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Optimized Calcium Hydroxylapatite Formulation and Its Injection Technique for Hand Rejuvenation: A Retrospective Study

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ABSTRACT

Introduction: Hand rejuvenation treatment is in high demand in cosmetic medicine. Radiesse®, a commercially available formulation of calcium hydroxylapatite (CaHA), is safe, biocompatible, and provides long-lasting results.

Objective: The study aimed to retrospectively evaluate the efficacy and safety of the presented formulation of Radiesse® and its injection procedure.

Methods: The hands of 58 women were treated employing Radiesse® diluted with lidocaine. The treatment was performed using a blunt cannula following the proximal-to-distal fanning technique at two entry points on the dorsum of the hands. The patients received 1–4 treatments over a follow-up period of up to five years.

Results: The hands of 58 females were evaluated using the Merz Hand Grading Scale (MHGS) and treated with the presented CaHA formulation. After the first treatment, 55 patients (94.8%) achieved a 1-point improvement, and 19 patients (32.8%) did not receive further treatment, being satisfied with the results. The remaining 39 women (67.2%) received 2–4 follow-up treatments. At the end of the treatment(s), 46 women (79%) achieved a final improvement of one point, and 12 women (21%) a final improvement of two points. Three minor adverse events were registered.

Conclusions: Radiesse® diluted with lidocaine is an excellent choice for hand rejuvenation. The formulation and technique proved to be safe and efficient. In our experience, a blunt cannula should be employed for optimal vein correction. The treatment was highly satisfying, although planning a second treatment during the 1-month follow-up visit is recommended to best achieve long-lasting results.

Introduction

The hands, face, and neck display the body's aging process most prominently. For women in particular, the appearance of the dorsum of the hands is as relevant as the appearance of the face [1,2]. While face rejuvenation has been performed widely in recent decades, hand rejuvenation has only recently become more practiced in cosmetic medicine [3,4]. Several reasons have contributed to the increase in interest, first of all, the need to reduce the gap between a youthful face and an aging hand. Moreover, as the use of face masks became routine during and after the COVID-19 pandemic, hands have become the first visible indication of the aging body [2,3].

Aging of the hands consists in the progressive atrophy of subcutaneous muscles and loss of subcutaneous fat, resulting in deepened intermetacarpal spaces and protruding bones, tendons, and veins on the dorsum of the hand [5,6]. High exposure to ultraviolet (UV) light contributes to capillary fragility and changes in cutaneous pigmentation. Furthermore, the reduction in collagen and connective tissue causes a thinning of the dermis, which also loses elasticity [7]. Protruding veins and tendons are the most relevant alterations affecting the hands' visual appeal. Hand rejuvenation procedures aim to regain the lost volume of the dorsal hand to obtain a smoother contour [8].

Understanding the anatomy of the subdermal space of the dorsum of the hands is extremely important to select the safest and most efficient procedure [9]. The dorsum of the hand is characterized by the presence of three laminae of fat, separated by fascial layers. The dorsal superficial lamina (DSL) is the first between the skin and the dorsal superficial fascia (DSF) and does not contain essential structures [8]. The second fatty layer is the dorsal intermediate lamina (DIL), between the DSF and dorsal intermediate fascia (DIF). This lamina comprises two compartments, containing the dorsal venous plexus above and the dorsal cutaneous nerves below, separated by the subvenous fascia [5]. The deepest fat layer, the dorsal deep lamina (DDL), contains the extensor tendons and is located between the DIF and dorsal deep fascia (DDF) [8]. The fat loss in the aging hand results in a loss of thickness of the three fatty laminae, mainly in the DIL, leading to adherence between the DSF and the dermis, exposing veins and tendons. Due to these characteristics, the DSL and the DIL are the most targeted space for hand augmentation procedures [2].

