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Systemic side effect in lipodissolve using phosphatidylcholine and deoxycholate containing formula: A systematic review

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ABSTRACT

Background: The use of phosphatidylcholine (PC) and deoxychholate (DC) as injection to remove unwanted fat pads is banned in some countries, and has not been approved by United States Food and Drug Administration. This condition triggered attempts of lipodissolve practitioners to fight for the approval of PC/DC use for lipodissolve purposes. They claimed that PC/DC injections do not cause serious systemic side effect. **Aim:** To systematically review the original studies on the use of PC/DC for lipolysis of unwanted fat deposits to get a better understanding on the systemic side effects. **Methods:** All text search using keywords: 'phosphatidylcholine' or 'deoxycholate' in combination with 'lipolysis' and 'clinical trial' or 'case report' or 'pilot study'. Data extracted were: number of study participants, injection site, lipolytic agent, depth of injection, total volume, and systemic side effects. Total amount of PC/DC and systemic side effects were compared. Further, search for the explanations for possible causes of the various systemic side effects were done. **Results:** 9 of 25 articles reported systemic side effects including acute liver dysfunction and acute renal failure. **Conclusion:** High total DC concentration is supposed to be the major cause of severe inflammation that may lead to serious systemic side effects.

KEYWORDS

Phosphatidylcholine;
Deoxycholate;
Lipolysis;
Lipodissolve;
Acute renal failure;
Acute liver dysfunction;
Side effect.

INTRODUCTION

The use of phosphatidylcholine (PC) and deoxychholate (DC) containing formula (Lipostabil ®) as 'off label' injection was first published in a journal by dr. Patricia Rittes from Brazil for correction of lower lid bulging due to prominent fat pads[1, 2]. Since then, they have been used as subcutaneous injection to induce lipolysis (lipodissolve) and subsequent fibrosis. In certain countries, they are popular as lipolytic agents and are widely used for cosmetic purposes to remove small fat deposits and to treat skin laxity. However, in many countries, the practice has not been approved, and is banned in Brazil due to improper use[1,3] by lay persons in nonmedical settings[4,5], or by self injection[1], which caused serious side effects[1,3,4]. Further, another ban was introduced in France, though the ban was suspended temporarily[6]. Moreover, United States Food and Drug Administration (US FDA) launched a warning to potential lipolysis consumers and provided some

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facts, i.e.: FDA has not evaluated and approved PC and DC as lipolytic agents, and is not aware of the evidence of their efficacy in lipolysis. Further, their safety is unknown[7], though a recent result of FDA approved phase 1 clinical trial on PC and DC was published[8].

Recently, DC alone was developed as a lipolysis substance under the name ATX-101, and has entered a phase 3 multi-centre study. ATX-101 is taken care to be licensed by Kythera Inc and Intendis, though the use of DC alone for fat reduction purposes was prohibited in the Netherlands[6].

To balance the contra opinions, lipolysis practitioners have formed a worldwide network named 'network lipolysis' and their website http://Network-Lipolysis.com provides recent information in the form of regular newsletter and training courses concerning lipolysis. The newsletter provides recent advances in regulations in many countries, and the results of the struggle to make lipolysis substances get approved to be used in subcutaneous injection, thus free from their 'off label' use[1,6].

The struggle to make lipolysis substance recognized for subcutaneous use was hampered, and one of the cause is the fact that lipolysis is a lucrative business that interferes with other business in liposuction, as can be seen in the quote: '"We saw dark forces at work, e.g. plastic surgeons concerned about losing their liposuction business, and engaged in conspiracy theories"[9].

Apart from the pro and contra opinions, in recent years, publications concerning the use of phosphatidylcholine and deoxychholate as the main ingredients to treat skin laxity and excess fat in various areas of the body are accumulating, including several randomized clinical trials[8,10,11]. Lipodissolve practitioners claim the treatment as save, and devoid of serious systemic side effects, when it is done properly by trained experts. Therefore to attain a fair opinion, the aim of this study was to systematically review the original studies on the use of phosphatidylcholine and/or deoxychholate for lipolysis of unwanted fat deposits to get a better understanding on the systemic side effects that might be harmful for patients.

METHODS

We performed "all text" searches without time restriction on 22nd August 2012, and 29th December 2013 to get most recent additional publications, in Pubmed/Medline and Google Scholar using keywords: 'phosphatidylcholine' or 'deoxycholate' in combination with 'lipolysis' and 'clinical trial' or 'case report' or 'pilot study'; and an "all text" search in Cochrane library using 'phosphatidylcholine' and 'lipolysis'. In addition, relevant existing articles in our library were added.

