

Scientific Studies Aim to Dispel Controversy Surrounding Injection Lipolysis

By Adam M. Rotunda, M.D.

Technological advancements in body contouring procedures will soon redefine aesthetic medicine. Just as filler substances have met a significant need in the field of medical cosmetics for restoring volume, an injectable product may have a similar role in reducing unwanted fat tissue. Nonetheless, controversy relating to injectable lipolysis or Lipodissolve® and mesotherapy has overshadowed this novel technology which may eventually become a viable, non-surgical treatment for modest collections of subcutaneous fat.

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On one side of the body shaping spectrum (Figure 1) conventional, highly effective surgical procedures, such as abdominoplasty and liposuction, continue to be the most effective and most popular cosmetic surgical procedures. On the other end of the spectrum, new energy sources and injectable methods – such as injection lipolysis, Lipodissolve or mesotherapy – to reduce localized collections of subcutaneous fat, are rapidly gaining recognition.

in the upper thighs, abdomen, neck, dorsocervical region (buffalo hump), as well as lipomas.³⁻¹⁷ More recent double-blinded clinical trials have substantiated findings from small, uncontrolled, open-label case series.

This recent popularity of injection lipolysis can be attributed in large part to direct-to-consumer advertising by commercial treatment centers such as fig. (Newport Beach, California, U.S.) and MedSculpt (Rockville,

procedure, as well as state legislation banning or threatening to ban the procedure.¹⁸⁻²³

Lipodissolve is not manufactured by a pharmaceutical company, but rather produced by compounding pharmacies based on the Lipostabil formulation. Lipostabil is manufactured by Sanofi-Aventis (Paris, France) and is approved in select European countries for intravenous use as a treatment for fat embolism, dyslipidemia and alcohol induced cirrhosis. It consists of soy derived phosphatidylcholine (PC 5%), its solvent sodium deoxycholate (DC 2.5%) and dl-alpha-tocopherol (vitamin E), sodium hydroxide, ethanol and benzyl alcohol, in sterile water.

Although no standardized formulation exists, Lipodissolve typically consists of 5% PC with between 4.2% and 4.7% DC. Some physicians request that caffeine, collagenase, carnitine or other agents be compounded into the formulation to purportedly enhance its lipolytic effects, but no published clinical data can support the use of these adjunctive ingredients for that purpose.²⁴

In contrast to injection lipolysis, mesotherapy describes an injection technique that was first introduced in 1952 by French physician Michel Pistor.¹ Mesotherapy has been used in Europe for decades as a treatment for musculoskeletal pain and inflammatory conditions, lymphedema, cellulite, photo-aging and scarring, among other conditions. Treatments typically consist of numerous, epidermal, dermal or subcutaneous injections of vasodilators, anti-inflammatory medications, herbs, hormones, antibiotics, enzymes or co-enzymes.