Various techniques have been proposed over the years, which can be categorized into two groups: surgical and non-surgical. Autologous fat transfer is the surgical option of choice, in combination with laser or chemical treatments of the epidermis [10]. Non-surgical techniques include subcutaneous filler injections. Several options of synthetic biomaterials are available, although the most frequent fillers are hyaluronic acid (HA), poly-L-lactic acid (PLLA), and calcium hydroxylapatite (CaHA) [6,11].

CaHA is biodegradable and gets reabsorbed naturally by the host, guaranteeing a safe and minimally invasive approach. CaHA shows more efficiency and longer-lasting results than fat grafting and HA fillers [12,13]. Radiesse® (Merz, Frankfurt, Germany), a commercially available formulation of CaHA, was the first filler approved by the FDA in 2015 for hand volumizing procedures and received the *Conformité Européenne* (CE) certification mark for use in Europe [14,15].

Objectives

The objective of this study was to retrospectively analyze the results obtained over a period of up to five years for 58 women treated at the dorsum of the hands with Radiesse® diluted with 2 mg/ml lidocaine, using a blunt cannula and following the proximal-to-distal fanning technique [9], where each hand was injected at two entry points. We share our recommendations regarding hand augmentation using CaHA formulation and its injection technique.

Methods

Selection of Patients and Grading of Hands

A total of 58 females (mean age 63 years, range 53-79 years) underwent hand rejuvenation procedure(s). The hands were evaluated according to the Merz Hand Grading Scale (MHGS), with scores from 4 (severe loss of fatty tissue and pronounced visibility of veins and tendons) to 1 (mild loss of fatty tissue and subtle presence of veins and tendons), as shown by Cohen et al., 2015 [16].

The patients were treated at our clinic in Rome, Italy, between 2011 and 2023. All patients provided their informed consent and agreed on the use of the images for publication purposes.

Preparation of the CaHA Filler Mixture

Radiesse® is a filler composed of smooth regular synthetic microspheres (diameter of 25–45 µm) consisting of 30% calcium hydroxylapatite suspended in a gel of glycerin and carboxymethylcellulose [12]. The use of Radiesse® for hand volumizing treatments and the practice of mixing CaHA with lidocaine for pain reduction were approved by the FDA [14,15]. The filler mixture for two hands was prepared by diluting 1.5 ml Radiesse® with 0.4 ml lidocaine 2%, 0.1 ml epinephrine, and 2 ml saline solution. The syringe containing Radiesse® was emptied into a 5 ml syringe containing the saline-lidocaine-epinephrine solution using a sterile

female-to-female Luer Lock connector. The final volume of 4 ml was sufficient to inject a 2 ml filler mixture in each hand (Supplementary File Video S1).

Injection Technique

The injection of the CaHA filler mixture was performed following the proximal-to-distal fanning technique [9], and the injection was performed at two entry points at the dorsum of the hand. The first entry point was located at the middle of the proximal transverse dorsal wrist crease, while the second entry point was in the center of the dorsum of the hand, 4 cm distal to the first entry point. Each hand was cleaned using chlorhexidine before the procedure, and a puncture of lidocaine 2% with epinephrine was performed with a needle at the two entry points to reduce bruising and pain from cannula insertion. CaHA filler solution, 1 ml, was injected in each entry point using a 25 g × 6 cm blunt cannula for a total of 2 ml of filler mixture in each hand. The filler solution was slowly injected in the subdermal plan and distributed in the DSL, starting above the veins to reduce their visibility and then distributing on the whole dorsum of the hand [14]. After the product was spread from both entry points, the hand was massaged thoroughly with an antibiotic cream (gentamicin) to evenly distribute the filler and ensure a smooth contour of the dorsum (Supplementary File Video S1).

Follow-up Evaluations and Treatments

All patients received a follow-up evaluation within two months of the first injection. The hands were graded according to the MHGS [16], and photographic documentation was collected. Based on the procedure's success and the patients' satisfaction, follow-up treatments were planned and performed using the filler mixture preparation and technique previously described. The patients were evaluated for up to five years and received between one and four total treatment(s). Adverse events were assessed immediately after the procedure and at each follow-up by checking the condition of the patients and the status of the hands.

