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Original article

The use of poly-lactic acid to improve projection of reconstructed nipple

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ABSTRACT

Purpose: Nipple-areola reconstruction represents an important step for final mammary reconstruction. Many techniques have been described. The drawback is the progressive nipple projection loss with time from 50% to over 70% of the initial projection. In this report, we evaluated the effect of injectable poly-lactic acid (PLLA) to improve projection of reconstructed nipples.
Results: We selected 12 patients with a residual nipple projection between 0.1 and 2 mm. The patients were injected locally inside the nipple with 0.5 ml of PLLA (dilution 1:4) every 4 weeks for 4 times. At the study end, patients were satisfied with results. No adverse effects were observed. After one year, an increase of nipple projection ranging from 0.5 to 3.5 mm was obtained with an average increase of 2.3 mm (282%) and this variation was statistically significant ($p < 0.0001$).
Conclusion: The use of injectable PLLA is a simple and effective procedure to improve projection of reconstructed nipple.

Introduction

Nipple-areola reconstruction is an important step in mammary reconstruction to achieve a satisfactory aesthetic result after mastectomy.

Breast reconstruction requires different surgical steps after mastectomy. The first step is the creation of the breast mound with autologous tissue and/or prosthetic implant followed by different procedures as required by the selected method of reconstruction. The final step is represented by the nipple-areola reconstruction. Thus, the complete reconstruction process requires various surgical steps that require general and local anesthesia, and often this is not well accepted by patients themselves. Women, which are strongly motivated and seek for a better final result, complete the entire reconstructive program even if in disagreement in performing multiple surgical procedures under anesthesia. Besides, nipple-areola reconstruction is associated with an high aesthetic patient's satisfaction.

When planning a nipple reconstruction, its position on the breast mound should be chosen first on the basis of the breast mound, the contralateral nipple and breast, the overall appearance and the patient desire.

During the last decades, many techniques have been described for nipple reconstruction: toe pulp graft,[1,2] nipple sharing,[3] and local flaps such modified arrow flap,[4] C-V flap,[5] star and skate flap.[6] Currently, local flaps represent the preferred reconstructive technique.

Although the reconstructed nipples have initially a good shape and projection, especially with local flap techniques, over time an important nipple projection loss occurs.[6] The explanation of the decrease in nipple projection can be found in Schwager et al's article.[20] They pointed out that normal human nipples have a dense connective tissue layer. This layer is twice as thick in normal nipples when compared to inverted nipples. Furthermore, they considered the underlying rigid connective tissue support as a very important factor for nipple projection.

To prevent the nipple projection loss, incrementing the support to reconstructed nipples, many techniques combined to local flaps have been proposed, like the transplant of autologous rib cartilage[7] or auricular cartilage,[8] fat grafting,[9] tissue engineering,[10] the use of cylinder or injection of micronized Human Acellular Dermal Matrix (ADM).[11] Drawbacks of these techniques are that the harvest of cartilage, fat or combined tissue requires increase of surgical time, the performance of surgery in different body areas and further scars.[7,8] When using human acellular dermal matrix, it is even described the possibility of extrusion.[11]

Recently, the use of permanent injectable fillers has been proposed to increase projection of flattened reconstructed nipples as an alternative of repetitive surgeries. In particular, Evans

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experimented the use of calcium hydroxyapatite (Radiesse, Bioform Inc., Franksville, WI)[12] and Panattiere proposed the use of hydroxyethylmetacrylate and ethylmetacrylate in a hyaluronic acid suspension (Dermalive™, Dermatech, Paris, France)[13] in selected breast reconstruction patients.

In the present study, we tested the use of injectable poly-lactic acid (PLLA) (Sculptra®, Sanofi Aventis, Paris, Europe), an absorbable filler, to realize a rigid support and improve projection of flattened reconstructed nipples.

Materials and methods

Between September 2005 and January 2009, 12 patients were enrolled and followed up in a prospective study at the Department of Plastic and Reconstructive Surgery of the University Hospital Policlinico Umberto I of Rome. Patients' age ranged from 29 to 45 years old. These patients previously performed monolateral mastectomy and submuscular implant breast reconstruction, followed by nipple restoration. The oncological follow up showed nor local neither distant metastasis, and negative tumor markers over a 3 years follow up.