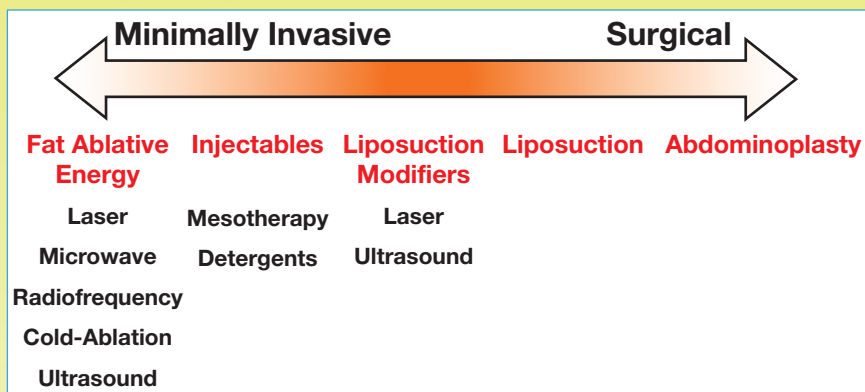


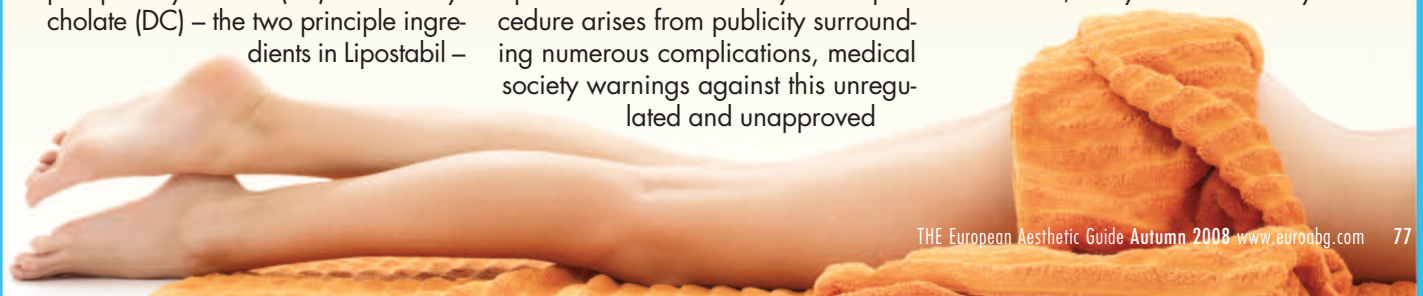
Figure 1: A spectrum of conventional surgical and innovative non-surgical procedures for the treatment of fat.

Injection lipolysis is not mesotherapy, instead it describes subcutaneous injections of pharmacologically active, physiologic detergents like bile salts to chemically ablate or destroy adipose tissue. Although the technique has been described as mesotherapy, it differs with regard to its historical beginnings, ingredients and injection technique.¹

Injectable fat treatments emerged on the international scene after Patricia Rittes, M.D., a dermatologist in São Paulo, Brazil, reported significant reduction in infraorbital fat injected with Lipostabil.² Numerous investigators subsequently reported localized fat reduction after injections of phosphatidylcholine (PC) and deoxycholate (DC) – the two principle ingredients in Lipostabil –

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Maryland, U.S. and Tysons Corner, Virginia, U.S.), as well as the branding of injectable treatments like Lipodissolve. The notoriety of this procedure arises from publicity surrounding numerous complications, medical society warnings against this unregulated and unapproved



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Similar to injection lipolysis, there are no standardized ingredients, although an increasing number of compounding pharmacies offer premixed cocktails or individually soluble ingredients that can be combined immediately before injection.

A recent publication by Mary K. Caruso, M.D., and colleagues has reported evidence of lipolysis *in vitro* as isoproterenol, aminophylline and yohimbe were incubated with adipocytes.²⁵ While these findings are promising, there has been no clinical translation of these data as a treatment for cellulite or subcutaneous fat.

With both injection lipolysis and mesotherapy, the use of most ingredients is not considered off-label. To date, no regulatory authority in the world has approved a pharmaceutical grade, subcutaneously injected preparation to treat fat.

The U.S. Food and Drug Administration (FDA) released this statement about Lipodissolve: "These are unapproved drugs for unapproved uses. In virtually all cases, the FDA regards compounded drugs as unapproved drugs, meaning they are not FDA approved, therefore the use of compounded drugs is not considered off-label use. If a physician uses an FDA approved drug for an indication not in the approved labeling this is considered off-label use. FDA approval of a drug includes approved labeling for use, and means that the FDA has evaluated the safety and efficacy for a specific use and population. Once approved, a drug may be prescribed by a licensed physician for appropriate use, based on their professional opinion. This prescribing is considered part of the practice of medicine, but it is expected that the physician is well-informed about the product and that the off-label use is based on sound

scientific rationale and adequate medical evidence."²⁶

Several U.S. states, including Nevada, Oregon, Kansas and Nebraska have established restrictions or considered bans on solutions with PC/DC or DC until there is additional safety and efficacy data that meets the standards set forth by the FDA. It is not confirmed, but likely that other states will follow this action.