Statistical Analysis

The Wilcoxon matched-pairs signed-ranks test was performed to evaluate the improvement level of the hand grading after each treatment.

Results

Efficiency of the First Treatment

Following the initial evaluation, the hands of 58 women received a mean MHGS score of 3.3. After the first treatment, the status of the patients' hands was evaluated during a follow-up visit within two months. The mean MHGS score after treatment improved by one point (2.4). Statistical analysis showed a significant difference between the hands' grading pre- and post-treatment. In general, 94.8% of the women (55) achieved a 1-point improvement after the first treatment (Table 1). Of the 58 women, 19 (32.8%) did not receive further treatments and considered themselves satisfied with one injection of Radiesse® (Table 2). These data show that only one treatment with the presented CaHA formulation allowed for significant volume restoration (Figure 1).

Importance of the Second Treatment

After the first treatment, 39 women (67.2%) received a second treatment. The mean MHGS score before the second treatment was 3.4. At the follow-up visit, all women improved by one point. Statistical analysis showed a significant difference between the hands' grading pre- and post-treatment (Table 1).

Interestingly, even though the follow-up visit was performed within two months from the first treatment, only five women received the second treatment within this time frame. Most patients (66.6%) received the second treatment after one year (Table 3), proving the high efficiency and long-lasting results of CaHA.

Of the 58 women, 14 (24.1%) received a total of two treatments, with 13 women achieving a final improvement of one point and one patient reaching a 2-point final improvement (Table 2). These data suggest that a second treatment is essential to increase and maintain the achieved hand augmentation (Figure 2A).

Third and Fourth Follow-Up Treatments

After the evaluation of the hands, 25 patients (43.1% of the total number of patients) received a third treatment, with the majority of women (64%) receiving the treatment two years after the first injection (Table 3). After the third procedure, the mean MHGS score decreased from 3.0 to 2.1, with 88% of the women reaching a 1-point improvement. Statistical analysis showed a significant difference between the hands' grading pre- and post-treatment (Table 1). Of all the 58 women, 11 (19%) received a maximum of three treatments, with four patients achieving a final improvement of two points (Table 2, Figure 2B).

Over a 5-year period, 14 women (24.1% of the total number of patients) received a fourth treatment, with the majority of women (11, 78.6%) receiving the injection between the third and fifth year (Table 3). The fourth treatment registered an improvement in the mean MHGS score, from 2.7 to 2.0, with a total of 10 patients (71.4%) achieving a 1-point improvement. Statistical analysis showed a significant difference between the hands' grading pre- and post-treatment (Table 1).

Of all 58 women, 14 (24.1%) received four treatments, with seven women achieving a general improvement of

Table 1. Outcome of Patients Treated for Hand Rejuvenation.

	1st Treatment		2nd Treatment		3rd Treatment		4th Treatment	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
No. patients (%)	58 (100)		39 (67.2)		25 (64.1)		14 (56)	
Mean grade (SD)	3.3 (0.48)	2.4 (0.53)	3.4 (0.55)	2.4 (0.55)	3.0 (0.49)	2.1 (0.53)	2.7 (0.47)	2.0 (0.39)
Median	3	2	3	2	3	2	3	2
P-value	$^{**}P<0.001$		$^{**}P<0.001$		$^{**}P<0.001$		$^{*}P<0.002$	
Max grade	4	4	4	3	4	3	3	3
Min grade	3	2	2	1	2	1	2	1
No. patients (%) with grade 4	20 (34.5)	1 (1.7)	17 (43.6)	0	4 (16)	0	0	0
No. patients (%) with grade 3	38 (65.5)	21 (36.2)	21 (53.8)	17 (43.6)	17 (68)	5 (20)	10 (71.4)	1 (7.1)
No. patients (%) with grade 2	0	36 (62.1)	1 (2.6)	21 (53.8)	4 (16)	18 (72)	4 (28.6)	12 (85.7)
No. patients (%) with grade 1	0	0	0	1 (2.6)	0	2 (8)	0	1 (7.1)
No. patients (%) with improvement after treatment	55 (94.8)		39 (100)		22 (88)		10 (71.4)	