Two patients underwent nipple reconstruction using contralateral nipple graft[3] and 10 using the star flap.[14]

All patients presented, between 1 and 2 years after nipple reconstruction, an important decrease in nipple projection varying from 65% to 80% (Table 1) and desired an improvement of it. Also, they refused any further surgical procedure. In the two patients reconstructed with contralateral nipple graft, nipple projection was 0.1 and 0.6 mm respectively, whist it ranged from 0.5 to 2 mm in those patients reconstructed with the local flap.

Patient were informed about the use and indications of PLLA, were asked to participate to the study and fully consented to it by signing a proper consent form.

Product characteristics

PLLA is a synthetic, biodegradable polymer widely used in different medical means, such as bone implants, sutures and soft tissue implants and as drug vector. Injectable PLLA have been undertaken to clinical study to assess its safety regarding sensibilization, genotoxicity and physicians' and patients' satisfaction. Two open-label multicenter clinical studies were performed, proving its efficacy in the improvement of facial vertical wrinkles in aged people and facial wasting in HIV patients.[15,16] These studies did not evidenced serious adverse events, confirming PLLA efficacy and safety. In August of 2004, injectable PLLA has been approved by U.S. Food and Drug Administration for restoration and correction of facial lipoatrophy. Furthermore, PLLA has been used to correct body depression (pectus excavatum), and for hand rejuvenation.[17]

PLLA is injected into the subcutaneous or deep dermal space and it is gradually metabolized by common metabolism pathway; after six months, neocollagen synthesis is observed in the injection site, together with increased number of fibrocytes and mononuclear macrophages cells.

Infiltration technique

Injections were performed every 4 weeks for four times. At each treatment session, 4 ml of sterile water was used for the dilution of PLLA 24 h before treatment. The phial was agitated by hands and then 0.5 ml of product was drawn into individual 1 ml syringes.

The product was injected into the subdermal space of the nipple using a 26 gauge needle. The depot technique was used with small bolus of product across the circular basement area of the nipple. The injection was done carefully tangentially, paying attention to pinch the nipple and to avoid the perforation of the underlying implant.

After injection, the physician massaged the area by pulling-up the nipple. The massage was continued by the patient herself at home twice a day for three weeks.

Nipple projection was measured with a caliper before each treatment session, one month after and one year after treatment end. The variation of this parameter was statistically analyzed with the Wilcoxon sum rank test.

Photographic documentation was taken in a standardized manner and nipple projection measured before each treatment session and one year after treatment end.

A visual analogue scale (VAS) was administrated to each patients to assess their satisfaction at the follow up end expressing their global judgments on nipple projection and appearance improvement from 1 (no improvement) to 10 (maximum improvement imaginable).

Results

In nipples reconstructed with local flap, the PLLA injection procedure was easier to be performed giving an immediate distension and projection increment due to the filling effect of the product. This gradually decreased in the following weeks until it took place the synthesis of new collagen. During the successive study visits, we evidenced the progressive nipple augmentation that progressively appeared of hard-elastic consistency. Also,

Table 1
Case study showing the used nipple reconstruction technique, the initial nipple projection, the projection loss before PLLA infiltration and the symmetry achieved 1 year after its infiltration.

Patient	Initial nipple projection (1 month after nipple restoration)	Nipple projection before PLLA infiltration (1–2 years after nipple restoration)	Percentage of nipple projection loss (from 1 month to 1–2 years after nipple restoration)	Nipple projection symmetry 1 year after PLLA infiltration		Nipple reconstruction technique
				reconstructed nipple	contralateral nipple	
1	4.28	1.5	65%	4	5	Star Flap
2	3	0.6	80%	2.5	5	Nipple graft
3	5.7	2	65%	4.5	5	Star Flap
4	4	1.4	65%	4	4	Star Flap
5	2	0.5	75%	4	4	Star Flap
6	5.7	2	65%	5	5	Star Flap
7	4.6	1.5	68%	4	4	Star Flap
8	0.5	0.1	80%	0.6	3	Nipple graft
9	5.88	2	66%	4.5	5	Star Flap
10	5.35	1.5	72%	4.5	5	Star Flap
11	2	0.5	80%	2	3	Star Flap
12	5.7	2	65%	4.5	4.5	Star Flap

Table 2
Nipple projection modification from baseline (t0) to one month after treatment end (t1).

t0, M[a] ± SD	t1, M ± SD[b]	*P*
1.3 ± 0.706	4.358 ± 1.428	<0.0001

[a] M, mean.
[b] SD, standard deviation.

patients noticed the progressive augmentation of nipple consistency and projection. The synthesis of new collagen was evident one month after treatment end (Table 2).

