doi.org/10.36721/PJPS.2025.38.5.REG.14005.1

Exploring the synergistic effects of poly-l-lactic acid (Sculptra®) and retinoic acid (tretinoin) in facial rejuvenation treatment for age-related skin laxity

Kuo-Liang Liao and Kuo-Hsiang Liao*
Sin-An Cosmetic Clinic, Taipei, China

Abstract: To investigate the synergistic effects of Poly-L-Lactic Acid (PLLA) and Retinoic Acid (RA) on age-related skin relaxation in the treatment of facial rejuvenation. 120 patients received facial rejuvenation treatment at Sin-An Cosmetic Clinic Hospital from April 2022 to August 2023 were divided into control group (n=42) and observation group (n=78). Both groups were treated with RA and observation group was added with PLLA. The outer corner wrinkles and lower eyelid wrinkles, nasolabial wrinkles, self-perception ratings of skin effects and adverse reactions incidence were compared between both groups. After treatment, the total improvement rates of outer eye corners, lower eyelid wrinkles and nasolabial folds, the improvement rate of the overall aesthetics of the mid-face, the scores of skin elasticity, water content, skin colour, pores and other skin conditions of the observation group were significantly higher than the control group and the scores of oil secretion and dark spots were significantly lower than the control group ($P<0.05$). The incidence of adverse reactions in the observation group was lower than the control group, but the difference was not significant ($P>0.05$). Combined treatment can improve patients' skin condition and promote facial rejuvenation, which has high clinical application value.

Keywords: Poly-L-lactic acid, retinoic acid, facial rejuvenation, skin laxity

Submitted on 14-06-2024 – Revised on 20-05-2025– Accepted on 13-06-2025

INTRODUCTION

Facial rejuvenation treatment has always been an important topic in the field of medical cosmetology, especially in the aging trend of the population today, this topic is particularly urgent (Urdiales-Gálvez *et al*., 2023).With age, the skin will undergo a variety of morphological and histological changes, including skin relaxation, wrinkle formation, decreased elasticity and pigmentation (*Griffiths et al*., *2023*). These changes not only affect the physical appearance of the individual, but also often bring psychological and emotional distress. Therefore, the exploration and development of effective facial rejuvenation treatment has important clinical significance and social value.

The aging process of skin is a complex biological process involving the interaction of many factors (*Ziai & Wright, 2022*).Among them, the accumulation of glycosylation products (AGEs) is an important factor leading to skin sclerosis. AGEs will gradually accumulate in the skin with age, causing the skin to harden and lose elasticity, affecting the activity of fibroblasts and collagen synthesis and increasing the oxidative stress of the skin (Nie *et al*., 2022). In addition, the decline of mitochondrial function and the increase of matrix metalloproteinases are also important mechanisms of skin aging (*Fisher et al*., *2024*).Therefore, effective facial rejuvenation treatment not only needs to intervene against these mechanisms, but also needs to comprehensively improve the overall state of the skin through a variety of ways. In medical beauty projects, there are more and more means to promote collagen regeneration or remodeling through different mechanisms to improve skin firmness, among which Poly-L-Lactic Acid (PLLA) and Retinoic Acid (RA) are two effective anti-aging ingredients. In recent years, the treatment of facial rejuvenation has been widely concerned and studied (Fisher *et al*., 2024; Milosheska & Roškar, 2022).

PLLA, one of the main components of Sculptra, is a biodegradable and biosoluble synthetic polymer derived from the alpha-hydroxy acid family (McCarthy *et al*., 2024).After PLLA is injected into the skin, it can induce fibroblasts to produce an immune response and promote the synthesis and secretion of collagen, thereby improving the texture and appearance of the skin (Dong *et al*., 2024). Multiple studies have shown that PLLA injections can significantly improve facial wrinkles and skin sagging and is a safe and effective facial rejuvenation treatment (Christen, 2022). RA is a derivative of vitamin A and is widely used in the field of dermatology and cosmetology. As the gold standard anti-aging drug, it mainly improves skin elasticity and texture by penetrating into the inner layer of the skin and promoting the production of collagen fibers and elastic fibers (Y. Wu *et al*., 2022). However, the use of RA is also accompanied by certain irritants and some patients are poorly tolerated, limiting its wide application (Althwanay *et al*., 2024).