The hands were graded following the Merz Hand Grading Scale (MHGS), with scores from 4 (very low) to 1 (very good). Hands were graded before each treatment (Pre) and at the follow-up visit after each treatment (Post). *P*-values were calculated using Wilcoxon matched-pairs signed-ranks test, $^{**}P<0.001$, $^{*}P<0.002$.

Table 2. Patients' Improvement Relative to the Total Number of Treatments.

	No. Patients (%)	Final Improvement of 1 Point	Final Improvement of 2 Points
General improvement	58 (100)	46	12
1 treatment	19 (32.8)	19	0
2 treatments	14 (24.1)	13	1
3 treatments	11 (19)	7	4
4 treatments	14 (24.1)	7	7

The hands were graded following the Merz Hand Grading Scale (MHGS), with scores from 4 (very low) to 1 (very good). The final improvement was evaluated by considering the scores before the first treatment and at the follow-up visit after the final treatment for each patient.

one point and another seven women achieving a general improvement of two points (Table 2).

Adverse Events

Only three adverse events (AEs) were registered. One case consisted of a subcutaneous bump around the cannula insertion point, which resolved spontaneously within 30 days. Two cases of persistent edema also occurred, which lasted four days and resolved with a short-term oral corticosteroid therapy [17] of 2 mg of betamethasone for two days and 1 mg for one day, prescribed according to our experience, following the national guidelines (AIFA, Italian Medicines Agency). These data indicate that the hand rejuvenation procedure used in this study is safe.

To sum up, 32.8% of the patients (19 women) were satisfied after one treatment, achieving a 1-point improvement in their hands' grading (Table 1, Figure 1); 14 women (24.1%) received a total of two treatments, and another 14 women received a maximum of four treatments, while 11 patients (19%) received three treatments (Table 2). The follow-up treatments were, on average, performed more than one year after the previous procedure (Table 3, Figure 2). At the end of all treatment(s), 79% of the women (46) registered a final 1-point improvement compared to their initial MHGS score, while 21% of the women (12) achieved a final improvement of 2 points compared to their initial MHGS score (Table 2).

These data confirm and underline the high effectiveness and long-lasting results of CaHA in hand augmentation and

