat. The failures were 5 inner thighs, 4 saddlebags, 2 arms, 2 abdomens with build up of fat above the navel, 2 inner knees. No significant difference was evaluated when comparing the results in males and females in the same area. However, irrespective of sex, localized android fat-type (abdomen and flanks) showed increased responsiveness to treatment over the gynoid-type liporeductive adiposity (saddlebag thighs, inner thighs, and inner knee).

Safety

Adverse events caused by the use of deoxycholic acid can be divided into 2 groups: minor adverse events, which are very frequent and major ones, which are extremely rare.[15,17–20] With the exception of allergic reactions (which never occurred in this study), for both groups, the adverse events can be ascribed to localized problems during treatment.[21–25] Minor adverse events were oedema in the first 72 hours (78%), mild pain lasting more than 12 hours (60%), bruising (41%), warmth (39%), numbness (30%), erythema (28%), and nodules lasting less than 1 month (14 %). Major adverse events were prolonged oedema lasting more than 72 hours (18 cases 2,1%), permanent nodules lasting more than 1 month (8 cases, 0.9%), skin irregularities (4 cases, 0.5%), skin necrosis (1 case, 0.01%), hyperpigmentation (0), permanent paresthesia/dysesthesia (0) and alopecia (0).

DISCUSSION

The results of the study are encouraging because they have shown a therapeutic success from both the viewpoint of specialist medical assessment and from the personal, subjective view of the patients treated. This success did not show any significant differences between sexes and age ranges. Even the different areas on the body did not show

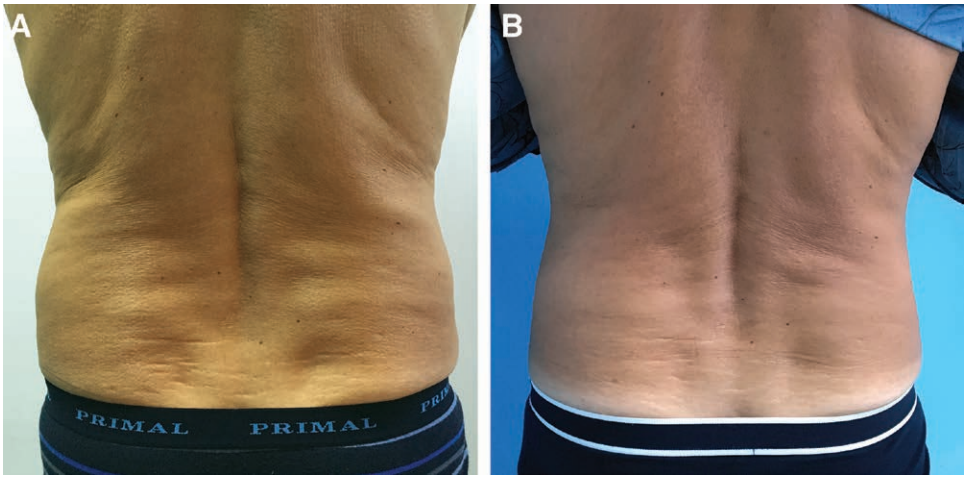

Fig. 1. Pretreatment (A) and posttreatment (B) photographs of flanks of a 48-year-old male patient. Three sessions, 3 vials per session.

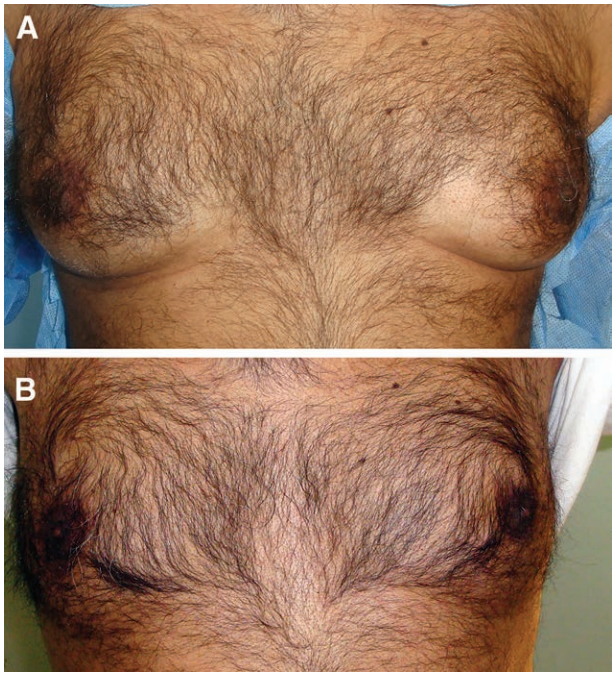

Fig. 2. Pretreatment (A) and posttreatment (B) photographs of pseudogynecomastia of a 43-year-old male patient. Three sessions, 2 vials per session.

