

Phosphatidylcholine and Sodium Deoxycholate in the Treatment of Localized Fat: A Double-Blind, Randomized Study

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BACKGROUND Recent articles have introduced the novel concept of chemical lipolysis through local injections. Phosphatidylcholine is the active drug in the commercial preparation used for this purpose, but some studies have suggested that sodium deoxycholate, an excipient of the preparation, could be the real active substance.

AIM We decided to investigate whether phosphatidylcholine and sodium deoxycholate have any clinical efficacy in chemical lipolysis and their respective roles. We also studied the safety and side effects of the treatments.

MATERIALS AND METHODS Thirty-seven consecutive female patients were studied for the treatment of localized fat in gynoid lipodystrophy. Each patient received injections of a phosphatidylcholine/sodium deoxycholate preparation on one side and sodium deoxycholate on the contralateral side, each single patient being herself the control. Four treatments were carried out every 8 weeks in a double-blind, randomized fashion. Metric circumferential evaluations and photographic and ultrasonographic measurements throughout the study allowed for final judgment. A statistical evaluation concluded our study.

RESULTS An overall reduction of local fat was obtained in 91.9% of the patients without statistically significant differences between the treated sides. Reduction values on the phosphatidylcholine/sodium deoxycholate-treated sides are in the order of 6.46% metrically and 36.87% ultrasonographically, whereas on the deoxycholate-treated sides they are in the order of 6.77% metrically and 36.06% ultrasonographically. Both treatments, at the dose used in the study, proved safe in the short term. The most common side effects were local and few, but were more pronounced on the deoxycholate-treated sides. No laboratory test was carried out.

CONCLUSION Both treatments have shown moderate and equivalent efficacy in treating localized fat, with sodium deoxycholate having a slower postoperative resolution, suggesting that sodium deoxycholate could be sufficient by itself to determine fat cell destruction and that phosphatidylcholine could be useful for obtaining a later emulsification of the fat.

The authors have indicated no significant interest with commercial supporters.

The use of lipolytic drugs to induce a nonsurgical fat reduction is a common method in cosmetic medicine, either through topical treatments (creams, fluids) or through local injections,^{1–3} but very little scientific evidence sustains its widespread use.³

Recent articles have brought attention to a possible role of phosphatidylcholine in determining a chemical fat cell lysis through unknown mechanisms.^{4–6}

Phosphatidylcholine (PPC), a phospholipid widely distributed in human cell membranes, is the main

active substance of a commercially available injection lipolysis agent (Lipostabil N i.v. 5 mL, Artesan Pharma, Lüchow, Germany), a drug present in the European market for a long time and whose main clinical indication is the treatment of fat embolism. Its subcutaneous injection is an off-label use that seems to be efficacious in reducing local adiposities.^{5–8}

An interesting study by Rotunda and colleagues⁹ investigated the effect of the drug on fat cell lysis and

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suggested a possible major adipocytolytic role of sodium deoxycholate (DEOX), an excipient contained in the PPC formulation that would act as a detergent on fat cell membranes. This was indeed an *in vitro* study and its conclusions are not completely transferable to *in vivo* human patients. Further studies have also shown the efficacy of DEOX¹⁰ and PPC/DEOX¹¹ in reducing the size of subcutaneous lipomas with intralesional injections of the drugs.

We decided therefore to investigate whether DEOX could be considered an active drug able to induce a chemical lipolysis and to study the possible activities of DEOX and PPC on fat cell lysis. The safety profile of both substances was also studied.

Materials and Methods

We selected 40 consecutive female patients presenting with bilateral gynoid lipodystrophy. Criteria of inclusion were localized fat as evaluated by the treating physicians, subcutaneous tissue thickness not less than 15 mm on ultrasound, no previous treatment for at least 6 months, no cutaneous diseases in the treatment area, no systemic diseases, no known allergies, age 20 to 55 years, and no pregnancy or lactation. Once included, criteria of exclusion were failure to follow the study protocol, concomitant diseases during the study, important adverse events, and weight gain or weight loss of more than 2 kg during the study. Each patient signed an informed consent to undergo a clinical trial with drugs used in off-label indication, according to the Declaration of Helsinki. The study protocol was approved by our institutional review board.