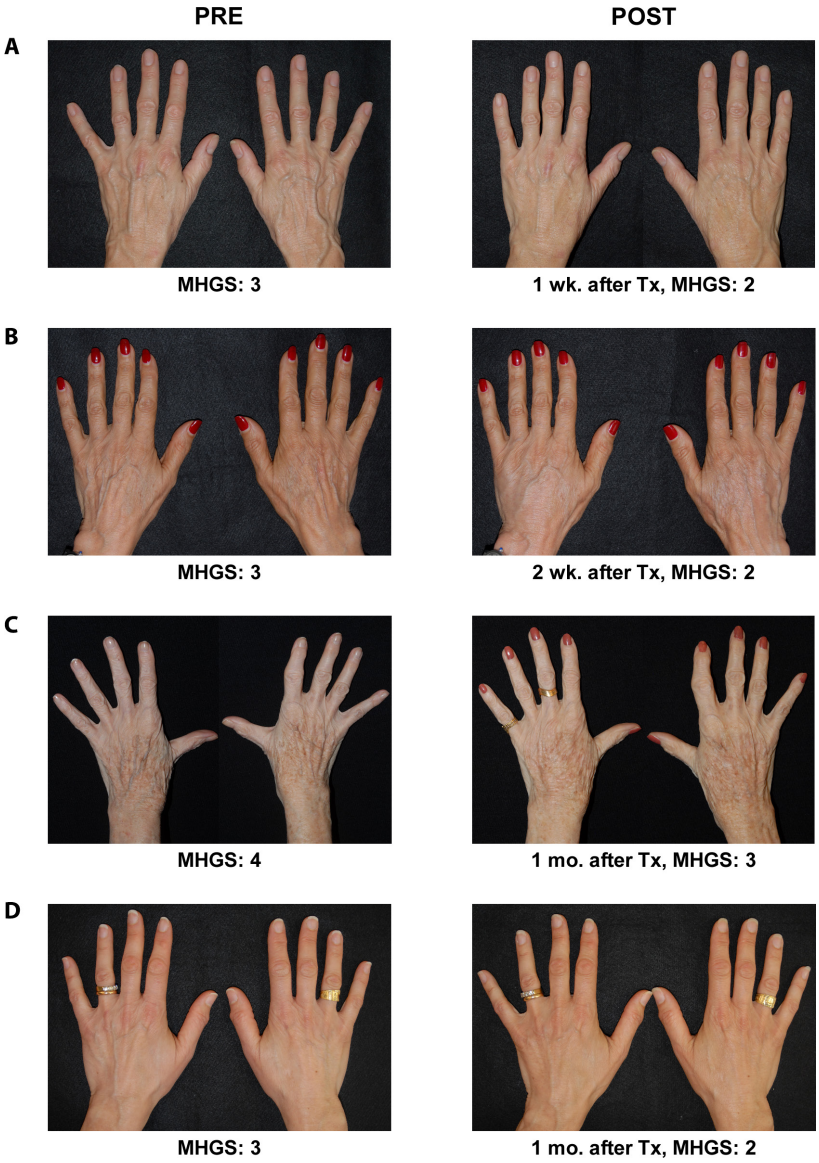

Figure 1. Appearance of the dorsum of the hands after one CaHA treatment. Hands belong to (A) a 64-year-old woman, (B) a 66-year-old woman, (C) a 79-year-old woman, and (D) a 58-year-old woman. Grading of the hands before and after treatment is indicated below each picture according to the Merz Hand Grading Scale (MHGS). PRE, hands before the CaHA treatment; POST, hands after treatment; wk., week(s); mo., month(s); Tx, treatment.

Table 3. Time Frames during which Patients Received Follow-Up Treatments.

	2nd Treatment	3rd Treatment	4th Treatment
Total no. of patients	39	25	14
0-2 months	5	0	0
2 months-1 year	8	0	0
1-2 years	23	9	0
2-3 years	3	12	3
3-4 years	0	4	8
4-5 years	0	0	3

