Evaluation of a New Adipocytolytic Solution: Adverse Effects and Their Relationship With the Number of Vials Injected

Hernán Pinto MD,[a] Carlota Hernández MD,[b] Cinara Turra MD,[c] Marisa Manzano MD,[d] Laura Salvador MD,[d] Paloma Tejero MD[e]

[a]Instituto de Investigaciones para las Especialidades Estéticas y del Envejecimiento, Barcelona, Spain
[b]Clínica Arts Médica, Valencia, Spain
[c]Beyou Medical Group, Málaga, Spain

ABSTRACT

Adipocytolytic therapies have always raised the interest of aesthetic medicine physicians, mainly because of the great potential to achieve spectacular results in localized adiposities reduction. In the last few decades, these results have been severely compromised due to the improper or reckless injection of these products, to the extent of some of them being banned in many countries. Today, there is a new adipocytolytic solution that has been approved, is effective, and has theoretic and empiric consensus regarding its safety. The aim of this study for which 331 therapeutic sessions were retrospectively analyzed is to provide evidence of its safety and efficacy.

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INTRODUCTION

The struggle to reduce the buildup of undesired adipose tissue in the human body is a century old.[1] After the revolution brought about by Klein´s liposuction innovations during the 90's, development of treatments for non-localized lipodystrophias blossomed and become well-established while development of localized lypodystrophia treatments stopped.[2,3] A few years later, phosphatidylcholine and sodium deoxycholate solutions gained recognition for their great capability for achieving results[4,5] and their relatively easy application. New research results have intensified an already established discussion[6] regarding a mechanism of action that is not 100% understood, even today.[7] Theorization continued[8] and the local vs systemic effects analysis got most of the attention.[9] The first effectiveness results started to appear,[10] but "off-label" uses,[11] sometimes even reckless, and the use of these products by non-qualified personnel, undermined society's confidence in this kind of procedures.

Today, there is an adipocytolytic solution that has become the starting point of a new generation of injectable products for localized fat reduction. It is commercialized in Europe as a medical device. New evidence for localized adiposity treatments with sodium deoxycholate surfaces on a daily basis.[12,13] However, the data available is almost exclusively focused on clinical results.[14,15] Other than empiricisms,[16] there is virtually no information of any kind regarding this procedure. In spite of this, it is important to stress that by the end of 2012 over 120,000 vials of this product had already been injected in Spain and up to that moment, to the best of the authors' knowledge, there had been no reports of ulcers, skin necrosis, or irreversible functional deficit due to the use of this specific product. The absence of reports (even if the data is biased to some extent) after such a huge number of applications suggests that this product is safe.

The primary aims of this study are to a) perform a descriptive analysis of the side effects that occurred after treatment and b) to evaluate the effect of the number of vials injected on the side effects recorded. A secondary aim was to analyze whether other variables such as gender, body mass index (BMI), age, number of previous sessions, total number of injected areas, and number of vials injected in each area may alter the influence of the number of vials injected on side effects.

MATERIALS AND METHODS

In the present study, 331 sessions on 145 patients who received treatment between July 1, 2011, and June 30, 2012, were analyzed. Each patient who fulfilled the inclusion criteria and was treated during this period was included. Inclusion criteria were as follows: a) 25-65 years old; b) 19.5-29 BMI; c) no systemic pathologies; d) not under chronic medication or treatment; e) not pregnant or breastfeeding; f) no other treatment in the same areas within a month prior to the first session; g) adipose panicle minimum thickness: 1.5 cm; h) application areas were limbs and trunk. The product injected was Aqualyx®, Ghimas S.p.a., Casalecchio di Reno, Italy. as per the technical specifications.[17] Each therapeutic vial consisted of the 8 ml commercial presentation unit and 0.2 ml of lidocaine 2% (no epinephrine) added to it. Special 100mm/24G and 70mm/25G needles were used for injection.

Graded scales were used for the assessment of adverse effect severity. Where possible, previously validated scales were used and if not possible, quantitative scales specifically designed for this study were drafted. For pain, the visual analogue scale (VAS) was used[18] where 0 = no pain and 10 = the worst pain imaginable. Stinging was analyzed independently from pain because it empirically proved to be a very frequent adverse effect of this treatment. A very similar scale was used for stinging: 0 = no stinging and 10 = the worst stinging imaginable. Hematomas were rated on a severity scale where 0 = no hematomas and 10 points = hematomas that a) had a diameter of 5 cm or more, b) took more than 2 weeks to resolve, or c) had a very dark color from the beginning. Erythema was rated on a severity scale where 0 points = no erythema and 10 points = painful, dark erythema with a diameter of 10 cm or more.

