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RCT systematic review

Polyacrylamide injection vs polylactic acid in HIV related lipodystrophy: a RCT systematic review

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Abstract: Lipodystrophy is an alteration of fat metabolism that commonly affects HIV-1 positive patients treated with antiretroviral therapy (ART). The facial area is most commonly affected by peripheral lipoatrophy, thus becoming a social stigma related to chronic HIV. Several treatments have been proposed such as modification of diet, lifestyle and both surgical and nonsurgical procedures. The goal of our systematic review is to examine published clinical studies involving the use of polyacrylamide filler for treatment of HIV FLA and to provide evidence-based recommendations based on published efficacy and safety data. Our research was performed on the published literature until April 2021.Polyacrylamyde gel is a volumetric gel, has been proven stable, nontoxic, nonallergenic, nonembryotoxic, and nonabsorbable. Poly-L-lactic acid (PLA) is a biocompatible, biodegradable, synthetic polymer derived from Lactic acid. We believe is essential to draft a pre and post injection and operative protocol to define an even setting for the clinical condition. Is desirable if such specification are included in a large randomized controlled trial and the follow up is longer than the studies that we found, because as we have seen in literature are reported adverse events even 3 or 5 years after the injections.

Keywords: HIV facial lipoatrophy; HIV lipodistrophy; facial volume loss; filler agent; highly active antiretroviral therapy; quality of life; polyacrylamide gel; polylactic acid.

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1. Introduction

Lipodystrophy is an alteration of fat metabolism that commonly affects HIV-1 positive patients treated with antiretroviral therapy (ART). Thanks to ART, the HIV patients' survival rate and quality of life increased, although new chronic complication and morphological changes such as lipodystrophy arose. Lipodystrophy is as a combination of

facial fat atrophy associated or not with peripheral lipoatrophy (leg arm and buttocks), intra-abdominal fat accumulation and a lipid redistribution: alterations of body-fat composition has in fact been reported in 40–50% of all ambulatory HIV-positive patients [1-3]. The main risk factor of this condition is the use of thymidine analogues inhibitors of the reverse transcriptase, such as estavudine (D4T) or zidovudine (AZT) [4].

The facial area is most commonly affected by peripheral lipoatrophy, thus becoming a social stigma related to chronic HIV (a.k.a. facial wasting) [5]. Psychological consequences may be significant in many patients leading to reduced self-esteem, problems in social and sexual relations, anxiety and depression, and as a result leading to a reduction in antiretroviral therapy adherence [2,6-8]. Several treatments have been proposed such as modification of diet, lifestyle and both surgical and nonsurgical procedures [9-15]. If the clinical condition is characterized by facial lipoatrophy and body lipohypertrophy, structural fat grafting may be a feasible option, since it is possible to restore the face volume and reshape the body at the same time [16,17]. On the other hand, if the clinical condition is mainly characterized by facial lipoatrophy other options are available such as the use of permanent, semipermanent or absorbable fillers [9,18,19].

Polyacrylamide gel was first introduced in aesthetic medicine in the Ukraine in the late 1980s [20]. Today it is mainly produced by Contura International with the trade name Aquamid, while other producers of polyacrylamide exist on the market (ARGIFORM, AMAZINGEL, BIO-FORMACRYL, BIOALCAMID, OUTLINE). The features of this gel make it a versatile tool, being used in female stress urinary incontinence, osteoarthritis and cosmetics, specifically in lip volume enhancement and facial contouring [21,22].

Polyacrylamide application is a minimally invasive and effective procedure, but possible complication related to the injection are reported as migration of the gel, fibrosis and visible accumulations [23]. Surgical intervention could be needed to deal with these cases [23,24], for these features Polyacrylamide is still not approved in many countries.

Polylactic acid (PLA) is an aliphatic polymer derived from Lactic acid and since 1970 it has been approved by the Food and Drug Administration (FDA) for direct contact with biological fluids.

PLA medical applications may vary, from tissue engineering, to sutures or bio absorbable medical implants [25].

