ASPS Policy Statement on Mesotherapy/Injection Lipolysis

Mesotherapy injection

The terms "mesotherapy" and "injection lipolysis" are often used interchangeably. While somewhat different, both therapies are advertised as a non-surgical alternative to liposuction. As the promotion and popularity of mesotherapy and injection lipolysis has increased, so too have the questions surrounding their use. The recent FDA approval of one formulation has led to increasing levels of evidence-based studies about that product. There are also valid concerns about its off-label use. Because similar therapies remain in use, it is necessary to critically evaluate each therapy's safety and efficacy and understand the federal and state regulations surrounding each therapy's use, before pursuing mesotherapy or injection lipolysis in practice.

Plastic surgeons should be aware of the medico-legal aspects associated with these therapies and the literature available on their outcomes.

1. Background

Originally developed in Europe, "mesotherapy" is a general term describing injection of compounds into the mesoderm (intra or sub-cutaneous injections) of pharmaceutical and homeopathic medications, plant extracts, vitamins, and other ingredients.[1-3] While mesotherapy has been touted for the treatment of a wide variety of ailments, one of its notable indications is for dissolving localized fat accumulations. The term "injection lipolysis" is used specifically in reference to the practice of injecting various phosphatidylcholine (PC) and/or deoxycholic acid (DCA, the acid form of deoxycholate) formulations into subcutaneous fat deposits. The injections are generally administered over multiple treatment sessions. In plastic surgery, mesotherapy has been applied to the treatment of cellulite, facial rejuvenation, local fat deposits, and body contouring.[4-6] Most mesotherapy agents have not been approved for cosmetic use. Kybella is a noted exception. In 2015, DCA injection (Kybella™ by Kythera Biopharmaceuticals, Inc) became the first FDA approved drug for "improvement of moderate to severe convexity or fullness associated with submental fat in adults".[7]

This article summarizes the most current data available on mesotherapy/injection lipolysis.

2. Regulatory Environment

• Food and Drug Administration (FDA) Approval: Currently, Kybella™ is the only FDA-approved injectable solution for lipolysis. Physicians who wish to use other agents in the literature for adipose reduction may be subject to some degree of liability as the FDA may review individual occurrences on a case-by-case basis for enforcement action.

• Compounding: The FDA regulates drugs bought and sold in the United States as well as establishes protocols for compounding drugs, the process of mixing drugs by a pharmacist or physician to meet the unique needs of a patient. PC and DCA acid are both FDA approved for use, but only the latter is approved for injection lipolysis. However, the legality of compounding them for the purpose of injection lipolysis is controversial, because combining PC and DCA would produce a "new drug" that is not approved by the FDA for subcutaneous injections. As part of a statement issued February 1, 2008, the FDA clearly stated that *most compounded drugs are not FDA-approved drugs.*[8] Physicians pursuing this compounding approach to administer injection lipolysis may be subject to enforcement actions by the FDA if their practices do not meet the criteria outlined in the Federal Food, Drug, and Cosmetic Act, particularly sections 503A and 503B on human drug compounding.[9] In addition, medical providers and pharmacists are bound to adhere to state regulations governing the process of compounding, which is itself determined by individual state regulatory bodies.

• Off-label Use: Compounded drugs should not be confused with the "off-label" use of drugs. FDA approval of a drug indicates use of the drug for a specific purpose. Once a drug is approved by the FDA, a licensed physician may prescribe a drug for uses other than the indicated purpose, provided there is scientific evidence/literature to support such use. However, because the mixture of drugs and other ingredients in mesotherapy formulations produce a new drug that is not FDA approved for any purpose, its use would not be considered "off-label" use.

• State Regulation: The FDA shares regulatory authority over the use of drugs with individual states.

3. Available Scientific Evidence

There is increasing evidence for injection lipolysis, including level I evidence for DCA. There is lesser quality evidence available for PC therapy, which has been commonly used in Europe for decades. For other mesotherapy treatments, the data is even more limited, and should be evaluated cautiously.