The treatment sides and their respective drugs were randomized by computer. Each patient underwent a 7.5-MHz ultrasonographic evaluation (CGR Scanel 300, Villenoy-Meaux, France) before treatment to rule out subcutaneous fatty tissue thickness.

PPC/DEOX (Lipostabil, Natterman) and DEOX (Laboratorio Pineda, Sao Paulo, Brazil) were the active pharmacologic substances investigated.

The PPC/DEOX preparation has a composition of 250/125 mg per vial (50–25 mg/mL in 5-mL vials). The DEOX preparation has a composition of 237.5 mg per vial (47.5 mg/mL in 5-mL vials).

To have comparable deoxycholate values, the dosing of the treatment was set to 1,000/500 mg for the PPC/DEOX compound (four 5-mL vials) and 475 mg (two 5-mL vials) for the DEOX formulation, according to the known safety limits (15 mg/kg) of the PPC/DEOX formulation.^{12,13} Both formulations were diluted in saline to have 40 mL of solution per infiltration side.

Each patient received bilateral subcutaneous injections in the gluteotrocanteric region with PPC/DEOX on one side and DEOX on the contralateral side, each single patient being herself the control. The level of subcutaneous injections was approximately 10 mm. Twenty-seven-gauge needles (0.4 × 13 mm; BD Microlance-3, Becton Dickinson, Franklin Lakes, NH) were used. Each point of injection received about 0.5 mL of the pharmacological solution with an angle of injection to the plane of the skin of about 75° to 90° (almost perpendicular). According to previous literature, the area of treatment was strictly limited to 80 cm² per side, with a mean number of 80 infiltrations per side, spaced approximately 1 cm apart.^{5,7} Because previous research had shown a resolution time of approximately 8 weeks for the postinfiltrative nodular reaction,^{14,15} four sessions of treatment were programmed, once every 8 weeks in a double-blind, randomized fashion, with a final evaluation 8 weeks after the last treatment.

Our clinical evaluations included a circumferential metric measurement of the thighs at the level of the subgluteal fold, an ultrasonographic measurement at the level of the trocanteric fat pad, from skin to muscle fascia, and a photographic evaluation on a metric panel whose vertical lines were spaced 5 cm apart. Owing to the impossibility of getting exact measures with a photographic evaluation, this was intended for 5% (approx. 2.5 cm) figure variations.

All subjective and objective signs and symptoms following each treatment session were recorded. A specific issue was devoted to the evaluation of pain in the area of treatment, with the help of a 0 (no pain at all) to 10 (intolerable pain) grading scale, that each single patient was asked to judge. No blood testing was carried out.

All these evaluations were performed at every step of the study and 8 weeks after the last treatment for a final judgment. A statistical evaluation concluded our study.

Results

Thirty-seven of 40 patients completed the study, 2 patients were excluded for excess weight loss during the study, and 1 patient was lost to follow up. Three patients of 37 (8.1%) had no improvement at all and can be considered nonresponders. Thirty-four patients of 37 (91.9%) had some improvement.

At the end of the study the majority (30) of patients had become slimmer. For the whole study group, the mean weight reduction was of 1.44% (58.53–57.69 kg), with a mean body mass index value reduction of 1.3% (21.49–21.21 kg). The efficacy of treatments was evaluated in terms of overall reduction of thigh circumferences (metric measure) and subcutaneous thickness (ultrasound measure).

An overall reduction of local fat was clinically obtained in 34 patients without statistically significant differences between the treated sides. The mean circumferential metric value changed from 58.48 to 54.70 cm, with a 6.46% reduction on the PPC/DEOX-treated side, and from 58.67 to 54.70 cm, with a 6.77% reduction on the DEOX-treated side (Figure 1).