significant differences in terms of results, even if, however, the primary-gynoid deposits required more treatment sessions compared with the secondary-android ones. This is due to the fact that localized fat deposits on the body have different histological characteristics: the primary deposits are prevalently hyperplastic, whereas the secondary ones are hypertrophic.[26]

From a safety viewpoint, the study showed that DB125 used in intralipotherapy and at the correct dosage, is safe. This is due to the fact that:

- Deoxycholic acid has a partial selectivity toward mature adipocytes.[27] Deoxycholic acid is a nonselective surfactant, meaning it causes damage to the cell through emulsification where it is injected. However, it has been shown that it is more effective if there is a lower protein percentage in the cell: this means that mature adipocytes are extremely more vulnerable to deoxycholic acid (because the protein content is less than 5%) than other cell lines with a higher concentration of protein (for example, the myocyte has a protein percentage of more than 95%).
- Administration using intralipotherapy makes it possible to used the deoxycholate sodium correctly.[11] Making only 1–3 access points in the area to be treated (reducing the risk of DB125 contact with epidermis and derma), the possibility to modulate the depth at which to release the deoxycholic acid (therefore, never on the surface, that is, on the subdermal layer), fragmentary retrograde release (never in bolus) make it possible to correctly distribute the solution through the fatty layer and avoiding surface and deep structures.

The study showed a very low incidence of major adverse events. Alopecia, nerve injury, hyperpigmentation never occurred during this study. Nevertheless, it is good to stress that a larger number of cases would have certainly been more significant. The only case of skin necrosis that occurred in this study, limited to a small area of around 1 cm^2, should be ascribed to the incorrect execution of the technique, as confirmed by the medical operator who released an excessive amount, too close to the surface (immediately under the derma) DC125 on the site of necrosis. This stresses the importance of using an appropriate technique, educational training, and to have suitable experience.[28] Prolonged oedema and permanent nodules are closely tied to the anatomical areas being treated: the almost complete totality of cases occurred on treatment of the knee and abdomen. Two factors, such as the force of gravity and the lymphatic system probably play an important role in these areas.

In Italy, BD125 is classified as a nonprepackaged industrial galenic based on Legislative Decree no. 219[29] of 24 April 2006 "Implementation of the directive 2001/83/EC[30] pursuant to a community code concern-

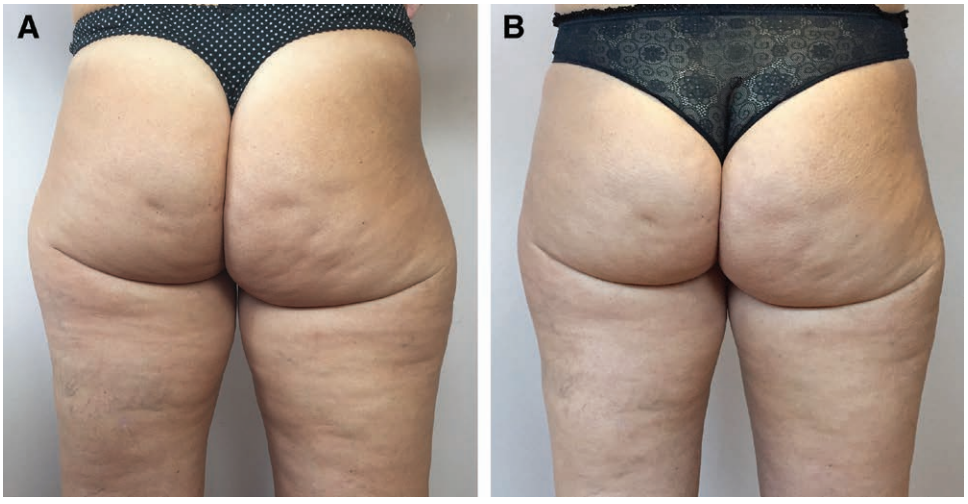

Fig. 3. Pretreatment (A) and posttreatment (B) photographs of saddlebag thighs of a 46-year-old male patient. Three sessions, 3 vials per session.

ing medicines for human use, and directive 2003/94/EC".[31] BD125 is only produced on the presentation of a specific request from a physician who undertakes to use it on his or her own patients or patients in the facility in which s/he works, under his/her direct responsibility and compliant with the current standards. A written request from a physician exonerates these medicines from the issue of a specific, preventive marketing authorization by the pharmaceutical company manufacturing it, but which nonetheless must hold a Manufacturing Permit for the pharmaceutical form requested. For the purposes of the prescription, the provisions envisaged for medicines listed in article 5 of legal decree no. 23 of 17 February 1998, 23, converted, through amendment by law no. 94 of 8 April 1998.[32]

CONCLUSIONS

The study showed that the injectable solution containing sodium deoxycholate 1.25% is effective and safe to treat different localized fat deposits. This solution is considered second generation because it is free from phosphatidylcholine. The high degree of effectiveness shown in the study was not associated with a lesser degree of handling because, at the doses indicated and with the use of intralipotherapy, the occurrence of adverse events was minimal.

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