Only in two cases of nipples reconstructed using local flap, we noticed difficulties during infiltration due to the presence of fibrotic adherences. We tried to release these adherences cutting them with the needle point and then performing the product infiltration. In these cases, during the successive treatment sessions, the product injection was easier.

Also, the injection procedure was difficult in the two nipples reconstructed with contralateral grafts.

Nipples with a bigger surface (roof + floor + lateral surfaces) had the best result and the treatment was easier to be performed.

One year after treatment end, an increase of nipple projection ranging from 0.5 to 3.5 mm was obtained with an average increase of 2.3 mm. This projection increase corresponded to almost three times the initial value (282%) and this variation was statistically significant ($p < 0.0001$, Table 3).

After one year, an average projection increase of 2.65 mm was obtained in nipples reconstructed with local flaps (Figs. 1 and 2) whereas it was of 1 mm in the two nipples reconstructed with contralateral nipple graft (Figs. 3 and 4).

From one month to one year after treatment end, it was noticed a moderate decrease of nipple projection (in average of 0.7 mm) that was statistically significant ($p < 0.0001$, Table 4).

During the study period, no adverse effects were documented.

Patients' compliance was high and they were satisfied (Table 5) even when the result obtained was fair. All the patients at the end of follow up referred to agree to further PLLA infiltration in the future, if required.

Discussion

Nipple-areola restoration represents the final step of breast reconstruction after mastectomy, being the most important factor affecting patients' satisfaction after mammary reconstruction.[18]

The main problem after nipple reconstruction with different techniques is the nipple projection loss ranging from 50% to over 70%[6] and this should be born in mind when choosing the reconstructive technique and making the surgical plan.[4,19]

We found interesting the observations of Schwager et al. about nipple characteristics.[20] They pointed out that normal human nipples have a dense connective tissue layer support that is a very important factor to maintain nipple projection. This thick layer is missing in reconstructed nipples. On the basis of these observations, to realize a rigid support, we injected reconstructed nipple with PLLA, a not permanent filler able to achieve a nodular connective reaction.

Table 3
Nipple projection modification from baseline (t0) to one year after treatment end (t12).

t0, M[a] ± SD[b]	t12, M[a] ± SD[b]	*P*
1.3 ± 0.706	3.675 ± 1.298	<0.0001

[a] M, mean.
[b] SD, standard deviation.

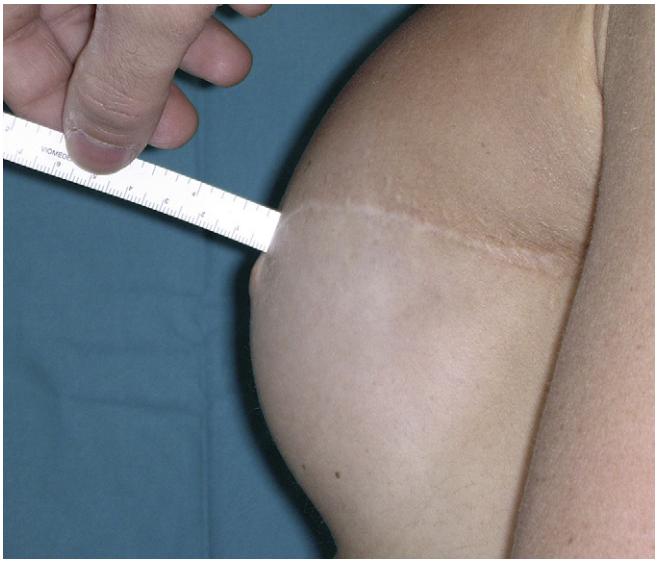

Fig. 1. Nipple reconstructed with nipple sharing before PLLA treatment.

Two other studies used fillers to increment nipple projection, one with calcium hydroxyapatite[12] and the other with metacrylates in a hyaluronic acid suspension acid.[13] These two are considered permanent fillers because are only in part absorbed, remaining in the organism.[21]

In the study of Evans et al.,[12] calcium hydroxylapatite was injected to maintain or restore nipple projection after an average of 8 months from reconstruction in six patients. No local anesthesia was required. The average follow up time was 6 months. Patient satisfaction and external observers subjective evaluation were recorded, and photographic documentation taken. In the short term, an 100% patient satisfaction was reported, with minimal loss of projection, and no complications. No objective measurements were taken during follow up. The authors stated that injectable soft tissue fillers such as calcium hydroxyapatite may be useful in selected patients as a simple solution to the difficult problem of the lack of nipple projection following reconstruction, being an effective, safe, and reliable method in the