The ultrasound measures of the fat layer revealed much higher reduction values, again with no statistical difference. The mean ultrasonographic value changed from 36.13 to 22.81 mm on the PPC/DEOX-treated side, with a 36.87% reduction,

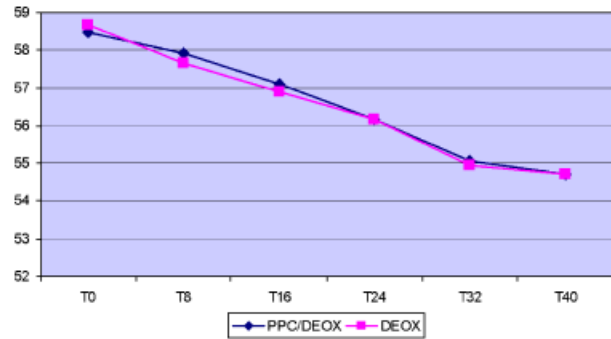


Figure 1. Circumferential metric values.

and from 36.11 to 23 mm on the DEOX-treated side, with a 36.06% reduction (Figure 2). The photographic evaluation resulted in an average 5% reduction as measured on a metric panel (Figure 3).

In those seven patients whose weight was not changed, the mean reduction was of 4.73% circumferentially (57.1–54.4 cm), 28.71% ultrasonographically (32.4–23.1 mm), and 5% photographically on the PPC/DEOX-treated side and 4.92% circumferentially (57–54.2 cm), 32.77% ultrasonographically (35.1–23.6 mm), and 5% photographically on the DEOX-treated side. Side effects of treatments are detailed in Table 1.

The treatment was quite painful for all patients: the pain at the injection site, usually short-lived, was more common (100% vs. 78.4%) and intense on the DEOX-treated side, with a mean grading of 6.2 for the DEOX side and 4.6 for the PPC/DEOX side on a 0 to 10 pain grading scale. Bruising was due to the

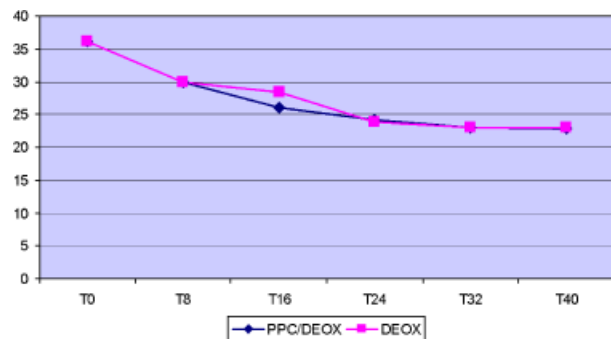


Figure 2. Ultrasonographic values.



Figure 3. Photographic evaluation.

large number of subcutaneous infiltrations and was more important on the DEOX-treated side (91.9% vs. 83.8%). All bruises always resolved spontaneously.

Other signs and symptoms are typical of any inflammatory reaction: a stinging and burning sensation (100%) was present in all patients for both treatments for some hours after the infiltration; edema (100%) lasted 1 to 2 days with more prominent swelling and induration on the DEOX-treated side (89.2% vs. 67.6%); erythema in the infiltration area (100%) lasted 2 to 12 hours; and itching, persisting for 1 day, was seen exclusively on the PPC/DEOX-treated side and could be provoked by a histamine release, which PPC is known to induce.^{13,14}

TABLE 1. Side Effects

	PPC/DEOX (%)	DEOX (%)
Pain on injection	78.4	100
Bruising	83.8	91.9
Erythema	100	100
Stinging/burning	100	100
Swelling	100	100
Induration	67.6	89.2
Itching	18.9	—
Hematoma at injection site	—	—
Hives	—	—
Dizziness/light-headedness	5.4	5.4
Nausea/malaise	10.8	10.8
Diarrhea/steatorrhea	16.2.4	16.2

PPC, phosphatidylcholine; DEOX, sodium deoxycholate.

The posttreatment clinical evolution also featured some systemic cholinergic symptoms (dizziness/light-headedness, malaise/nausea, diarrhea/steatorrhea), whose etiology is not clear. Diarrhea and malaise were the most common and were always observed in the first 24 hours posttreatment. We are not able to judge which treatment could be responsible for those effects because both treatments were performed in the same session, and no blood sampling was performed.