Inclusion criteria

All original prospective and retrospective human studies, including case reports that used phosphatidylcholine alone, or in combination with deoxycholate, and/or other additives were included.

Exclusion criteria

Lipoma cases, studies without data concerning number of study participants, injection site, lipolytic agent, total volume, and systemic side effects.

Data extracted

Number of study participants, injection site, lipolytic agent, depth of injection, total volume, and systemic side effects.

Data analysis

Injection sites, lipolytic agents, depth of injection, total volume, systemic side effects, and proportion/percentage of side effects were noted. Proportion/percentage of side effects was calculated from the number of study participants when no proportion/percentage was available. The data were tabulated, and compared to conclude the safety of composition of lipolytic agent. Comparison was done on computed total amount of PC/DC to the injection sites and systemic side effects. Further, search for the explanations for possible causes of the various systemic side effects were done.

RESULTS

We got 25 articles that contained information concerning the lipolytic agent, total volume, and systemic side effects, which were summarized in TABLE 1. However, some studies did not reveal the detailed composition of the lipolytic agent, and only refer the lipolytic agent as PC[2,12-14], without further explanation of the manufacturer, so that the detailed composition was not

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TABLE 1 : Injection site, agents used, depth of injection, total volume, and systemic side effects

Ref no	Injection site	Agent	Injection		Systemic side effects
			Depth	Total volume	
16	face	PC 5%, DC	SC	0.2-5 mL	-
20	Face	PC 5%, DC 4,75%, add	0.5cm	0.4 mL	-
12	Face	PC 5%	2 cm BCS	0.4 mL	-
2	Face	PC 5%	In fat pad	0.4 mL	-
21	Face	PC 5%, DC 1-2% or PC, add (1/1)	1 cm BCS	Max 3 mL	-
11	Face	PC 5%,DC 1-4.75%	NA	1-2 mL	-
22	Abdomen	PC 5%, add (diluted 1:2)	12mm	40 - 63.5 mL	-
19	Abdomen	PC 5%, DC 4.2%	SC	26 mL	-
23	Abdomen	DC 0.5% -1.25% + add	1.3 cm	10 mL	-
24	Abdomen	PC 5%, DC 2- 2.5%	13 mm	8-10 mL	Diarrhea, steatorrhea – 20% -
8	Abdomen	PC 5%, DC 4.2%, add	NA	Max 50 mL	Nausea, diarrhea, DL, IMB (3%)
19	Back	PC 5%, DC 4.2%	9mm	NA	Nausea (1/20)
25	Gluteal region	PC 5%, DC 4.75%	SC	70 mL	Nausea, vomitus, ALD, ARF (1/1)
26	Gluteo-trochanteric region	PC 5%,DC 2.5% or DOC 4.75% diluted 8x	10 mm	40 mL	Dizziness 5.4% Nausea/malaise 10.8% Diarrhea/steatorrhea 16.2%
27	calves	PC 5%, DC 4.75%	SC	10 mL	-
28	Various places	PC 2.5 - 5%, DC (2.37-4.75%), w/wo add, or DC (2.37-4.75), or others	NA	100 or 50 mL, or more	Nausea (24%D, I= <10%, >3000mg), diarrhea -18.6%D, I= <2%, >3000 mg), dizziness (34.6%D, I= 5%,)
29	Various places	PC 25%, DC 2.5%	1 cm BCS	Max 50 mL	-
13	Various places	PC 5%	In fat	5 mL	-
30	Various places	PC 5%, add diluted 1:1	12 mm (in fat)	40-100 mL	stool increase & soft, twice menstrual bleeding (4/441)
14	Various places	PC 5%	In fat	5-30 mL	-
31	Various places	PC 5%, DC 4.75%	In SC fat	0.3 mL	-
5	Various places	PC 25%, PC Pure or diluted	1-2cm BCS, in fat	Max 10 mL	-
32	Various places	PC 5%, DC 4.75%	In fat pad	Max 40 mL	-
17	Various places	PC 2.5%, DC	6-13 mm	Max 100 mL	Nausea, diarrhea (% NA)
33	Various places	PC 5%, DC 4.75%, add	6-13 mm	0.1-0.4 mL	-
34	Various places	PC 5%, DC 4.2-4.7%	SC	Max 50 mL	Diarrhoea (1.5%), nausea (0.7%), DL (0.7%), IMB (0.1%)

PC= phosphatidylcholine, DC= (sodium) deoxycholate, add= additives/preservative, SC= subcutaneous, NA= not available, BCS= below cutaneous surface, T= total, Max= maximum, ALD= acute liver dysfunction, ARF= acute renal failure, DL= dizziness/ light headedness , IMB= intermenstrual bleeding, D= reporting doctors, I= Incidence

known, while it is well known that PC should be combined with DC or other additives to make it soluble[15].