Animal studies

Animal study data exists for both DCA and PC use. A randomized control trial (RCT) of 20 rabbits was done to assess the histological effects of PC therapy. Saline vs PC was injected into the truncal fat deposits of the study rabbits. Cell necrosis was noted in 75-100% of the rabbits.[10] A second histological study of rabbits, using pc and saline as the

control arm did not however show any cell necrosis. This study did, however, note considerably higher rates of cell fibrosis and inflammation in the study rabbits. [11]

Cellulite

Level III clinical evidence is available that examines the efficacy of mesotherapy in the treatment of cellulite.[12,13] A prospective study analyzed twenty female subjects who underwent injection of ALIDYA™ (Ghimas, Italy; poliaminoacidic gel, a-D-(+) glucopyranose, 1-4 glycosidic, ethylenediaminetetraacetic sodium) into the posterior thigh. At four weeks post- injection, high frequency ultrasound was used and showed showed decreased hypodermal thickness, and decreased surface area of serrated hypodermis-dermis junction. Clinical cellulite grade measured by the Nurnberger-Muller scale was significantly reduced. There was also a reduction of cellulite on thigh palpation. Along with this thigh circumference, measurements were significantly reduced.[12] Another clinical trial prospectively compared infusion of subcutaneous carboxytherapy (twenty- four subjects) and injection of PC (twenty- four subjects) into the thigh, and concluded that at 6 months, thigh circumference and cellulite grade were significantly reduced in both groups.[14]

Facial rejuvenation

Level II and III clinical study evidence reviewing the efficacy of mesotherapy in facial rejuvenation is available.[14-16] A prospective randomized trial compared treatment of one hemiface with no needle and the other hemiface with microneedle delivery of 20% L-ascorbic acid in seventeen volunteers. Cutometer, multiprobe adapter, corneometer and mexameter were all used for evaluation of skin firmness, elasticity, hydration, and skin tone. All of these parameters improved significantly. Micro needling specifically led to significantly more improvement when compared to the no needle method. No negative controls were used.[16] There are several level three evidence studies that suggest improved skin texture with the use of different mesotherapy solutions including hyaluronic acid with mannitol, hyaluronic acid with vitamins, amino acids, minerals and coenzymes, hyulorunic acid and idebenone, and hyulorunic acid and PRP.[17-20] One of these studies showed decreased expression of IL-1β, IL-6, and MMP1, and an increase in collagen 1 in random biospies taken at 3 months. No negative control was used and not all subjects underwent biopsy.[18] In another clinical trial, platelet-rich plasma injection was shown to increase dermal collagen levels.[19] Several other studies report no efficacy of mesotherapy treatment in facial rejuvenation. Ten subjects underwent injection of multivitamin and hyuloronic acid followed by a skin biopsy at six months. No difference in subjective skin appearance or light microscopy were noted. Electron microscopy showed a decrease in the diameter of collagen fibers.[15] Another prospective study evaluated the effect of multivitamin and hyuloronic acid injection on periorbital wrinkles in six subjects and concluded that there was no clinically visible difference, and no difference in type I, III, VII collagen, elastin, and tropoelastin on histology.[14]

Local fat deposits

Level I evidence for the use of mesotherapy in treatment of submental fat (SMF) deposits exists. Several clinical trials were performed prior to the FDA approval of Kybella™.[21] In phase three clinical trials, four randomized, double- blind placebo- controlled studies

evaluated safety and efficacy of ATX-101 (DCA). Scale based assessments by clinicians and subjects, as well as caliper measurements, showed that in patients randomized to ATX-101, SMF was significantly reduced. Patient satisfaction was high and the negative psychological impact of SMF was significantly reduced [22-25]. On MRI, submental volume was significantly reduced.[22,24] The most common side effects were at the injection site (swelling, bruising, numbness, erythema, induration). Marginal mandibular nerve injury occurred in 4.3% of subjects.[22-25]

Another randomized double-blind clinical trial used a total of 28 patients (no controls) to assess the efficacy of DCA use with or without PC after injection into SMF. Physical exam, and photo assessment revealed overall minimal aesthetic improvement.[26] In a randomized open label study, seven women were treated using PC-DCA injections into their abdominal tissues. The treatments showed significant reduction in anterior subcutaneous abdominal fat.[27] Yet another histologic study found that injections of PC and DCA into abdominal tissue led to fibrosis, micro-abscess formation, panniculitis, fat necrosis with micro calcifications and cyst formation.[28] Another retrospective clinical study of 50 patients using photographic analysis demonstrated the effects of PC injections. In this study, patients received injections of 5 ml (50 mg/ml) of PC into small areas of the back. Reportedly all patients had at least a modest improvement (4 year follow up). No long term complications were reported.[29]

Two additional open label case series demonstrated the results with injections into infraorbital fat pad areas. Fifty one patients underwent injection of 0.4 ml (50mg/ml) of PC into infraorbital fat pads and showed cosmetic improvements in 96% of patients.[30,31] The same compound has been used in other series for the treatment of localized fat in the face and has shown comparable successes.[32,33]