Mesotherapy formulations, in contrast, may contain some FDA approved

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medications for subcutaneous injection, such as hyaluronidase and lidocaine. Yet, a majority of the ingredients that comprise these formulations are not approved distinctly for the treatment of fat and/or cellulite.²⁴

PC's role in the Lipodissolve formulation appears to be only speculative. Early publications describing injection lipolysis suggest that the phospholipid, PC, was the major active ingredient in the formulation.^{2,4} It was assumed that PC's effects on fat *in serum* could explain why localized fat loss is observed after subcutaneous injection. This phospholipid was conjectured to: induce a cascade of intracellular signaling – leading to lipolysis; directly lyse cell membranes; and/or facilitate transit of triglycerides across fat cell membranes, yet, an unexpected discovery revealed that isolated DC produced evidence of significant cell death and cell lysis in keratinocyte cell cultures and extracted (ex vivo) porcine fat (Figure 2).²⁷

Moreover, the addition of PC to DC had negligible effects that could account for the activity of the formulation. Sanja Schuller-Petrovic and colleagues²⁸ recently replicated these

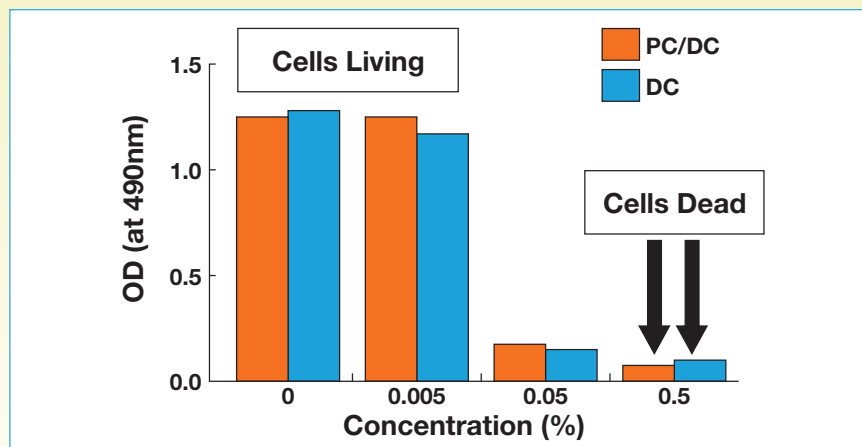


Figure 2: MTS cell viability assay measuring living keratinocytes exposed to phosphatidylcholine/deoxycholate (PC/DC) and deoxycholate (DC). Absorbance (OD) is directly related to cell viability. Increasing concentration of either PC/DC or DC alone augments cell death. Inclusion of PC in the PC/DC formulation has minimal effect compared to utilizing DC alone. Modified with permission from Blackwell Publishing, from Rotunda AM and Kolodney MS. Mesotherapy and phosphatidylcholine injections: historical clarification and review. *Dermatol Surg* 2006;32:465–480.

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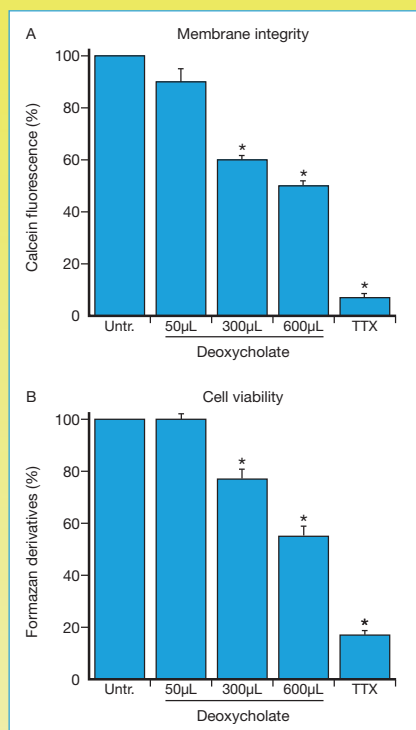