In addition, in studies using PC/DC formula, several studies did not specify the DC concentration. A study explained the composition of the formula, but did not reveal the concentration of DC[16]. Further, a study highlighted the use of PC/DC[5], and a study referred to a PC/DC containing lipodissolve formula, but both with-

out revealing the concentration of DC[17], which plays a major role in causing fat cell necrosis[18,19].

Most studies reported that there was no systemic side effect. However, nine studies reported systemic side effects, which were dizziness/lightheadedness, nausea, vomitus, diarrhea, steatorrhoea, menstrual disorder, acute liver dysfunction, and acute renal failure (TABLE 1). In addition, there is a study that was not included in this review due to incomplete data, but reporting delirium as a systemic side effect[35].

DISCUSSION

Mechanism of action of fat tissue reduction after PC/DC injection is due to detergent effect of DC that causes cell lysis and necrosis[18,19], while PC without DC do not cause cell lysis[19], but causes apoptosis of adipocytes[15], though previously this latter point of view was dispelled[19], and possibly also due to pyroptosis[36]. Therefore, severe local inflammatory reaction is most likely due to the presence of DC in PC/DC formula, as apoptosis do not cause inflammatory reaction. Inflammatory cells produce inflammatory cytokines, and it is aggravated by cell death due to pyroptosis[36]. Pyroptosis was initially recognized in microbial pathogen infected monocytes, macrophages, and dendritic cells. However, pyroptosis can also be induced in non-infected non-macrophage cells due to cytoplasmic content release of necrotic cells, and the mechanism involves caspace-1. Pyroptotic cell death show both apoptotic and necrotic cell features. i.e. lost of mitochondrial membrane potential, and plasma membrane integrity, DNA fragmentation and nuclear condensation. Lost of plasma membrane integrity causes release of cytoplasmic content[37], which causes inflammatory reaction. Moreover, pyroptosis caused release of inflammatory cytokines, which may in turn aggravate the inflammation.

All studies using PC/DC formula reported local side effects such as pain, burning sensation, swelling, and erythema, which are signs of inflammation. Further histopathological studies revealed that inflammatory reaction occurred on the injection site after injection of PC/DC combination[38,39], and DC alone caused more prominent inflammation and at earlier time point compared to PC/DC formula[19]. Therefore, Duncan et al (2009) conclusions are: 1) the presence of PC in the formula acts as a buffer as its pH is 7.0, compared to DC, whose pH is 8.08; 2) DC alone causes immediate localized fat cell necrosis at a concentration of 4.2%, thus do not disperse to a wider area. Further, PC forms a noncovalent bond with DC to allow wider diffusion around the injection site, and therefore acts as drug delivery system for DC; 3) the presence of PC reduces the degree and intensity of fat cell necrosis, and delays the whole process, thus causes a gradual process, and reduces the excessive formation of fibrous tissue, and therefore minimizes local adverse reactions and inflammation[19].

Systemic side effects are most likely not due to the presence of PC and/or DC and the preservative/additives in the circulation, as PC, DC, and preservative/additives (Lipostabil ®) was actually indicated to be used as intravenous treatment in emergency cases to dissolve atheroma plaques in cardiovascular disease[5].

Therefore, local severe inflammatory reaction is the most likely cause of systemic side effects due to the release of proinflammatory cytokines into circulation. Systemic Inflammatory cytokines are associated with various pathological conditions, including dizziness/lightheadedness[40], nausea[41], vomitus[42], diarrhea[43], steatorrhoea[44], menstrual disorder and intermenstrual bleeding[44], delirium[45], acute liver dysfunction[46], and acute renal failure[47], which were found in this systematic review.