Body contouring

Level II evidence analyzing the efficacy and safety of mesotherapy in body contouring has been published.[6,34] In a prospective, case- controlled study over three months, a mixed solution (aminophylline, buflomedil, and lidocaine) was injected into the medial aspect of one thigh versus no treatment on the other thigh in twenty women. There was no difference in thigh girth, or lipid profile. Diagnostic studies (CT) showed no difference in cross sectional area or thickness of fat layer between groups. Patient satisfaction was reportedly poor.[6] Another prospective randomized trial with no control group compared injection of PC/DCA versus caffeine versus Conjonctyl® in 75 women. Injections were performed in different body parts including abdomen, waist, hips, thighs, and knees. Seventy-two subjects experienced significant circumference reduction (on average 4.41cm in group 1, 2.99 cm in group 2, and 2.10 cm in group 3) and weight loss (5.33 ± 1.09 kg in group 1, 3.74 ± 1.51 kg in group 2, and 2.82 ± 1.43 kg in group 3). Seventy-four subjects had a decrease in body fat percentage. Patient satisfaction was high and no serious side effects were observed. Local skin reactions were mild (inflammation, burning, urticaria, ecchymosis, and pruritus).[34] A double blind, RCT on 37 patients compared PC with DCA vs. DCA alone, and found similar reductions on thigh circumference on both sides (average 6.6%). This was not compared to any negative controls.[35]

Side effects and adverse events

The following adverse events have been reported in recent studies.[2]

1. Local skin reactions (ecchymosis, urticaria, pruritus, urticarial, edema, induration, hyperpigmentation, numbness, abscesses, skin ulcers, granulomas) [22-25,34,36-42]
2. Inferior alveolar nerve injury [22-25]
3. Atypical mycobacterial infections [43-46]
4. Panniculitis [47,48]
5. Alopecia [40,49]
6. Skin Ulcers [39]
7. Systemic symptoms: Nausea, diarrhea, dizziness [35]

In conclusion, literature on mesotherapy/Injection lipolysis is limited. For most applications low-level evidence has been published (excluding DCA for SMF injection). The evaluation of data is difficult given the variability of solutions, body parts, areas injected, and the mixed outcome measurements used in studies. Additionally, most studies do not have effective negative control groups. Information on the formulation of solutions, recommended dosages, and injection technique is not available. There are currently no recommendations for standardized treatment protocols. Side effects and adverse reactions can occur and the safety profile for solutions remains unclear. Therefore, further evidence is required to make recommendations for proper use. Until more data is available, we cannot recommend routine clinical use of mesotherapy injections. Although the use of ATX-101 (DCA, Kybella™) has been approved by the FDA for the treatment of submental fat with reasonable safety and efficacy profile, we caution members on the use of DCA for other applications.

4. Policy Statement

1. It is the individual physician's responsibility to understand and abide by all applicable Federal, State, and local regulations.

2. Only FDA-approved uses of drugs may be commercially advertised; it is illegal to commercially advertise any non-approved or off-label use.

3. Each physician must ensure that a means for providing the appropriate informed consent for each patient has been established prior to the treatment. The consent should mention that there is little scientific evidence available to confirm the safety or efficacy of any mesotherapy treatment beyond the use of deoxycholic acid for the treatment of submental fat.

4. As safety and efficacy cannot be ascertained from the available body of English literature for non-FDA approved mesotherapy, ASPS believes further scientific testing of fat reduction mixtures is needed before making formal recommendations on their use.

5. As there are no agreed upon standards (except for Kybella), physicians administering mesotherapy treatments should be aware of the chemicals/drugs being injected, dosages, particular side effects, and potential interactions.

6. Records of injected substances and dosages administered should be available in the patient's medical record and accessible to other treating physicians.

7. When interpreting and applying these guiding principles to their individual practice, physicians should use their personal and professional judgment.