PLA is been successfully used in cosmetic medicine to treat HIV associated lipodystrophy [26]. As any injectable filler, PLA may cause adverse events related to the procedure, the most common including erythema, oedema and discomfort that generally resolve spontaneously. Papules and nodules are late-onset complications that tend to arise several weeks after the treatment. A rare but serious complication is the inflammatory granuloma, an aggressive host rection to the filler, usually treated by the means of steroids or antimetabolites and 5-fluorouracil [27].

The aim of this systematic review of randomized controlled trials was to investigate the efficacy and safety of polyacrylamide gel injections compared to polylactic acid injection in restoring facial wasting.

2. Materials and Methods

Methods and inclusion criteria of this work were specified in advance and documented in a protocol, according to quality standards described in the PRISMA 2020 checklist [28].

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2.1. Eligibility criteria 93

The following focus question was developed according to the population, intervention, comparison, and outcome (PICO) study design: in patient affected by lipodystrophy HIV associated (P) is the polyacrylamide gel (I) effective in lipodystrophy correction (O) compared to polylactic acid found in literature (C)? The studies eligible for review were English written randomized controlled trials, describing patients with facial lipoatrophy HIV-related treatment. The participants and control group received either polyacrylamide gel or polylactic acid. The studies included had to report a follow up of at least 24 weeks, and at least one efficacy outcome. Articles were excluded when not reporting any of the efficacy outcome. 94 95 96 97 98 99 100 101 102

2.2 Information sources 103

The research was carried out up to April 7, 2021 on electronic databases PubMed/MEDLINE, Embase, and Cochrane. Article language was limited to English using the provided filters. 104 105 106

2.3 Search Strategy 107

The keywords were used and combined with Boolean operators, adapted for every database, both as text words and Medical Search Headings (MeSH terms) as follows: (polyacrylamide OR PAM OR PAGE OR polyacrylamide gel OR polyacrylamide hydrogel OR polyacrylamide hydro-gel OR polyacrylamide hydro gel) AND (human immunodeficiency virus OR HIV OR lipodystrophy) 108 109 110 111 112

2.4 Selection and data collection process 113

Two reviewers (L.P., G.L.G.) performed eligibility assessment, full-text inclusion and data extraction independently. Disagreements between reviewers were resolved by consensus. When consensus was not reached, a senior member mediated (R.R.). A standard chart form of the obtained data was prepared to facilitate comparison among the articles. 114 115 116 117

2.5 Data items 118

The following data from each study were extracted: Author's name, publication year, country, ClinicalTrials.gov identifier/NCT number; enrolment criteria, type of dermal filler used, adverse effects related to the procedure, efficiency measures. 119 120 121

2.5. Study risk of bias assessment 122

Two independent reviewers (G.L.G., L.P.) performed quality assessments of the included studies, in cases of results discrepancies, a third senior reviewer (R.R.) was consulted. RoB 2 tool was used to assess randomized studies [29]. Three levels (Low, High Some Concerns) were used to present the risk of bias Robvis visualization tool web app was used to create "traffic light" plots of the domain-level judgements for each individual result and weighted bar plots of the distribution of risk-of-bias judgements within each bias [30]. 123 124 125 126 127 128 129

2.6 Effect measures 130

Injection points were expressed as integer numbers. Type of filler was expressed with molecule name and concentration in milliliter (ml). Adverse effects and efficiency measures were listed.

2.7. Additional analyses

No additional analyses were performed.

3. Results

3.1 Study Selection

The PubMed search strategy identified 56 articles, the Cochrane Library search gave 82 results, the Embase search reported 62 articles that were screened for abstract and language. After duplicate removal and eligibility assessment, 10 full-text articles were finally selected for further evaluation. Of the 10 papers, 8 were excluded because they did not met the inclusion criteria, 7 were prospective studies 1 was a cross sectional study finally two paper were selected. Excluded works did not meet the inclusion criteria because even if they were catalogued as controlled randomized trial reading the entire text resulted in other kind of works: prospective, nonrandomized, case report, commentary (Figure 1).