Figure 3: Effects of DC (2.5%) on rat fat cell membrane integrity (A) and cell viability (B) after repetitive dosing. Effects were observed after 30 days following application of 50, 300 or 600 mL of DC on days 0, 7 and 28. Triton (TTX) 0.5% served as positive control. Reproduced with permission from Schuller-Petrovic S, Wolkart G, Höfler G, Neuhold N, Freisinger F, Brunner F. Tissue-toxic effects of phosphatidylcholine/deoxycholate after subcutaneous injection for fat dissolution in rats and a human volunteer. *Dermatol Surg* 2008;34:529-4.

studies in living tissue (Figure 3). Apparently, reduction of fat at the sites of PC/DC injections is due to rupturing of fat cell membranes by DC alone.²⁷ Additional clinical evidence that human lipomas¹⁷, abdominal¹² and upper thigh fat,⁵ as well as submental fat²⁹ are reduced (Figure 4) after DC injections have confirmed these experimental studies.

Currently, there are no laboratory or clinical studies investigating the effect of PC as an adipolytic, apoptotic or detergent agent in isolation from DC in adipose tissue. The research is limited in part because PC is insoluble in water. In order to perform studies on adipose

tissue, PC requires a solvent to dissolve it in an aqueous solution. However, PC solvents such as DC, another bile salt, or even ethanol, would similarly produce cell lysis and confound the results.²⁷

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Although the definitive role of PC is undefined, speculation exists that it may decrease the severity of adverse reactions that are frequently seen after injection lipolysis. Giovanni Salti, M.D., and colleagues⁵ injected the upper thighs of thirty-seven women with PC/DC in one side and just DC in the contralateral side. After four injection sessions, spaced two months apart, they found that 90% of the patients responded. There were no significant differences in efficacy between the formulations as both groups experienced similar reductions in upper thigh measurements (7%) and ultrasonically confirmed subcutaneous fat thickness (40%).

However, the formulation containing PC produced less pain, bruising,

swelling and less persistent nodularity than the DC treated side. It was theorized that PC somehow emulsified and removed the fat destroyed by DC, although no mechanism was provided. This data contradicts an unpublished, exploratory, double-blind clinical trial injecting up to 2 mL of either DC or PC/DC into the submental fat.³⁰ In this trial, there were no obvious differences between treatment groups in the nature, intensity or duration of adverse events, suggesting that under the study conditions PC did not reduce the severity or duration of adverse effects.

Combining PC and DC in a solution causes mixed micelle aggregates to form.^{30,31} Reduction of free DC by PC in these aggregates may reduce the active DC capable of inducing lysis. This may explain the benefits of a formulation containing PC, as reported by Salti *et al*, but additional comparative studies are needed. While phosphatidylcholine may reduce the morbidity of injection lipolysis treatment, decreasing deoxycholate concentration or adding lidocaine appears to be a reasonable approach as well.

While the FDA has not approved these drugs for use, scientific data does support the use of biologic detergents for chemical fat ablation. Deoxycholic acid (Figure 5) is a secondary bile acid produced by intestinal bacteria after the release of primary bile acids (cholic acid) in the liver.³² Bile acids, which are stored in the gall bladder and secreted into the duodenum, consist of free and conjugated bile acids that solubilize ingested lipids. A majority (90% to 95%) of DC is subsequently reabsorbed, however, excreted DC is replaced by *ab initio* synthesis



Figure 4: Profile of a patient before (left image) and after (right image) treatment of her submental fat with subcutaneous injections of 10 mL of 1% DC and 1% lidocaine (7.5 mL DC and 2.25 mL lidocaine) monthly for four months. Middle image is 24 hours after second injection session, revealing significant edema and areas of ecchymoses.