These guiding principles should not be construed as a rule and are not meant to serve as the standard of medical care

References

1. Rotunda AM, Kolodney MS. Mesotherapy and phosphatidylcholine injections: historical clarification and review. *Dermatol Surg.* 2006;32(4):465-480.
2. Sarkar R, Garg VK, Mysore V. Position paper on mesotherapy. *Indian J Dermatol Venereol Leprol.* 2011;77(2):232-237.
3. Atiyeh BS, Ibrahim AE, Dibo SA. Cosmetic mesotherapy: between scientific evidence, science fiction, and lucrative business. *Aesthetic Plast Surg.* 2008;32(6):842-849.
4. Rohrich RJ. Mesotherapy: what is it? Does it work? *Plast Reconstr Surg.* 2005;115(5):1425.
5. Matarasso A, Pfeifer TM, Plastic Surgery Educational Foundation DC. Mesotherapy for body contouring. *Plast Reconstr Surg.* 2005;115(5):1420-1424.
6. Park SH, Kim DW, Lee MA, et al. Effectiveness of mesotherapy on body contouring. *Plast Reconstr Surg.* 2008;121(4):179e-185e.
7. FDA. Highlights of Prescribing Information-Kybella. 2015; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206333Orig1s000Approv.pdf. Accessed 9/23/18, 2018.
8. Adminstration USFaD. Public Statement in response to the practice of using Lipo-dissolve. 2007.
9. FDA. Human Drug Compounding. 2018; https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/. Accessed 12/31/18.
10. Rittes PG, Rittes JC, Carriel Amary MF. Injection of phosphatidylcholine in fat tissue: experimental study of local action in rabbits. *Aesthetic Plast Surg.* 2006;30(4):474-478.
11. Salles AG, Valler CS, Ferreira MC. Histologic response to injected phosphatidylcholine in fat tissue: experimental study in a new rabbit model. *Aesthetic Plast Surg.* 2006;30(4):479-484; discussion 485.
12. Sylwia M, Krzysztof MR. Efficacy of intradermal mesotherapy in cellulite reduction - Conventional and high-frequency ultrasound monitoring results. *J Cosmet Laser Ther.* 2017;19(6):320-324.
13. Eldsouky F, Ebrahim HM. Evaluation and efficacy of carbon dioxide therapy (carboxytherapy) versus mesolipolysis in the treatment of cellulite. *J Cosmet Laser Ther.* 2018:1-6.

14. El-Domyati M, El-Ammawi TS, Moawad O, et al. Efficacy of mesotherapy in facial rejuvenation: a histological and immunohistochemical evaluation. *Int J Dermatol.* 2012;51(8):913-919.
15. Amin SP, Phelps RG, Goldberg DJ. Mesotherapy for facial skin rejuvenation: a clinical, histologic, and electron microscopic evaluation. *Dermatol Surg.* 2006;32(12):1467-1472.
16. Zasada M, Markiewicz A, Drozdz Z, Mosinska P, Erkiert-Polguj A, Budzisz E. Preliminary randomized controlled trial of antiaging effects of l-ascorbic acid applied in combination with no-needle and microneedle mesotherapy. *J Cosmet Dermatol.* 2018.
17. Taieb M, Gay C, Sebban S, Secnazi P. Hyaluronic acid plus mannitol treatment for improved skin hydration and elasticity. *J Cosmet Dermatol.* 2012;11(2):87-92.
18. Savoia A, Landi S, Baldi A. A new minimally invasive mesotherapy technique for facial rejuvenation. *Dermatol Ther (Heidelb).* 2013;3(1):83-93.
19. Abuaf OK, Yildiz H, Baloglu H, Bilgili ME, Simsek HA, Dogan B. Histologic Evidence of New Collagen Formulation Using Platelet Rich Plasma in Skin Rejuvenation: A Prospective Controlled Clinical Study. *Ann Dermatol.* 2016;28(6):718-724.
20. Markiewicz A, Zasada M, Erkiert-Polguj A, Wieckowska-Szakiel M, Budzisz E. An evaluation of the antiaging properties of strawberry hydrolysate treatment enriched with L-ascorbic acid applied with microneedle mesotherapy. *J Cosmet Dermatol.* 2018.
21. Dayan SH, Humphrey S, Jones DH, et al. Overview of ATX-101 (Deoxycholic Acid Injection): A Nonsurgical Approach for Reduction of Submental Fat. *Dermatol Surg.* 2016;42 Suppl 1:S263-S270.
22. 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 e787.
23. 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.
24. 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.
25. 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.
26. Rotunda AM, Weiss SR, Rivkin LS. Randomized double-blind clinical trial of subcutaneously injected deoxycholate versus a phosphatidylcholine-deoxycholate combination for the reduction of submental fat. *Dermatol Surg.* 2009;35(5):792-803.