**Corresponding author:* e-mail: joseph28375@hotmail.com

Facial rejuvenation treatment is a complex problem involving multiple disciplines, which requires comprehensive consideration of skin physiology, molecular biology, materials science and aesthetic medicine (Contini *et al*., 2023). PLLA and RA are two potential facial rejuvenation treatments and their combined application may bring new treatment strategies and clinical effects. However, there is a paucity of research on the combined use of the two. Previous studies have focused on monotherapy or the combination of other facial rejuvenation tools, but systematic investigations combining PLLA and RA are rare. The novelty of this study lies in the fact that it is the first controlled clinical trial to explore the synergistic effect of these two components in facial rejuvenation treatment for age-related skin laxity. This innovative attempt is expected to break through the limitations of traditional monotherapy and open up new treatment strategies. Through rigorous trial design and collection of systematic clinical data, it will provide a solid scientific basis for clinical application, fill the research gap in this field and bring a new development direction for facial rejuvenation treatment.

MATERIALS AND METHODS

General information

Participants

A total of 120 patients who received facial rejuvenation treatment in Sin-An Cosmetic Clinic Hospital from April 2022 to August 2023 were included and divided into control group (n=42) and observation group (n=78) according to different treatment plans. Among them, the control group: 3 males, 39 females; The average age was (51.22±5.39) years, ranging from 46 to 58 years. Observation group: 5 males and 73 females; The average age was (53.06±5.21) years, ranging from 47 to 59 years. There was no significant difference in gender, age and other baseline data between the two groups, that is, they were comparable.

Inclusion criteria

- Meet the needs of facial rejuvenation, such as loose skin, more wrinkles, facial depression and other features, GSP score≥33 point.
- Age 45-60 years old.
- Informed and consented to this study.

Exclusion criteria

- History of allergy to the ingredients of the drug used in this study.
- Acne, eczema and other skin diseases.
- Recent (within six months) experience in facial beauty treatment, such as plastic surgery, laser treatment, chemical peels, etc.
- Obvious scar or scar constitution.
- Impaired skin barrier or sensitive skin.
- Pregnant or lactating women.

Method

- **Control group**: Before using RA, patients need to prepare their skin, such as cleaning their skin and avoiding the use of other irritating cosmetics. Early low concentration (0.025%) to establish tolerance, 2 times/week, applied to the face, the cycle of about 1 month. Later, replace the normal concentration (0.05% or 0.1%), apply every day or every other day and apply to the face for about 5 months. The total treatment period was 6 months. The dosage of RA is strictly in accordance with the instructions. The same concentration of RA for all patients is produced by the same manufacturer. RA: National Drug Code H31020126, Manufacturer: Shanghai Xinyi Yan'an Pharmaceutical Co. Ltd. Specification: 10g:2.5mg (0.025% concentration), 10g:5mg (0.05% concentration), 20g:20mg (0.1% concentration).

- **Observation group**: PLLA injection treatment was performed on the basis of the control group (injection was performed after RA tolerance period was established) : after ensuring the injection environment was clean and sterile; PLLA powder was prepared into a uniform suspension using 5 mL sterile water for injection and 18 G sterile needle and was left for 2 h to ensure that PLLA powder formed a homogeneous suspension.. Before injection, mark the injection point with a marker pen and sterilize the injection area with a cotton pad. Use a 25G or smaller needle for injection, using cluster injection or cross injection (tunnel) technology; In group injection, the amount of a single injection should be controlled in the range of 0.05~0.3mL, depending on the injection site and the doctor's judgment. When cross-injected, multiple injections should be given at different points to ensure an even distribution of the drug. A total of 4 injections were completed in the total course of treatment, with a single injection interval of 6 weeks (RA was not used within 3 days after injection) and the total treatment cycle was 6 months. Note: The PLLA powder used by all subjects was produced by the same batch of manufacturers. After the injection, the pateint should avoid sunlight or ultraviolet exposure, so as not to affect the injection effect. This experiment was approved by Sin-An Cosmetic Clinic Hospital Ethics Committee.(No. 2022(036))