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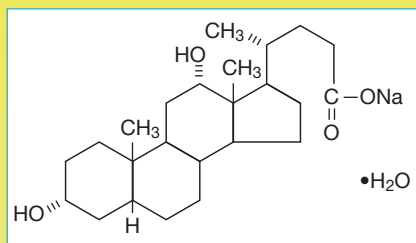


Figure 5: Chemical structure of deoxycholate (DC).

from cholesterol in the liver. Since bile acids are end products of cholesterol, they are not degraded into other catabolites. Approximately 1 gram of DC is present at any time in an adult human, confined mostly to the enterohepatic circulation, but DC is also present in the peripheral blood (0.56 $\mu\text{mol/L}$) and can be elevated in patients with certain liver conditions or after surgery.³²

Deoxycholic acid has been used by investigators as a laboratory detergent for decades, and it is common practice for pharmaceutical companies to incorporate physiologically compatible solvents such as DC for intravenous formulations, including Amphocin® from Pfizer (New York, New York, U.S.) as well as Lipostabil.³³

However, histologies of animal and human tissue exposed to DC, as well as PC/DC combinations demonstrate hemorrhaging, inflammation and tissue necrosis (Figure 6). By acting like

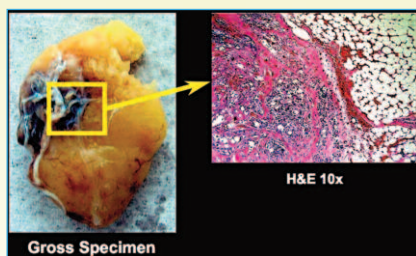


Figure 6: Excised lipoma two days after injection with sodium deoxycholate (1%) revealing a well demarcated area of hemorrhage (grossly) that corresponded microscopically to acute inflammation, extravasation of erythrocytes and necrosis (hematoxylin and eosin, original magnification 10x). Modified with permission from Blackwell Publishing, from Rotunda AM and Kolodney MS. Mesotherapy and phosphatidylcholine injections: historical clarification and review. *Dermatol Surg* 2006;32:465-480.

a non-ionic detergent DC can induce pores in cellular membranes;³⁰ leakage of cytoplasmic contents; membrane destabilization; and subsequent lysis, which likely account for the rapid inflammation after injection.

Non-standardized dosing and formulations have lead to numerous complications. Published data consistently confirms predictable post treatment sequelae, which ranges from mild to significant in severity. The most common of these effects are immediate edema, erythema, itching and/or burning; ecchymoses and significant swelling typically ensue for days to weeks; residual tenderness, hyperpigmentation, nodularity and cutaneous numbness may last weeks to a month or longer.

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Nodularity at the treatment site is an anticipated reaction. This benign but unsettling effect is a focus of necrotic and inflammatory tissue.^{12,17,28} Anecdotal reports of unresolved nodules are likely due to improper technique or use of a high concentration of DC (> 2.5%). Gastrointestinal effects may be related to a bolus type of effect from PC or DC as it becomes absorbed systemically. Less frequent but other systemic effects, such as light headedness and intermenstrual bleeding have been reported with high doses of PC/DC combinations,^{5,9,11} leading some investigators to recommend limiting doses of PC to 2.5 g per injection session.¹¹

Aside from injection amount, some consider injection depth the most critical safety issue.¹¹ Although there is some (unpublished) evidence that DC has relative specificity to fat, haphazard or inadvertent injection deep into muscle or superficially into the dermis, may induce necrosis. Concentrations as low as 0.5% DC (in exclusion of PC),¹² as well as the standard Lipodissolve concentrations of PC/DC, lead to muscle and vasculature necrosis.²⁷ Although these findings have not translated to rampant morbid complications, accounts of skin ulceration²¹⁻²³, as well as ecchymoses, are likely related to these non-specific detergent effects on tissue.

Skin ulceration is exceedingly rare, at least according to one published report⁹ and appears to be technique dependent. Skin ulceration may be similarly observed when sclerosing solutions miss their vascular target during sclerotherapy.³⁴ Similar to other injectables, proper technique and experience will avert undesirable effects and confer a superior outcome.