27. Reeds DN, Mohammed BS, Klein S, Boswell CB, Young VL. Metabolic and structural effects of phosphatidylcholine and deoxycholate injections on subcutaneous fat: a randomized, controlled trial. *Aesthet Surg J.* 2013;33(3):400-408.
28. Park EJ, Kim HS, Kim M, Oh HJ. Histological changes after treatment for localized fat deposits with phosphatidylcholine and sodium deoxycholate. *J Cosmet Dermatol.* 2013;12(3):240-243.
29. Rittes PG. The use of phosphatidylcholine for correction of localized fat deposits. *Aesthetic Plast Surg.* 2003;27(4):315-318.
30. Rittes PG. The use of phosphatidylcholine for correction of lower lid bulging due to prominent fat pads. *Dermatol Surg.* 2001;27(4):391-392.
31. Treacy PJ, Goldberg DJ. Use of phosphatidylcholine for the correction of lower lid bulging due to prominent fat pads. *J Cosmet Laser Ther.* 2006;8(3):129-132.
32. Hexsel D, Serra M, Mazzuco R, Dal'Forno T, Zechmeister D. Phosphatidylcholine in the treatment of localized fat. *J Drugs Dermatol.* 2003;2(5):511-518.
33. Hexsel DM, Serra M, de Oliveira Dal'Forno T, Zechmeister do Prado D. Cosmetic uses of injectable phosphatidylcholine on the face. *Otolaryngol Clin North Am.* 2005;38(5):1119-1129.
34. Kutlubay Z. Evaluation of mesotherapeutic injections of three different combinations of lipolytic agents for body contouring. *J Cosmet Laser Ther.* 2011;13(4):142-153.
35. Salti G, Ghersetich I, Tantussi F, Bovani B, Lotti T. Phosphatidylcholine and sodium deoxycholate in the treatment of localized fat: a double-blind, randomized study. *Dermatol Surg.* 2008;34(1):60-66; discussion 66.
36. Vedamurthy M. Mesotherapy. *Indian J Dermatol Venereol Leprol.* 2007;73(1):60-62.
37. Rosina P, Chieregato C, Miccolis D, D'Onghia FS. Psoriasis and side-effects of mesotherapy. *Int J Dermatol.* 2001;40(9):581-583.
38. Urbani CE. Urticarial reaction to ethylenediamine in aminophylline following mesotherapy. *Contact Dermatitis.* 1994;31(3):198-199.
39. Al-Khenaizan S. Facial cutaneous ulcers following mesotherapy. *Dermatol Surg.* 2008;34(6):832-834; discussion 834-835.
40. Kadry R, Hamadah I, Al-Issa A, Field L, Alrabiah F. Multifocal scalp abscess with subcutaneous fat necrosis and scarring alopecia as a complication of scalp mesotherapy. *J Drugs Dermatol.* 2008;7(1):72-73.
41. Gokdemir G, Kucukunal A, Sakiz D. Cutaneous granulomatous reaction from mesotherapy. *Dermatol Surg.* 2009;35(2):291-293.
42. Palmer M, Curran J, Bowler P. Clinical experience and safety using phosphatidylcholine injections for the localized reduction of subcutaneous fat: a multicentre, retrospective UK study. *J Cosmet Dermatol.* 2006;5(3):218-226.
43. Sanudo A, Vallejo F, Sierra M, et al. Nontuberculous mycobacteria infection after mesotherapy: preliminary report of 15 cases. *Int J Dermatol.* 2007;46(6):649-653.

44. Centers for Disease C, Prevention. Outbreak of mesotherapy-associated skin reactions--District of Columbia area, January-February 2005. *MMWR Morb Mortal Wkly Rep.* 2005;54(44):1127-1130.
45. Correa NE, Catano JC, Mejia GI, et al. Outbreak of mesotherapy-associated cutaneous infections caused by Mycobacterium chelonae in Colombia. *Jpn J Infect Dis.* 2010;63(2):143-145.
46. Del-Castillo M, Palmero D, Lopez B, et al. Mesotherapy-associated outbreak caused by Mycobacterium immunogenum. *Emerg Infect Dis.* 2009;15(2):357-359.
47. Polat M, Ustun H. A case of mesotherapy-induced panniculitis. *Cutan Ocul Toxicol.* 2016;35(2):163-164.
48. Tan J, Rao B. Mesotherapy-induced panniculitis treated with dapsone: case report and review of reported adverse effects of mesotherapy. *J Cutan Med Surg.* 2006;10(2):92-95.
49. Duque-Estrada B, Vincenzi C, Misciali C, Tosti A. Alopecia secondary to mesotherapy. *J Am Acad Dermatol.* 2009;61(4):707-709.

Approved by the ASPS EC in July 2008;
Updated and Approved by the ASPS EC in June 2019