Systematic Review

Polyacrylamide Injection vs. Polylactic Acid in HIV Related Lipodystrophy: A RCT Systematic Review

Gianpaolo Tartaro 1, Ludovico Pinto 1*, Giorgio Lo Giudice 2*, Romolo Fragola 1*, Pierfrancesco Bove 3, Giuseppe Mario Rauso 4, Nicola Zerbinati 5 and Giuseppe Colella 1

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 the treatment of HIV FLA, and to provide evidence-based recommendations based on published efficacy and safety data. Our research was performed on published literature until April 2021. Polyacrylamide gel is a volumetric gel that 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 it is essential to draft a pre- and post-injection and operative protocol to define an even setting for the clinical condition. It is desirable that 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 the literature there are reported adverse events even 3 or 5 years after the injections.

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

1. Introduction

Lipodystrophy is an alteration of fat metabolism that commonly affects HIV-1 positive patients treated with antiretroviral therapy (ART). Thanks to ART, HIV patient survival rates and quality of life have increased, although new chronic complications and morphological changes such as lipodystrophy arose. Lipodystrophy is a combination of facial fat atrophy associated with peripheral lipoatrophy (leg, arm and buttocks), intra-abdominal fat accumulation and lipid redistribution. Alterations in body-fat composition have 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 stavudine (D4T) or zidovudine (AZT) [4].

The facial area is most commonly affected by peripheral lipoatrophy, thus becoming a social stigma related to chronic HIV (also known as 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, as a result leading to a reduction in antiretroviral therapy adherence [2,6–8]. Several treatments have been proposed, such as the 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 Ukraine in the late 1980s [20]. Today, it is mainly produced by Contura International with the trade name Aquamid, though other producers of polyacrylamide exist on the market [Argiform (Bioform, Moscow, Russia), Amazingel (NanFeng Medical Science and Technology Development Co., Ltd., Shijiazhuang, People’s Republic of China), Bio-formacryl (Polymekon, Brindisi, Italy), Bioalcamid (Polymekon, Brindisi, Italy). 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 complications related to the injection are reported, such as migration of the gel, fibrosis and visible accumulations [23]. Surgical intervention could be needed to deal with these cases [23,24], and for these reasons 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 bioabsorbable medical implants [25].

PLA has been successfully used in cosmetic medicine to treat HIV-associated lipodystrophy [26]. As with 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 inflammatory granuloma, an aggressive host reaction 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 injections 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].

2.1. Eligibility Criteria

The following focus question was developed according to the population, intervention, comparison and outcome (PICO) study design: in patients affected by HIV-associated lipodystrophy (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 and controlled trials, describing patients with HIV-related facial lipoatrophy 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 outcomes.
2.2. Information Sources

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

2.3. Search Strategy

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).

2.4. Selection and Data Collection Process

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.

2.5. Data Items

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.

2.6. Study Risk of Bias Assessment

Two independent reviewers (G.L.G., L.P.) performed quality assessments of the included studies. In cases of result discrepancies, a third senior reviewer (R.R.) was consulted. The RoB 2 tool was used to assess randomized studies [29]. Three levels (low, high, some concerns) were used to present the risk of bias. The 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].

2.7. Effect Measures

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

2.8. 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 and the Embase search reported 62 articles that were screened for abstracts and language. After duplicate removal and eligibility assessment, 10 full-text articles were finally selected for further evaluation. Of the 10 papers, eight were excluded because they did not meet the inclusion criteria, seven were prospective studies and one was a cross-sectional study. Ultimately, two papers were selected. Excluded works did not meet the inclusion criteria because, even if they were catalogued as a controlled randomized trial, reading the entire text resulted in other kinds of work: prospective, nonrandomized, case report and/or commentary (Figure 1).

3.2. Study Characteristics

The included studies for analysis are listed in Table 1 [31,32].

The primary outcome of Lafaurie’s study was to demonstrate the non-inferiority of polyacrylamide 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’ quality of life and anxiety.

3.3. Risk of Bias in Studies

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

![Flow diagram of literature search and study selection.](image)

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

![RoB 2 traffic light plot bias assessment.](image)

**Figure 2.** RoB 2 traffic light plot bias assessment.
Table 1. General findings of included studies.

| Author          | Publication Year | Country | NCT Number | Enrolment Criteria                                                                 | Type of Filler                  | Adverse Effect                                                                 | Efficiency Measures             |
|-----------------|------------------|---------|------------|------------------------------------------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------|----------------------------------|
| Narciso et al. [31] | 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 $>100 = \text{mm}^3$; HIV-RNA $< 1000$ copies $= \text{mL}$; and stable HAART therapy for at least 6 months 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 | 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. [32] | 2013             | France  | 00383734   |                                                                                     | 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.
3.4. Results of Individual Studies

Narciso in 2009 made a randomized and controlled open-label single-centre study and assessed the 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 evaluated changes in dermal thickness. The follow up was after 27 weeks for the immediate group and 25 weeks for the delayed group. Secondary outcomes evaluated 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 polyactic acid [32]. A total of 148 patients were included in the study and were randomly assigned to receive intradermal injection with PH or PLA. The total duration of the study was 96 weeks. The primary outcome was determining patient satisfaction at week 48, which was assessed using a visual analogue scale. The secondary endpoint of the study evaluated quality of life, cheek thickness and skin fold. Adverse events led the evaluation and safety.