Descriptive statistics were used to analyze the sample, the frequency of adverse effects, and their severity. For quantitative variables, means and standard deviations were used as measures of central tendency and dispersion. For qualitative variables, absolute and relative frequencies were used. Univariate analysis was performed in order to assess the relationship between the adverse effects and the number of vials injected. Simple linear regression models were built for each adverse effect. Variations introduced by other variables were also assessed with multiple linear regression models (backward elimination). Statistical analysis was performed with SPSS software for Windows® (version 17, SPSS Inc., Chicago, IL).

RESULTS

Descriptive Analysis

331 therapeutic sessions on 145 patients with a mean age of 41.79 years old (SD: 8.96) and a mean BMI of 24.78 kg/cm^2 (SD: 4.23) that were retrospectively analyzed. 90.9% of the sessions were performed on women. 31.03% of the 145 patients received one session, 29.65% received two sessions, 24.82% received three sessions, and 14.48% received four or more sessions.

Abdominal application was the most frequent, representing 64.95% of the total number of sessions. Flanks were treated in 52.26% of the sessions, and peritrochanteric areas were treated in 18.73%. See absolute frequencies in Figure 1.

The great majority of the adverse effects recorded were inflammatory (Figure 2) and mild. There were four cases of vagal symptomatology (1.2%) and sixty-one cases of nodules (18.5%). No cases of ulcers, skin necrosis, scars, or functional deficit were recorded.

The dosage was different based on area. For abdominal treatments a maximum of four vials were injected, with a mean of 1.82 vials (SD 0.76) per session. Flanks were treated with a maximum of five vials, with a mean of 1.84 vials (SD 0.672) per session. The maximum number of vials per session for peritrochanteric areas was five, with a mean of 2.21 vials (SD 0.926). For other areas, the mean number of vials per session was 1.83 (SD 0.813).

FIGURE 1. Areas of treatment: abdomen (Ab), flanks (Fl), peritrochanteric (Tr) and other areas (O). X-axis: anatomical area. Y-axis: number of sessions when it was treated.

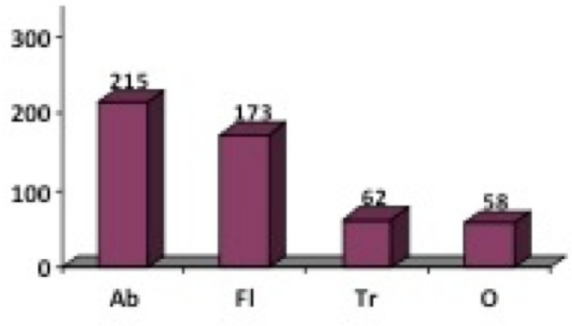
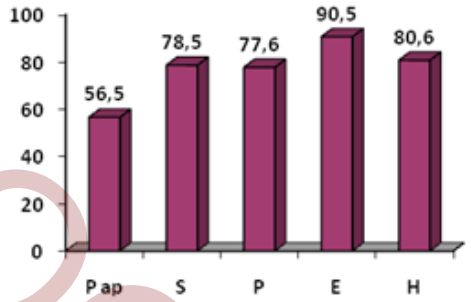


FIGURE 2. Inflammatory adverse effects frequencies. X-axis: adverse effect. Y-axis: relative frequency (%). P ap = pain during application; S ap = stinging during application; P = pain at post-operatory; E = erythema at post-operatory; H = hematoma at post-operatory.



Univariate Analysis

For the purpose of evaluating the relationship between adverse effects and the number of vials injected, simple linear regression models were built (Table 1). It was confirmed that the number of vials injected per session was directly proportional to the severity of the adverse effects observed (Figure 3). Since this analysis required independent observations, it was performed only on the data from the first sessions on the 144 patients: n= 144.