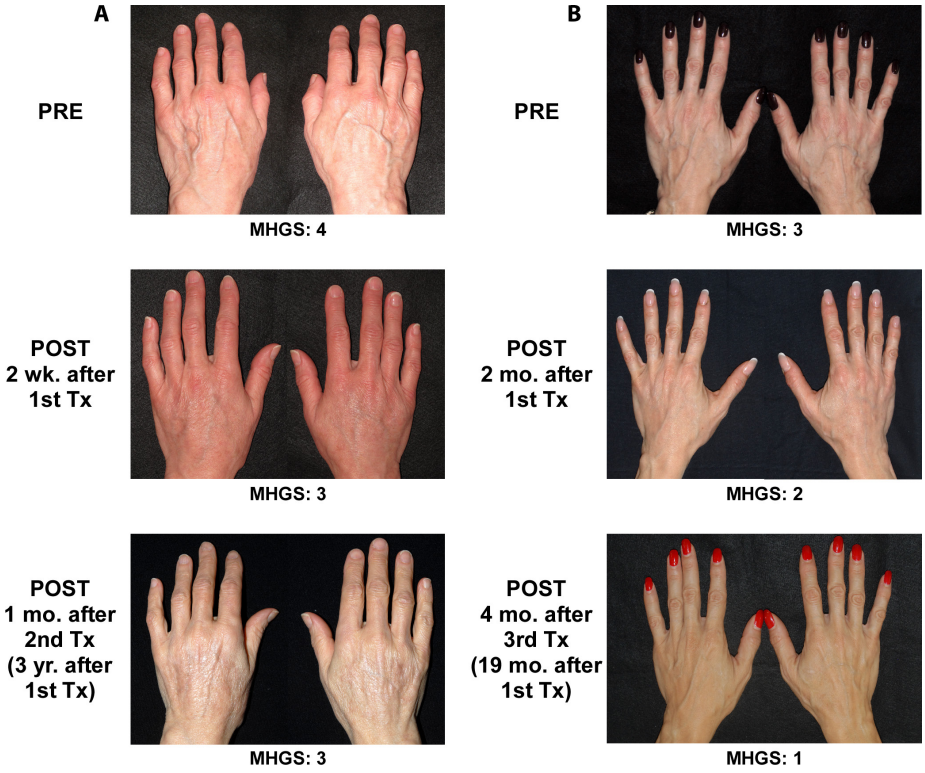

Figure 2. Appearance of the dorsum of the hands after repeated CaHA treatments. The hands belong to (A) a 62-year-old woman and (B) a 53-year-old woman. Grading of the hands before and after treatments is indicated below each picture according to the Merz Hand Grading Scale (MHGS). PRE, hands before the CaHA treatment; POST, hands after treatment; wk., week(s); mo., month(s); yr., year(s); Tx, treatment.

indicate that the formulation and technique implemented in this study offer significant benefits for hand rejuvenation.

Discussion

Hand rejuvenation is a relatively new treatment in cosmetic surgery. Several approaches are available and most aim to regenerate the skin texture and pigmentation [3]. However, as the hands age, loss of subdermal fat and collagen organization result in an excavated appearance of the dorsum of the hand, with protuberant veins and tendons, making volume restoration an increasingly demanded procedure [2]. In the last two decades, injection of soft tissue fillers has become the procedure of choice, primarily due to its non-surgical nature and a significant reduction in side effects compared to the more invasive autologous fat grafting [3]. Different filler types and injection techniques have been investigated and applied over the years, with poly-L-lactic acid (PLLA), hyaluronic acid (HA), and (CaHA) being the most popular [18].

In our experience, among the different fillers, CaHA has given the most satisfying results in hand rejuvenation and corrections of vein visibility and prominence. In a comparison study for the treatment of nasolabial folds, patients treated with CaHA showed a higher level of satisfaction compared to patients treated with HA [13]. CaHA causes no severe AEs, in contrast with other treatments like PLLA which carries a high risk of nodule formations [19,20].

Following years of off-label use, Radiesse®, a commercial formulation of CaHA, obtained FDA approval for hand rejuvenation treatments in 2015, making CaHA the first filler to be authorized for hand augmentation [14].

The composition and mechanism of action of Radiesse® makes it an excellent choice for hand rejuvenation. It is 100% biocompatible and composed of calcium and phosphate, which are already present in the epidermis. Furthermore, CaHA is also found in bones [21]. The carboxymethylcellulose (CMC) carrier gel provides a prompt filling effect, giving immediate augmentation results. As the CMC gel is reabsorbed by macrophages within a few weeks from injection, the CaHA microspheres are released and, by stimulating fibroblast activity, they boost the synthesis of collagen type I fibers, providing volume at the dorsum of the hand [15,22]. This results in longer-lasting effects compared to PLLA and HA, with an average longevity of 12-18 months, and reports of up to two years post-injection [15]. Polycaprolactone (PCL), a newer filler, is reported to have similar lasting results, pending confirmation from more extended follow-up studies [23].