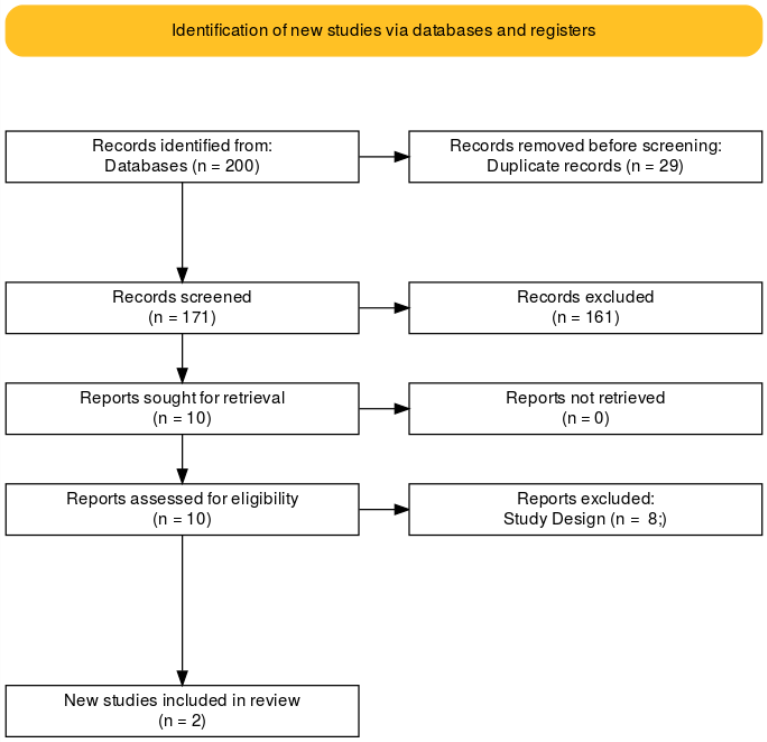

Figure 1. Flow diagram of literature search and study selection.

3.2 Study Characteristics

The included studies for the analysis were listed in Table 1 (Narciso et al. 2009; Lafaurie et al., 2013) [31,32].

Author	Publication year	Country	NCT number	Enrolment criteria	Type of filler	Adverse effect	Efficiency measures

Narciso et al.	2009	Italy	N.A.	18 years of age or older; HIV-related lipodystrophy syndrome with severe FLA, eligible on the basis of physician's recommendation for corrective surgery; CD4 count > 100=mm3 ; HIV-RNA < 1000 copies=ml; and stable HAART therapy for at least 6 months	Polylactic acid; Polyacrylamide hydrogel	Minimal edema after 7 days (7.5%), ecchymoses after 7 days (4.5%), bleeding (4.5%), local cutaneous injury (4.5%), and subcutaneous noninflammatory nodules (1.5%) were the adverse effects observed	HRQoL, (EQ-5D); change in FLA grading score using a validated FLA severity scale that ranged from grade 1 (mild lipoatrophy) to grade 5 (most severe lipoatrophy) ; HRQoL, (EQ-5D)
Lafaurie et al.	2013	France	00383734	Eligible patients were HIV-infected adults, with antiretroviral therapy-induced facial lipoatrophy and stable antiretroviral treatment for at least 3 months	Polylactic acid; Polyacrylamide hydrogel	Bleeding and haematoma at the injection site, vagal hypertonia during injections and oedema post-injections were the most frequently reported adverse events, vagal hypertonia	patient satisfaction at week 48, assessed using a VAS , HRQoL (MOS-HIV)

A total of 314 patients treated with dermal filler were evaluated.

The primary outcome of Lafaurie's study was to demonstrate the non-inferiority of Poly-acrilamide vs Polylactic acid using a visual analogue scale (VAS) at week 48. In

Narciso's study the primary objective was to compare the change from baseline to the end of filling intervention for the immediate group or before the filling intervention for the delayed group in terms of the severity grade of the FLA assessed by physicians. Secondary outcomes were to evaluate patients's QoL and anxiety.

3.3 Risk of bias in studies

The analysis of the paper quality assessment is presented in Figure 2.