Multivariate Analysis

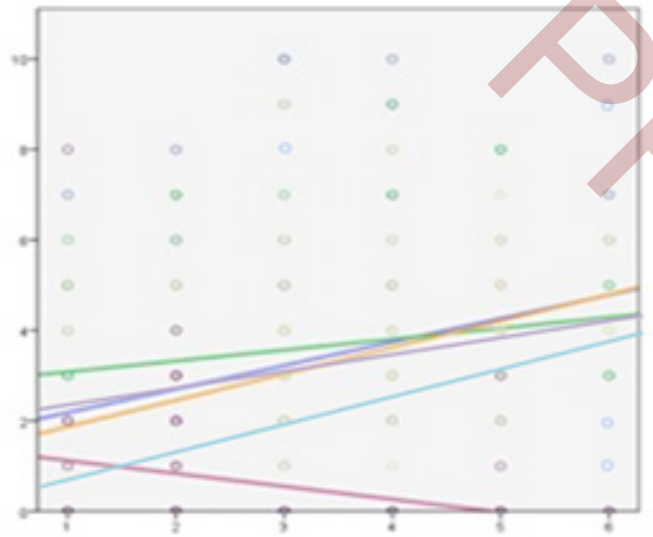
For the purpose of evaluating the influence of other variables on the adverse effects observed, a multiple linear regression model was built, using the conventional backward elimination procedure (Table 2). The variables analyzed were gender, age, BMI, number of sessions previously received, number of vials injected in a specific area, and number of total areas where treatment was performed.

TABLE 1.

Univariate Analysis Predictor			
Dependent Variable	B	CI 95% of B	*P*
Pain[1]	0,606	0,361 a 0,852	< 0,001
Stinging[1]	0,354	0,115 a 0,593	< 0,004
Pain[2]	0,529	0,259 a 0,799	< 0,001
Erythema[2]	0,239	0,025 a 0,454	< 0,029
Hematoma[2]	0,589	0,392 a 0,786	< 0,001

Number of vials injected. B: Beta regression coefficient, CI: confidence interval, *P*: statistical significance, [1]during application, [2]during post-operatory.

FIGURE 3. Pain at application (light blue), stinging at application (violet), pain during the postoperative period (blue), erythema during the postoperative period (green), hematoma during the postoperative period (orange), and nodules during the postoperative period (red magenta), according to the number of injected vials in one area. X-axis: number of vials. Y-axis: score in severity scales.



DISCUSSION

The manufacturer claims some features that set this product apart from all other adipocytolytic solutions previously used: a) sodium deoxycholate has been subjected to various attenuation processes, and b) an hexose polymer (3:6-anhydro-L-galactose and D-galactose) was included in the formulation. This polymer has been attributed several important functions; it attracts water and exchanges it for molecules of the active principle, releasing it slowly, according to interstitial pressure. This polymer is mostly responsible for the controlled release of the active principle. In conjunction, the claimed attenuated aggressiveness and controlled release support the theoretical biochemical rationale for the safety of this treatment, previously confirmed empirically, and now witnessed and analyzed in this study.

TABLE 2.

Multiple Linear Regression				
Predictor Variable	B	CI 95% for B	*P*	Dependent Variable
Constant	2,143	0,410; 3,976	-	Pain when injected
Male	2,160	1,486; 2,833	< 0,001	
BMI	-0,967	-0,119; -0,014	0,013	
Abdomen: No. of vials	0,613	0,380; 0,845	< 0,001	
Flank: No. of vials	0,509	0,300; 0,718	< 0,001	
Peritrochanteric: No. of vials	0,728	0,471; 0,985	< 0,001	
Other areas: No. of vials	0,768	0,503; 1,034	< 0,001	
Constant	0,755	-0,466; 1,976	-	Stinging when injected
Male	1,399	0,809; 1,988	< 0,001	
BMI	-0,052	-0,098; -0,006	0,026	
Abdomen: No. of vials	0,758	0,555; 0,961	< 0,001	
Flank: No. of vials	0,711	0,528; 0,894	< 0,001	
Peritrochanteric: No. of vials	0,895	0,671; 1,120	< 0,001	
Other areas: No. of vials	0,832	0,599; 1,064	< 0,001	
Constant	1,655	0,122; 3,209	-	Pain at post-operatory
Male	1,499	0,754; 2,244	< 0,001	
BMI	-0,079	-0,137; -0,021	0,008	
Abdomen: No. of vials	0,880	0,623; 1,137	< 0,001	
Flank: No. of vials	0,553	0,322; 0,784	< 0,001	
Peritrochanteric: No. of vials	0,940	0,655; 1,224	< 0,001	
Other areas: No. of vials	0,807	0,513; 1,101	< 0,001	
Constant	0,330	-0,993; 1,493	-	Erythema at post-operatory
Age	0,025	0,0003; 0,049	0,05	
Abdomen: No. of vials	0,422	0,185; 0,660	0,001	
Flank: No. of vials	0,396	0,182; 0,609	< 0,001	
Peritrochanteric: No. of vials	0,754	0,492; 1,015	< 0,001	
Other areas: No. of vials	0,731	0,463; 0,999	< 0,001	
Constant	0,849	0,327; 1,370	-	Hematoma at post-operatory
Abdomen: No. of vials	0,642	0,327; 1,370	<0,001	
Flank: No. of vials	0,687	0,474; 0,900	< 0,001	
Peritrochanteric: No. of vials	1,097	0,838; 1,356	< 0,001	
Other areas: No. of vials	0,715	0,447; 0,983	< 0,001	

B: Beta regression coefficient, CI: confidence interval, P: statistical significance. BMI: body mass index.