The current retrospective study analyzed the results obtained for 58 women treated on both hands with Radiesse®. The number of patients included in the study is higher than the average sample size of similar studies in the literature. Moreover, the current study offers a significant long-term evaluation, compared to similar trials [1]. One study in particular included a larger sample size (114 patients), however, over a follow-up period of 12 months [24]. In line with the reported cases in the literature, we observe long-lasting results over a follow-up period of up to five years. At the end of all treatment(s), all women reported improvement of 1–2 points of the MHGS. One-third of the women were satisfied after one treatment. Thirty-nine women received two or more treatments (with a maximum of four). Follow-up treatments were performed, based on the evaluation of the hands during the follow-up visits and on the patients' satisfaction level. Even though the follow-up visits were performed within two months of each procedure, most women received the follow-up treatments one year after the previous procedure, as they reported a high level of satisfaction. Even if 11 women received a total of three treatments and 14 women underwent a fourth treatment, it is important to consider that all of these patients had already achieved improvements in the hands' grading after the first and second treatment. This consideration suggests that the third and fourth treatments are mainly performed to maintain the results, following the patients' satisfaction. Considering our results, a second treatment is therefore strongly recommended to maximize hand augmentation, guaranteeing longer-lasting effects.

The method of manually mixing Radiesse® with a lidocaine solution prior to injection was approved by the FDA in 2009 and is well documented to significantly reduce pain during treatment [15,25]. The formulation used in the current study proved to be optimal, as it allowed for balancing best results, pain relief, and limited bruises. Dilution of Radiesse® with lidocaine solution is also essential for reaching the perfect viscosity and elasticity level, which are higher than other dermal fillers. In literature, several dilutions of CaHA have been described for the treatment of the dorsum of the hand, ranging from 2:1 to 1:5; however, the general recommendation is not to dilute less than 1:1 [12,26]. Obtaining the optimal level of viscosity and elasticity is essential to ensure that the product remains in its injected area, without spreading to other tissues and without deforming under the pressure of hands' movement [27].

Considering these properties, the choice of the technique and site of injection is therefore critical to minimize AEs and to obtain optimal results. The approach adopted in this study was the proximal-to-distal fanning injection technique, using a 25 g × 6 cm blunt cannula [9]. However, in our experience, the dermal filler injection should be performed at two entry points in the subdermal plane, in the DSL, between the DSF and the DIF.

In our experience, placing the filler in the subdermal plane is crucial as it allows an optimal correction of the veins, minimizes the risk of AEs, and drastically reduces pain, as this layer does not contain any relevant structure, such as veins or tendons [9,14]. In fact, the blunt cannula can easily reach the entire dorsum of the hand from the two entry points, optimizing the spread of the filler in a uniform manner and reaching all the necessary areas without applying pressure. Indeed, in the current study, out of 58 women, only three minor side effects were reported. Two women reported persistent edema, and only one showed subcutaneous bumps around the cannula insertion point. In all cases, the adverse effects were only temporary and resolved quickly.

Limitations

This study presents a few limitations. The absence of a control group limits the study's ability to compare outcomes with a baseline or alternative treatment. However, this is an observational real-life study of patients who have visited our clinic. The retrospective nature of the study and its being conducted in a single clinic carry limitations such as a selection bias. However, the aim of the study was to provide valuable preliminary insights, sharing our recommendations, which should be validated and expanded upon in future research.

Conclusions

CaHA proved to be an efficient and long-lasting filler. Our recommendation is to use the following formulation for hand augmentation: 1.5 ml Radiesse® diluted with 0.4 ml lidocaine 2%, 0.1 ml epinephrine, and 2 ml saline solution. Moreover, our recommendation is to perform a follow-up visit one month after treatment to evaluate the conditions of the hands and to plan a second treatment, as, in our experience, the second treatment is essential to guarantee long-lasting and impactful effects.

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