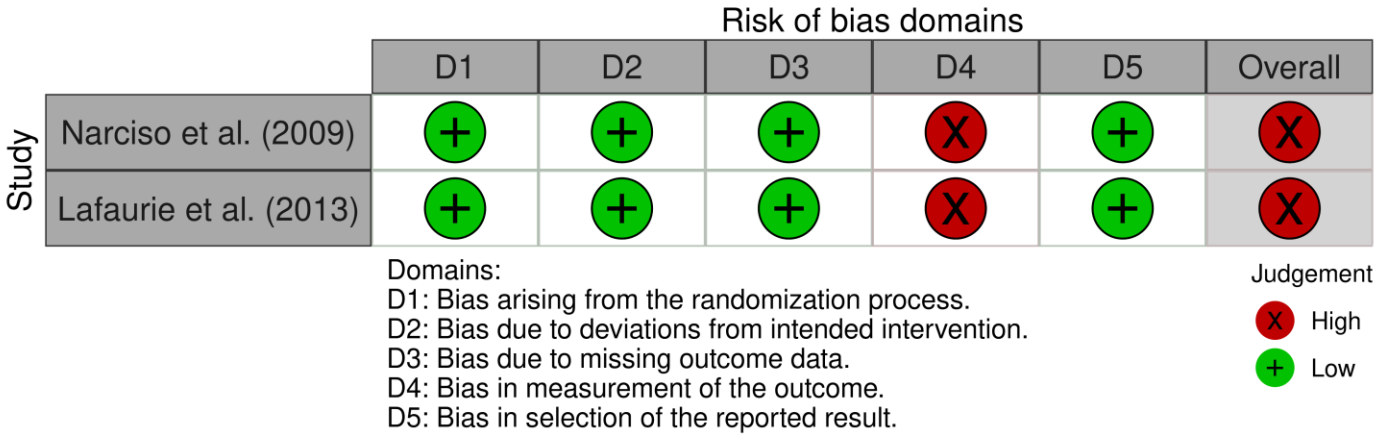

Figure 2. ROB-2 Traffic Light Plot bias assessment.

3.4 Results of individual studies

Narciso in 2009 made a randomized, controlled, open-label single-center study and assessed efficacy and safety of the treatment of HIV associated facial lipoatrophy using facial injections of Poly-l-lactic acid or Polyacrylamide gel [31]. A total of 134 patients with lipoatrophy were randomly assigned to the immediate treatment arm or the delayed one. Using a facial lipoatrophy severity scale they valuated changes on dermal thickness, the follow up was of 27 weeks for the immediate and 25 for delayed group. Secondary outcomes valuated in the study were safety with adverse events, quality of life and anxiety.

Lafaurie in 2013 made a randomized single blinded trial comparing Polyacrylamide gel and Polylactic acid [32]. A total of 148 patients were included in the study were randomly assigned to receive intradermal injection with PH or PLA, the total duration of the study was of 96 weeks. Primary outcome was the patient satisfaction at week 48 assessed using a visual analogue scale, as secondary endpoint the study valuated quality of life, cheek thickness and skin fold. Adverse events let the evaluation and safety.

4. Discussion

Facial lipoatrophy is a distressing clinical condition for HIV patients treated with antiretroviral therapy, psychological impact is significant in many patients it even lead to a lack of compliance and adherence to the treatment [12].

Biological and synthetic fillers have been developed for soft tissue augmentation and facial contouring, but none of these have been considered the method of choice to treat lipoatrophy.

Humans, from the dawn of time, searched the eternal youth as a key of happiness; face for its features is always been an important region where we concentrated efforts: facial painting, tattooing, piercing have been used to enhance appearance. Over the years aging leads to a modification of the countenance, genetic factor and environment plays an essential role. Even if skin probably shows the most visible aging damage, modification of the deeper anatomic levels has an important role especially skull and facial fat pad [33]. Considering facial filler agents the aim since their use is to find the perfect substance to replace volume and fill lines in the face. The first filler developed is been paraffine in 1850s and in the late 1800s is been introduced autologous fat injection for facial augmentation, its use is still popular today, but presents unpredictable longevity [34,35]. In 1940s was first introduced liquid silicone, at the beginning in Japan for breast augmentation, in 1960s it became a popular cosmetic treatment all over the world, in 1979 FDA condemned the use of injectable silicone for the disastrous sequelae, such as granuloma and fistula [36].

In 1981 FDA approved bovine collagen for cosmetic use, Zyderm (Allergan, Inc., Irvine, CA) [37].