With regard to the variable "number of vials injected in one area", both the univariate and the multivariate analyses have shown a directly proportional relationship between the number of vials injected and the severity of the adverse effects observed. This relationship was observed in all application areas under study. Flanks were the areas where lower adverse-effect frequency, lower severity scores, and lower severity score increments for additional injected vials were recorded. The opposite was true for peritrochanteric areas, where higher adverse-effect frequency, severity scores and severity score increments for additional injected vials were recorded. In the abdomen, the frequency and severity of adverse effects were intermediate.

The great majority of patients reported some degree of pain or stinging throughout the process, although such pain and/or stinging were always reversible, described as *tolerable* and in general, mild. The mean severity scores of pain and stinging during application were 2.98 and 3.98 points respectively, and 4.07 points for postoperative pain. These findings are perfectly consistent with the empirical adverse-effects-distribution models we had before this retrospective analysis was performed.

"Both the univariate and the multivariate analyses have shown a directly proportional relationship between the number of vials injected and the severity of the adverse effects observed."

Ninety percent of patients had local erythema during the postoperative period (mean severity score 3.72) or any kind of hematomas (mean severity score: 3.46). This frequency was so high that it could be stated that erythema, pain and hematomas –though reversible and mild– are not only normal occurrences but also expected and virtually unavoidable consequences of this procedure. On the other hand, no severe inflammatory lesions were observed. No cases of ulcers, skin necrosis, scars, or irreversible deficits of any kind were recorded. The frequency of these adverse effects was 0%, suggesting not only that they are not to be expected, but also that they are highly unlikely and extremely rare.

With the exception of nodules, the frequency of iatrogenic adverse effects was null. Considerations regarding nodules are different than for the other adverse effects observed in this study because they are a consequence of an inappropriate injection technique. Although all the nodules observed were reversible, it should be noted that their frequency was inversely proportional to the treating physician's experience. Of the 61 sessions where nodules were recorded, 53 belonged to 19 patients treated at the same medical center where the physician had little or no previous experience with this kind of procedure. 95.08% of nodules received a severity score between 1 and 3 points, 3.2% of nodules received a severity score of 4 points, and 1.72% were graded above 4 points. The nodule frequency recorded was 18.5%, with a mean severity score of 2.11. However, when nodules were analyzed in a real and thus much more helpful context as regards the clinical perspective (excluding the learning curve data), their frequency dropped to 3.12% with a similar mean severity: 2.87 points.

The variable "total number of treated areas" did not alter the frequency of adverse effects, nor their severity. This was a very important finding, since it accounted for the local nature of adverse effects, supporting the empirical evidence of the lack of systemic adverse effects as a consequence of product accumulation when treating a large number of areas.

Male patients showed higher sensitivity to pain and stinging in the postoperative period and during application. However, the small number of male patients in this study has made it impossible to arrive at any meaningful conclusions.

The age variable did not show any statistically significant variations for the frequency of any adverse effect.

The BMI analysis revealed that when it remained between 20 and 29, it was associated with a protective effect. For each BMI point increment, a reduction of 0.967 (CI 95% = -0.119 to -0.014) points in the "pain during application" severity scale (P<0.013), a reduction of -0.052 (CI 95% = -0.098 to -0.006) points in the "stinging during application" severity scale (P<0.026), and a reduction of -0.079 (CI 95% =-0.137 to -0.021) points in the "pain during the postoperative period" severity scale (P<0.008) were recorded.

Finally, it is important to state the need of new efficacy studies that may correlate: results vs numbers of vials injected, side effects vs number of sessions, and most of all, side effects vs results.

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DISCLOSURES

Dr. Hernán Pinto is an external medical advisor of Real Lasting S.L. that distributes Aqualyx® in Spanish territory.

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AUTHOR CORRESPONDENCE

Hernán Pinto MD
E-mail:..... hpinto@ageback.es