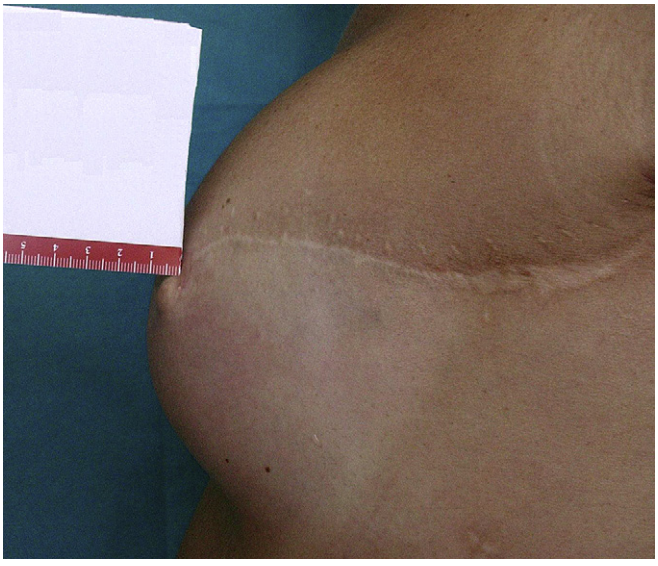

Fig. 2. Nipple reconstructed with nipple sharing one year after PLLA treatment.

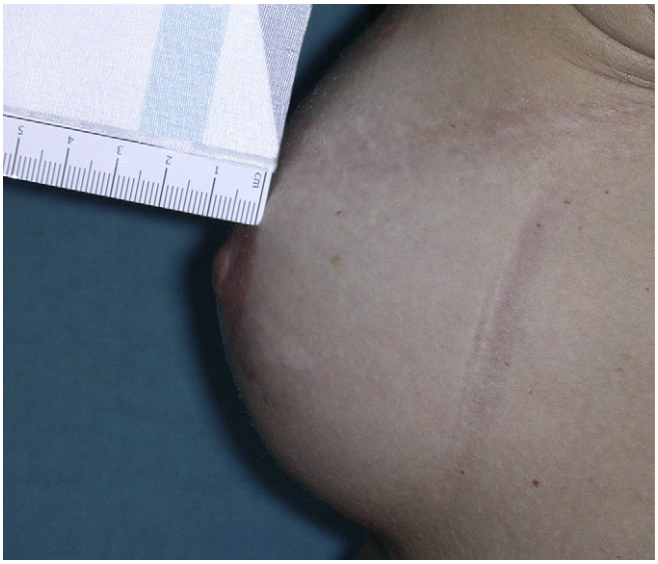

Fig. 3. Nipple reconstructed with local flap before PLLA treatment.

short term. Our concern about nipple infiltration with calcium hydroxyapatite is its radiopacity that is a theoretical interference with X-ray and mammography. Although the risk of cancer is minimal after mastectomy and reconstruction, some oncologists still mammogram the reconstructed breast and not experienced radiologists may encounter some problem in tumor differential diagnosis.

In the study of Panettiere et al.,[13] 90 reconstructed nipples were injected with hydroxyethylmetacrylate and ethylmetacrylate in a hyaluronic acid suspension two months after reconstruction in 70 patients. When necessary, a second nipple injection was performed 2 months afterward, followed by a third injection 3 months later. Nipple projection was measured during a 6–12 months follow up. Nipple projection was satisfactory in all cases with low projection loss and comparable with that of the contralateral nipple. No complications occurred, except for one positron emission tomography (PET) false-positive result. The authors stated that the described method is simple and safe. It provides precise projection