4. Discussion

Facial lipoatrophy is a distressing clinical condition for HIV patients treated with antiretroviral therapy. The psychological impact is significant in many patients, and it may 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, since the dawn of time, have searched for eternal youth as a key to happiness. Facial features have always been an important region where we concentrated efforts. Facial painting, tattooing and piercing have been used to enhance appearance. Over the years, aging leads to a modification of the countenance, genetic factors and environment playing an essential role. Even if skin shows the most visible aging damage, modification of the deeper anatomic levels has an important role, especially in the skull and facial fat pad [33]. Considering facial filler agents, the aim of their use is to find the perfect substance to replace volume and fill lines in the face. The first filler developed was paraffine in the 1850s, and the late 1800s introduced autologous fat injections for facial augmentation. Its use is still popular today but presents unpredictable longevity [34,35]. The 1940s saw the first introduction of liquid silicone, first used in Japan for breast augmentation, and in the 1960s it became a popular cosmetic treatment all over the world. In 1979 the FDA condemned the use of injectable silicone for its disastrous sequelae, such as granuloma and fistula [36].

In 1981, the FDA approved bovine collagen for cosmetic use, released as a product called Zyderm (Allergan, Inc., Irvine, CA, USA) [37].

The movie industry and society of the 1980s and 1990s 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. Thanks to its features, HA remains the most widely used filler material [35].

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

Although, some cases of significant complications, such as cold and hot abscesses 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 orthopaedic procedures [41]. Intradermal injections overlying facial lipoatrophic areas lead...
to a dermal width increase due to fibroblast recall and collagen deposition, which 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 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 are still lacking. Rauso et al. proposed 2 mL of product (1 vial = 1 mL) be 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 mega-filling approach and a gradual build-up, but it did not show differences in terms of safety. Nevertheless, he concluded that with the mega-filling procedure patient satisfaction is achieved earlier, and it also leads to a reduction of hospital costs.

Faundez et al. proposed a sonographic evaluation after the filling procedure to identify filler deposits, which show up as anechoic pseudocystic structures. It also allowed for 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 the study by Uzzan et al. 317 patients with HIV-related lipodystrophy were treated using—in 96% of the cases—their periumbilical fat. Other areas used were the nape and the sacrum [45].

This technique used was created by Sydney Coleman (named LipoStructure®). After taking the fat from the donor area, in order to reduce its reabsorption once injected it has to be centrifuged for 3 min 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 and an asymmetry of results. Results were evaluated one month after the procedure and then 6 months later. Lipofilling intervention had different results depending on the treated area. Intervention on the temporal region registered less satisfaction compared to the zygomatic area or premaxillary region. Since the study did not register any adverse events, it is possible to define the technique as safe. If we compare to other filling procedures, with lipofilling there is no risk of systemic manifestation, nodules or granulomas. For these reasons, the author believes lipofilling should be the elected 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. It used a validated facial lipoatrophy severity scale, rated by the two plastic surgeons that undertook the interventions. The scale ranged from grade one (mild lipoatrophy) to grade five (most severe lipoatrophy) [47].

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

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 difference 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, or ABCD) or in anxiety-related concerns (self-rated anxiety scale SAS).

The author indicates relevant improvements in the FLA severity scale when treating with both fillers, without providing which is the better solution. In addition, the authors wish for the creation of a validated and reliable patient-centred instrument to evaluate how lipoatrophy impacts the quality of life of HIV-infected patients.
Lafaurie evaluated using a visual analogue scale (VAS) the efficacy of PLA and PH, ranging from 0 (very dissatisfied) to 10 (very satisfied). This was analysed and compared at weeks 28, 48, 72 and 96, measuring at each visit cheek 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 one point or less in the VAS for the PH group compared to the PLA group. The main analysis was the intention-to-treat analysis (ITT) at week 48. Results demonstrated the non-inferiority of PH vs PL, respectively 7.5 and 7.1 with a difference of +0.4. Measurement at week 96 confirmed the non-inferiority of PH vs. PL, 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 evaluated as a secondary efficacy outcome. It used the MOS-HIV score, which gave similar results in the two treatments.

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. Studies that evaluated PLA injections to treat HIV-related lipoatrophy had positive results as well [48–52].

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

In the evaluated studies, the most frequent complications described were bleeding and ecchymoses at the injection site, vagal hypertonia during injections, minimal oedema post-injections and subcutaneous nodules. All the complications and adverse events were mild, did not lead any patient to give up the trial and were treated with conservative procedures.

In Lafaurie’s study it was registered that four patients, 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 a spontaneous resolution.

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

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

Limitations

Our study has several limitations.

The research of RCTs did not show any recent articles. Using filters on the research and reducing it to only randomized controlled trials, it came out that most of them, even if they were catalogued as RCTs, were cross-sectional studies that did not have any randomization or were prospective studies.

Another limitation that we found was the absence of an RCT with a long period of follow up. As we have seen described in the literature, there are long-term complications that can be even more serious than the early onset ones. In a study by Negredo et al., a cross-sectional study was performed to evaluate the safety of polyacrylamide hydrogel after 10 years [58].

In a study by Mundada, it is proposed that an imaging study could be done with MRI and PET CT to evaluate the distribution of facial fillers and complications [59].
5. Conclusions

Due to the high risk of biased 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 obtain an objective evaluation of the tissue after the treatment, and eventually evaluate complications. Ultrasound evaluation is a cost-effective procedure to assess volume augmentation. Patient reported outcomes with a standard test should be used.

We believe it is essential to draft a pre- and post-injection and operative protocol to define an even setting for the clinical condition. It is desirable that 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 the literature, there are reported adverse events even 3 or 5 years after the injections.

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