Etiopathological cause of inflammation and systemic side effects

Fat cell lysis and necrosis do not alter lipid profile in circulation[23]. Therefore, released lipid from lysed and necrotic fat cells should be metabolized at the site of injection into inflammatory lipid mediators such as leucotriene B4 (LTB4) and prostaglandin D2 (PGD2) that attract inflammatory cells[48]. Moreover, necrotic cells initiate a proinflamatory response and secrete inflamatory cytokines by activating nuclear factor kappa B (NF-KB) and mitogen activated protein kinases (MAPK)[37].

Further, local severe inflamatory reaction, may cause cytokine release into circulation. Cytokine release into circulation happened in local inflammation, such as appendicitis, and the extent of cytokine release correlates with the extent of inflammation[49]. Therefore, cytokine

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release from local inflammatory sites into circulation may also occur in case of lipolytic agent subcutaneous injection, in a dose dependent manner, i.e. the more severe is the inflammation, the more cytokines enter the circulation. Another example of substantial cytokine release (cytokine storm) into circulation occured in severe local inflammation due to burn injury. In burn injury, some of severe cases may have multiple organ dysfuction[50,51], which was elicited by massive cytokine relese that affect various distant organs[37]. Therefore, damages in distant organs may also happen in PC/DC injection with severe local inflammation.

In all cases of PC/DC injection with systemic adverse effects and in some burn patients with multiple organ dysfuction, the organ dysfunction may resolve. After severe inflammation, polyunsaturated fatty acid from released lipid may be converted into anti infllammatory lipid mediators[52], which may also enter the circulation and cause resolution of the systemic side effects.

Measures to reduce the occurence of systemic side effects

After analyzing the systemic side effects (TABLE 1), all studies with available DC concentration showed no systemic side effects, when DC dose did not attained 200 mg per session. Side effects appeared, when DC dose was 200 mg or more per session. However, three studies, i. e. Bechara et al (2008)[27], Myers (2006)[29], and Rittes (2007)[32], who used more than 200 mg per session, i.e. 475, 1,250, and 1,900 mg DC respectively did not show systemic side effects (TABLE 1). The reason might be due to the fact that in the Bechara et al (2008) study, the patients were given ibuprofen that is a potent antiinflammatory agent for pain relief[27], and in Myers (2006) study, the patients got acetaminophen to reduce discomforts, and 5% of the patients with severe inflammation were given antiinflammatory agent[29]. Acetaminophen is a weak antiinflammatory agent[53]. and may overcome inflammation to some extent, and prevent entry of inflammatory cytokine into circulation. Rittes (2007) study provided minimal data, therefore no data concerning the use of antiinflammatory agents[32].

The most severe side effect (acute liver dysfunction and acute renal failure) happened in one case who received 3,500 mg PC in combination with 3,325 mg DC[25], which was above the recommended PC maximum dose per session (2,500 mg)[28,54]. In a study, a total amount of 400-500 mg PC/200 mg DC per session caused diarrhea and/or steatorrhea in 20% of the cases[24]. This total amount per session was far below the recommended maximum dose per session for PC. Therefore, recommended maximum dose per session is more appropriate to be used for DC in DC containing formula. From TABLE 1, it can be concluded that DC maximum dose should be set to less than 200 mg per session to avoid severe inflammatory reaction, as it may lead to severe systemic manifestation.

There are some limitations in concluding this review, as when it is clear that DC causes fat cell lysis in a dose dependent manner[23], is not clear whether systemic side effects are also dose dependent, and the suggestion to set a maximum dose for DC to avoid systemic adverse events may need further evaluation. In addition, there is no study that revealed the presence of caspace-1 or pyroptotic cell death in local tissues or organs following PC/DC subcutaneous injection. Therefore, hypothetical supposition of cytokine induces pyroptosis in distant organ needs further studies to prove it.

In the future, studies need to be conducted to measure plasma cytokine level in PC/DC treated patients in relation with systemic side effects, to evaluate the safe total amount of PC/DC injection. As PC contribute in the lipolysis by causing apoptosis[15], development of PC/DC solution with lower DC content is advisable. However, further studies need to be conducted to test the efficacy of the new formula.

Recently, an extracorporeal cytokine filter was developed to reduce cytokine level, and was tested in 650 cases without serious adverse events[55]. Therefore, in case the hypothesis is true, for cases that need more than the save dose, cytokine level monitoring and the use of a cytokine filter may be advisable.

CONCLUSION

High total DC concentration is supposed to be the major cause of severe inflammation that may lead to serious systemic side effects.

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