In all patients we observed a quick and complete resolution of the immediate inflammatory reactions, but all patients evolved through subcutaneous nodules at the injection sites. On the PPC/DEOX-treated side, the nodules were clinically visible for approximately 2 weeks. Later on, the nodules were no longer visible, but were still palpable; some of them were also slightly painful to touch and were clinically resolved in approximately 1 month. At the

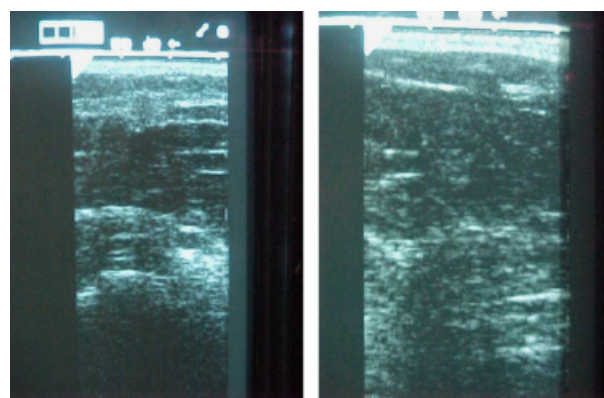


Figure 4. Phosphatidylcholine/sodium deoxycholate nodules.

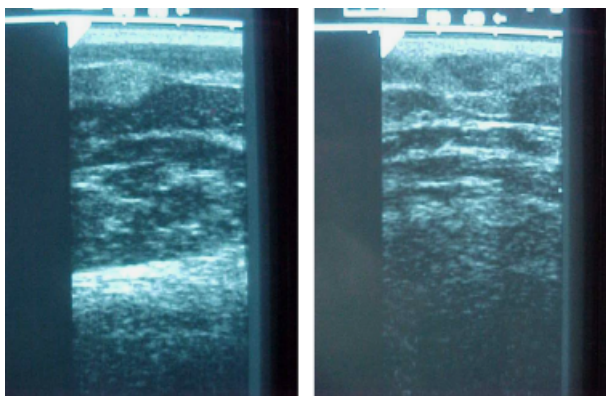


Figure 5. Sodium deoxycholate nodules.

ultrasonographic examination some nodules were still present 2 months after the previous treatment, with a hyperechogenic aspect and a diameter of approximately 4 to 5 mm (Figure 4).

On the DEOX-treated side, the nodules were sometimes visible even 1 month after the treatment and could be easily felt to the touch, as well as being moderately painful. Their clinical resolution was often not complete 2 months after the treatment. At the ultrasonographic examination, these nodules were larger (7 to 8 mm) and more hyperechogenic (Figure 5).

All nodules had a slow but complete clinical regression, independent of their causative drug. In conclusion, despite some important side effects, both treatments, at the dose used in the study, were completely safe in the short term.

Discussion

The field of nonsurgical lipolysis has grown enormously in the past few years, since several new techniques have been proposed.¹⁻³ The most simple and economic one is the use of subcutaneous injections of active principles able to achieve a local fat reduction through chemical lipolysis.

Our study was stimulated by previous articles⁴⁻⁶ reporting the efficacy of a PPC-based drug. The

exact mechanism of the drug action in this off-label indication remains substantially unknown.^{5,6} One hypothesis postulates that PPC could be responsible for an emulsification of the fat (Rittes P, personal communication, May 2001), whereas a more recent hypothesis suggests that the excipient, DEOX, could be the real active principle.⁸

In our study we verified that both treatments have a moderate lipolytic effect (a 6.46% metric reduction and 36.87% ultrasonographic reduction for the PPC/DEOX group and a 6.77% metric reduction and 36.06% ultrasonographic reduction for the DEOX group) without statistical significance between the groups. In conclusion, both treatments seem able to determine a moderate reduction in local fat and can be considered equivalent in terms of efficacy.

Owing to pharmacologic presentation issues, there was a small difference in the deoxycholate dosing between sides (500 mg vs. 475 mg), but it did not seem important in terms of efficacy. The DEOX-treated side, despite a slightly smaller dose of drugs, had the same results, but greater side effects and a much slower resolution.

Previous ultrasonographic evaluations¹⁵ showed that, after a treatment with the PPC/DEOX compound, the fat cell lysis possibly evolves through nodule formation and subsequent tissue resorption in a time span of approximately 8 weeks. Because the resorption of the nodules could be the mechanism of tissue reduction, we set our treatments at an 8-week interval from each other, but our study proves that DEOX seems to induce much slower reabsorbable nodules. Unfortunately we did not perform ultrasonographic controls in between treatments that could allow us to exactly quantify the duration of such deoxycholate-derived nodules.