Movies and society of 80s and 90s gave a big boost to the use of filler, a turning point was the approval of Hyaluronic Acid (HA) in 2003, it is a highly hydrophilic glycosaminoglycan that is part of the extracellular matrix of a large variety of tissues in all organisms, for its features HA remains the most widely used filler material [35].

Polyacrylamyde gel is a volumetric gel, consists of 2.5% cross-linked polyacrylamide and 97.5% pyrogen-free water. This filler has been proven stable, nontoxic, nonallergenic, nonembryotoxic, and nonabsorbable [38]. PH produces an increase in subcutaneous thickness of both nasolabial lines, which was maintained even after 36 months from its application [39].

Although some cases of impressive complications, such as cold and hot abscess 10 years following the injections have been reported [40,41].

Poly-L-lactic acid (PLA) is a biocompatible, biodegradable, synthetic polymer derived from Lactic acid that has been used since the mid 1990s in various maxillofacial and orthopedic procedures [41]. Intradermal injections overlying facial lipoatrophic areas lead to a dermal width increase due to a fibroblast recall and collagen deposition that reduce the physical signs of lipoatrophy [42].

PLA is generally well tolerated usually showing minimal adverse events. Occasionally there can be more serious adverse effects such as subcutaneous nodules or granulomas formation; some of the causes are thought to be derived from an inadequate dilution, an allergic or aberrant inflammatory response or a superficial injection technique [43].

Standard criteria for the use of permanent filler in HIV related lipodystrophy is still lacking. Rauso et al. proposed a 2 ml of product (1 vial = 1 ml) was injected in every filling session, this kind of approach was made to induce a very minimal tissue response [44]. The study compared outcomes between a megafilling approach and a gradual build-up but it did not show difference in term of safety, nevertheless he concludes that with the megafilling procedure patient's satisfaction is achieved earlier and it also leads to reduction of hospital costs.

Faundez et al proposed a sonographic evaluation after the filling procedure to identify filler deposits that was seen as an anechoic pseudocystic structure and it gave also the possibility to assess the rise in thickness of the treated area [39].

If the clinical condition of the lipodystrophy is characterized by facial lipoatrophy and abdominal fat accumulation a possible way of treating the patient is exploiting the excess fat and using it to restore facial features. In a study of Uzzan et al. 317 patients with lipodystrophy HIV related are treated using in 96% of the cases the periumbilical fat, other areas were nape and sacrum [45].

The technique used to is been described by Coleman (Lipostructure [R]), after taking the fat from the donor area, to reduce its reabsorption once injected, it has to be centrifuged for 3 minutes at 3000 rpm, then injected in the selected areas [46]. No immediate adverse events were recorded. The two main delayed adverse events were an excess of injected fat that needed to be aspirated, the second registred complication is been an asymmetry of results. Results were valuated one month after the procedure and then 6 month later, lipofilling intervention had different results depending on the treated area. Intervention on temporal region registered less satisfaction compared to zygomatic area or premaxillary region. Since the study did not registered any adverse event it is possible to define the technique as safe. If we compare to other filling procedure, with lipofilling there is no risk of systemic manifestation, nodules or granulomas, for the author these features should make lipofilling the election technique. Nevertheless, this technique depends on the quantity of abdominal fat to be a usable option.

In Narciso's study the primary objective was to evaluate the change from baseline to the end of the filling in the immediately treated group and only before surgery in the delayed group in term , it has been used a validated Facial Lipoatrophy severity scale rated by the two plastic surgeon that undertook the interventions, the scale ranged from grade one (mild lipoatrophy) to grade 5 (most severe lipoatrophy) [47].

At baseline most of the participants had an FLA severity grade of 3 or 4, the mean change for the immediate group was -3 and, naturally, 0.0 for the delayed group. Valuating the single filler used the study showed a mean value of -3.2 for the patients treated with PH and -2.7 for the PLA arms.

No significant differences between the immediate and delayed treatment groups were observed in terms of patient reported outcomes (PROs); the study was not able to show any significant diference between the two arms in Health Related Quality of Life (EQ-5D and ISSQoL), in social aspects, in relational-psychological consequences of body changes (Assessment of Body Change and Distress ABCD), as well as in anxiety-related concerns (self rated anxiety scale SAS).