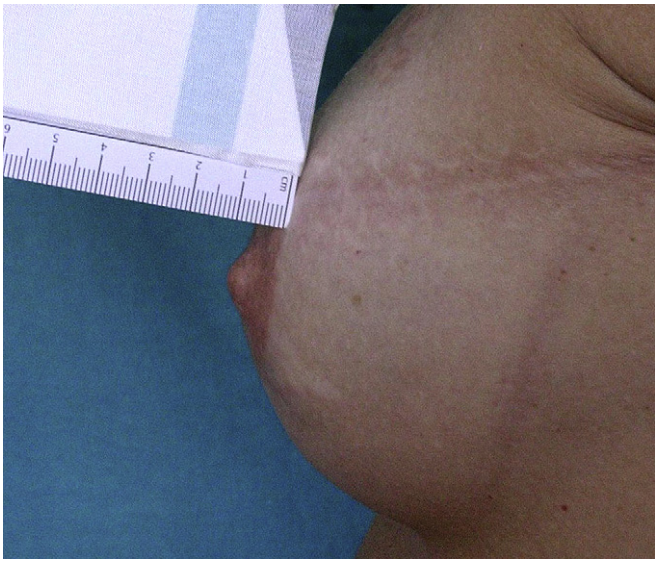

Fig. 4. Nipple reconstructed with local flap one year after PLLA treatment.

Table 4
Nipple projection modification from one month after treatment end (t1) to one year after treatment end (t12).

t1, M[a] ± SD[b]	t12, M[a] ± SD[b]	*P*
4.358 ± 1.428	3.675 ± 1.298	<0.0001

[a] M, mean.
[b] SD, standard deviation.

with no need for intraoperative forecasting of tissue reabsorption. Our concern about nipple infiltration with metacrylates is the possible foreign body reaction in the medium/long term follow up as described for this type of filler.[22]

In our study, the results showed an increase of nipple projection between 0.5 and 3.5 mm with the achievement of good aesthetic results (Figs. 1–4) and symmetry with the contralateral nipple during the study period (Table 1). We also notice that the best results were obtained in nipple reconstructed with local flap. This outcome can be explained by the fact that the regenerative action of PLLA is achieved by an inflammatory reaction in the deep dermis and subcutaneous tissue that needs the activation of fibroblasts. Where there is a bigger quantity of tissue there are more fibroblasts and so we can obtain a better projection improvement. Gokolewsky biopsies at 1, 3 and 6 months after PLLA injection showed that there is a progressive reabsorption of PLLA and its substitutions with inflammatory reaction that develop into synthesis of neocollagen and augmentation of fibroblasts.[23]

In our experience, PLLA is able to reduce subcutaneous adherences making easier successive infiltrations. The best results are obtained in those nipples without any adherence; in fact, in these cases there is an homogeneous distribution of the product and uniform growth in eight. Furthermore, this procedure is easy to be performed, reproducible and no time consuming; it is a minimally invasive treatment which provides good and lasting results, it is well tolerated by patients, avoiding any kind of anesthesia and invasive surgical procedure. All the patients at the end of follow up were satisfied with the results obtained (Table 5) and were in favour to repeat in the future PLLA infiltration, if required. We explain the positive patients' compliance with PLLA infiltration, because it seemed to us that they experienced this procedure as a cosmetic treatment and not as a invasive one. We consider this as an important factor for the patient psychological status, already proved by the disease and the successive long reconstructive program.

Drawback of this procedure is that the effect of the product is not permanent and it requires recall session overtime.[24] But at the same time, the fact that PLLA is completely absorbed with time eliminate the risk of complications of permanent fillers such prolonged foreign body reactions, migration of the product and extrusion.[21,22] Another disadvantage is the relatively high cost of the product (around 210 euro for each phial). But, it should be considered as a reconstructive option requiring only one operator for a short time, thus limiting expenses. For these reasons, this treatment should be offered to this category of patients by the national health system.

Table 5
Self assessment visual analogic scale of patients expressing their global judgments on nipple projection and appearance improvement one year after treatment end from 1 (no improvement) to 10 (maximum improvement imaginable).

VAS value	1	2	3	4	5	6	7	8	9	10
Patients' judgment					1	1	4	4	2	

Conclusions

The use of PLLA injection is an effective method to improve projection of reconstructed nipple after mastectomy, easy to be performed, reproducible, not invasive, not requiring local anesthesia and long-lasting. The best results can be obtained in nipple reconstructed with local flap, with a bigger total surface and having less adherences. First PLLA injection makes easier the successive injections in adherent tissues. The patients undergo to treatment with pleasure and remain satisfied from it even if results are fair.

Conflict of interest statement

All the authors disclose any financial and personal relationships with other people or organisation that could influence this work.

Anyone has received any equipment, materials or medications for this study, any funding to support our research for this article, we were not provided with any honoraria, payment or other compensation for work on this study. We didn't received any stock ownership or other valuable materials in conjunction with this study. We didn't received any financial support for travel or lectures to present the information covered in this study, we don't have any financial relationship with any entity, which may closely compete with the medications, materials or instruments covered by our study.

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