Scarring, contour irregularities or skin indentation, hyperpigmentation, skin infections (including atypical mycobacteria), gastrointestinal effects (nausea, diarrhea) and liver failure, related to injection lipolysis, have been reported anecdotally by the press and on the Internet.²¹⁻²⁴ Thus, a reasonable conclusion is that these procedures are inherently unsafe regardless of who uses them and how they are used. However, a likely explanation for most, but perhaps not all, of these deleterious outcomes are improper injection technique, such as utilizing large deposits of solution, close spacing of injections, injecting superficially (too much, too close, too high), as well as failing to adhere to standard aseptic injection techniques. As

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noted above, few of these negative reactions have been reported in peer-reviewed literature, where investigators have generally taken a relatively measured and conservative approach to treatment. Small (0.2 to 0.4 mL) aliquots of solution – containing 1% DC (alone) or 4.2% to 4.7% DC (with 5% PC) – spaced at least 1.5 cm apart and directed into the subcutaneous fat only, produce desired outcomes.

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The full safety profile of these medications in large patient populations is not known since they have not been rigorously studied in controlled FDA trials. In light of an appealing fat-dissolving injectable, current unrestricted use and manufacturing standards may expose patients to additional risks which may not occur with proper training and regulation. Presently, Kythera Biopharmaceuticals (Calabasas, California, U.S.), is conducting Phase II FDA trials with a detergent based lipolytic medication intended for aesthetic and medical purposes.³⁵

Despite the number of studies being performed with these formulations, the definitive fate of lysed fat cells is still unclear. A majority (> 75%) of the adipocyte volume is triglyceride.³⁶ In histological studies, injected sites demonstrate phagocytosis of lipids by macrophages and an intense lymphomononuclear infiltration.^{12,13,17,37,38}

Some assumptions can be made about the fate of lysed fat cells based on what happens to cellular components after blunt trauma,³⁸ but this is considered speculative until rigorous testing is performed. Released triglyceride is likely processed by lipoprotein lipases on extracellular membranes into glycerol and free fatty acids; then glycerol – the water soluble component of triglycerides – is transported to the liver via the serum; the balance of the triglyceride metabolism – free-fatty acids – will bind to albumin and be taken up by organs; cellular debris will be engulfed by macrophages, carried via lymphatics into the general circulation and metabolized by the liver.

To date, laboratory testing in humans treated with PC/DC¹⁰ and DC¹³ has not revealed any significant alterations in blood lipids. Comprehensive blood lipid testing which takes place at two hours, one day, two, four, six and eight weeks and six months after four abdominal treatments using a total of 40 mL of 1% or 0.5% DC did not reveal any adverse effects on blood lipids, nor any other chemistry or blood counts.¹² In light of the relatively small volumes of fat injected and slow resolution of inflammation,¹² it is unlikely that conservative (< 10 mL/session) injection lipolysis treatment leads to acute fatty liver, but definitive confirmation is essential. An analogous concern has been raised about the future of fat after ultrasonically ablated adipose tissue, but rigorous studies have neither revealed fatty infiltration of the liver nor any augmentation of blood lipids after injected lipolysis treatment.^{39,40}

Injection lipolysis has shown promising results



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and gained widespread use, but it will not replace liposuction. It is unrealistic to expect that a minimally invasive (non-surgical) body shaping technology will replace liposuction anytime in the near future. Patients undergoing injection lipolysis should anticipate localized reactions and not expect liposuction-like results. Fat volume reduction with injection lipolysis is significantly less than areas better suited for liposuction; multiple

sessions which produce localized tenderness and swelling are anticipated and may be required for efficacy. In contrast, liposuction generally produces a very effective outcome after one treatment session with perhaps less swelling and focal tenderness. Therefore, injectable detergents may not be as desirable as the relative one-time simplicity and efficacy of liposuction. So who then is injection lipolysis best suited for?

With further investigation, that meets the standards set forth by the FDA, injection lipolysis could become an approved therapy that serves to non-surgically correct liposuction irregularities and appeal to surgically averse patients who desire removal of modest collections of fat. ■

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