The author indicates relevant improvements in FLA severity scale treated with both fillers without providing which is the better solution. In addition, the Authors wish for the creation of a validate and reliable patient centred instrument to evaluate how lipoatrophy impacts on quality of life of HIV infected patients.

Lafaurie valuated with a visual analogue scale (VAS) the efficacy of PLA and PH, ranging from 0 (very dissatisfied) to 10 (very satisfied), it was analysed and compared at week 28, 48, 72 and 96 measuring at each visit chick thickness. PH was considered as non-inferior to PLA if the margin was less than 15% at week 48, this value corresponded to a difference of 1 point or less in VAS for the PH group compared to the PLA group. The main analysis was an intention to treat analysis at week (ITT) 48, results demonstrated the non-inferiority of PH vs. PLA, respectively 7.5 and 7.1 with a difference of +0.4. Measurement at week 96 confirmed the non-inferiority of PH vs PLA with values of 6.7 and 6.9 respectively and a difference of +0.2, having a slightly greater increase in the PH arms. In the study quality of life was valuated as a secondary efficacy outcome, it has been used the MOS-HIV score that gave similar results in the two treatment.

From our literature research data showed that with the use of PH for the treatment of facial lipoatrophy, it is possible to obtain favourable results with good aesthetic gains, as well as studies that valuated PLA injections to treat HIV related lipoatrophy with positive results [48-52].

Facial fillers represent an ever-expanding market, therefore an important topic in literature is, over their use, how to valuate and eventually treat their complications. These complications range from bruising to oedema to a small bump underneath the skin to more serious consequence such as vascular occlusion, that can lead to skin necrosis or permanent vision loss, depending on the injected vessel; in case of embolization proper and prompt use of hyaluronidase is mandatory [53-56].

In the valuated studies the most frequent complications described were bleeding and ecchymoses at the injection site, vagal hypertonia during injections and minimal oedema post-injections were the most frequently reported adverse events and subcutaneous nodules. All the complications and the adverse events were mild and didn't lead to give up the trial and were treated with conservative procedures.

In Lafaurie's study were registered four patients that between 15 to 23 months after Polyacrylamide injection developed a large inflammatory lesion at the injection site, surgical drainage was necessary only in two cases, three of them needed antibiotic treatment and one of them had spontaneous resolution.

Nevertheless in literature for polyacrylamide gel are described late onset complication, in an work of Liu et al. is been described two case series of patients that received Polyacrylamide injections, the first one after 6 years from the treatment created a bony defect and the chin tissue was mingled with a jelly material that needed a surgical intervention [57]. The second case is a patient that after 3 years from the PH injection developed ulcers in the site of the injection that needed debridement.

The study underlines the necessity of longer follow-up, possibly with randomized trials in order to have more reliable results.

4.1 Limitations

Our study has several limitations.

The research of RCTs didn't show any recent article, using filters on the research and reducing it to only randomized controlled trials it came out that most of them even if where catalogued as RCTs were cross-sectional study, didn't have any randomization, or were prospective studies.

Another limit that we found is the absence of an RCT with a long period of follow up, as we have seen before in literature is described the presence of long-term complication that can be even more serious that the early onset one. In a study of Negredo et al. it was performed a cross-sectional study to evaluate the 10 years safety of polyacrylamide hydrogel [58].

In a study of Mundada is proposed an imaging study with MRI and PET CT to evaluate the distribution of facial fillers and complications [59].

5. Conclusions

Due to high risk of bias studies, it is hard to evaluate the efficacy of a specific treatment, however article analysis and comparison suggested some effective insights.

MRI and CT might be used to have an objective evaluation of the tissue after the treatment and eventually valuate complications. Ultrasound evaluation is a cost-effective procedure to assess volume augmentation. Patient reported outcome with standard test should be used.

We believe is essential to draft a pre- and post-injection and operative protocol to define an even setting for the clinical condition. Is desirable if such specifications are included in a large randomized controlled trial and the follow up is longer than the studies that we found, because as we have seen in literature are reported adverse events even 3 or 5 years after the injections.

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