The clinical and ultrasonographic features of the hypodermic nodules are the major difference between treatments. The PPC/DEOX-treated sides had a much easier postoperative recovery, with less pain, fewer nodules, and faster resolution.

We can postulate a mechanism of action based on a fat cell destruction by the detergent action of DEOX on cell membranes, with a true adipocytolysis, as shown in previous research,^{9,10,16} and a later emulsification of the released fatty acids by means of the PPC.^{8,12} Deoxycholate by itself seems able to induce fat cell destruction (lipoclasia and not lipolysis) in an aspecific fashion due to its detergent action, but its more important and slowly resolving side effects probably mean that PPC has an active role in determining a faster elimination of the lipids from the treated area. According to a recent study,¹⁷ PPC seems not to have any effect on the reduction of fat tissue volume. It has however the capacity to stimulate lipase release and the consequent breakdown of triglycerides in free fatty acids, that are then eliminated.¹⁴ The itching sensation, reported only in the PPC/DEOX-treated areas, could indicate histamine release, which is frequently associated with lipase activity.¹⁴ The faster resolution of the PPC/DEOX-treated areas could be an effect of the lipidic drainage activated by PPC. Diarrhea/steatorrhea could be a clinical manifestation of fatty elimination. Unfortunately we did not take any blood samples to confirm this hypothesis.

The detergent action of DEOX could also be theoretically possible on other cell types, even if a few histologic studies seem to show an action that is limited to fatty tissue without damage to the surrounding connective and muscle tissue.^{16,18} For safety reasons, it seems therefore advisable to always perform an ultrasonographic evaluation of the subcutaneous layer to choose the length of the injection needle, while a simple way to assure a completely subcutaneous injection is to pinch the skin before every individual shot and/or to not be completely perpendicular to the skin when injecting. The nodular evolution of the treatments is consistent with the hypothesis of a real adipocytonecrosis, followed by an inflammatory reaction causing a final fibrosis with microscopic scarring.^{7,16,19}

Most of the side effects were local and few, being caused by an inflammatory reaction at the treatment

site or by mechanical trauma after injection. Among the systemic side effects, the most common are malaise and diarrhea/steatorrhea. We could not precisely identify the possible reasons for them.

We had three patients who did not respond at all to the treatment. One of these patients is affected by hypothyroidism and is on thyroid replacement therapy. It is possible that hypothyroidism could represent an inhibiting factor in the fat reduction process.

The study protocol considered a possible weight variation of ± 2 kg during the study, but because the majority of our patients became slimmer during the study, there is a possible bias in the evaluation of the effective ability of the treatment to determine local fat loss, and we must take into consideration that the fat reduction could be partially due to weight loss. In the seven patients whose weight did not change during the study, we recorded a smaller reduction (4.73% circumferentially and 28.71% ultrasonographically on the PPC/DEOX-treated side and 4.92% circumferentially and 32.77% ultrasonographically) in fat loss. This value should be exclusively dependent on the infiltrative pharmacologic treatment. This is too small a sample, however, to be evaluated statistically and we cannot draw conclusions on this point, even if it is a good indication in terms of unbiased efficacy of the treatment. Further studies with a larger sample of nonslimming patients would permit the efficacy of these drugs to be better judged.

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COMMENTARY

This is a thoughtful well-designed study to investigate any *in vivo* clinical benefits to the commercially available formulation of phosphatidylcholine (PPC)/sodium deoxycholate (Lipostabil) to sodium deoxycholate alone. Interestingly, it turns out that although PPC is not the active ingredient as originally thought, it seems to decrease the morbidity of the fat cell lysis by increasing free fatty acid removal from the subcutaneous department. Clinically this is manifested by more rapid resolution of the subcutaneous nodules posttreatment. One of the most important controls they instituted is strictly limiting the weight change in their subjects to keep this from confounding their results.

Therefore, it is a good study, but will mesotherapy replace liposuction? It is difficult to support the contention that this procedure has less morbidity than tumescent liposuction. It involves four sessions, spaced 8 weeks apart requiring 80 painful injections. It is limited to an 80-cm² area. The treated subcutis becomes erythematous, bruised, and pruritic and then develops tender nodules that last about 1 month. The mean decrease in thigh circumference is modest, approximately 4 cm on average. Call me a pessimist but I do not think I will retire my machine or cannulas just yet.

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