Observation index

Improvement of outer canthus and lower eyelid wrinkles

According to the guidelines of the Japanese Society of Aesthetic Sciences (Akita *et al*., 2014), The improvement of outer canthus and lower eyelid wrinkles were assessed and divided into 8 grades (grade 0 was smooth, grade 7 was deep static lines). The improvement degree is divided into 4 levels: no improvement (level unchanged), slight improvement (level increased by 1~2 levels), moderate improvement (level increased by 3~4 levels) and significant improvement (level increased by 5 levels or more). The evaluation was performed by the same experienced attending physician who was not involved in

the injection. The attending physician is only responsible for evaluation work and does not involve the patient's injection therapy process.

Improvement of nasolabial wrinkles

The evaluation was performed by the same experienced attending physician who was not involved in the injection. Evaluate by Wrinkle Severity Rating Scale (WSRS) (Day *et al*., 2004),The scale is divided into 5 levels: Level 1: no visible creases; Level 2: mild wrinkling; Level 3: moderately deep creases, disappear when stretched; Level 4: heavy and long and deep fold, < 2mm after extension; Level 5: extremely heavy and long and deep folds, stretching to see 2~4mm V-shaped folds. During follow-up, a 1-grade reduction on both sides was considered as a slight improvement, a 2-levels reduction as a moderate improvement and a 3-levels reduction or more as a significant improvement.

Overall aesthetic improvement of the middle face

The evaluation was performed by the same experienced attending physician who was not involved in the injection. Assessed by the Global Aesthetic Improvement Scale (GAIS) (Narins *et al*., 2003), The scale is divided into 5 levels: Level 1: the improvement is very obvious; Level 2: the improvement is obvious but not as significant as level 1; Level 3: There is some degree of improvement; Level 4: No change; Level 5: Worse than before treatment. During the follow-up, levels 1 to 3 were regarded as improvement and the improvement rate was the percentage of the improvement cases in the total number of cases.

Skin condition test results

The evaluation was performed by the same experienced attending physician who was not involved in the injection. VISIA face detector was used to detect skin elasticity, moisture content, oil secretion, dark spots, skin color, pores and other relevant indicators of skin condition. Each item scored 80 points. The higher the score of skin elasticity, skin color, pores and water content and the lower the score of oil secretion and dark spots, the better the skin condition. (3 groups of repeated tests and the results were averaged).

Self-sensory evaluation of patients

Patients themselves evaluated skin firmness, wrinkle improvement, skin texture and overall effect before and after treatment (X. Wu *et al*., 2022), The degree of improvement is divided into 0 to 4 levels, which are expressed as "no improvement", "slight improvement", "moderate improvement", "significant improvement" and "perfect improvement" in turn.

Incidence of adverse reactions

The patients were followed up for 6 months after treatment and the occurrence of adverse reactions (allergy, redness/bruising, itching, dryness/peeling) in both groups were counted.

STATISTICAL ANALYSIS

SPSS 22.0 was used for statistical analysis. Measurement data were represented by ($\bar{x} \pm s$), T-test and counting data were represented by n (%) and χ^2-test. $P < 0.05$ was considered statistically significant.

RESULT

The improvement of outer canthus, lower eyelid wrinkles and nasolabial furrows

After the last treatment, the total improvement rates of outer canthus, lower eyelid wrinkles and nasolabial furrows in the observation group (94.87%, 97.44%, 97.44%) were significantly higher than those in the control group (78.57%, 80.95%, 73.81%) (χ^2=7.509, 9.710, 15.776, $P < 0.05$). (fig. 1)

Overall aesthetic improvement of the middle face

After the last treatment, the overall aesthetic improvement rate of the middle face in the observation group (92.31%) was significantly higher than that in the control group (42.86%) (χ^2=35.604, $P < 0.05$). (table 1)

Skin condition test results

After the last treatment, skin elasticity, moisture content, skin color, pores and other skin status scores in the observation group were significantly higher than those in the control group (t=14.836, 10.635, 11.073, 13.525, $P < 0.05$). The scores of oil secretion and dark spot were significantly lower than those of control group (t=9.331, 9.475, $P < 0.05$). (table 2)

Self-sensory evaluation of medical patients

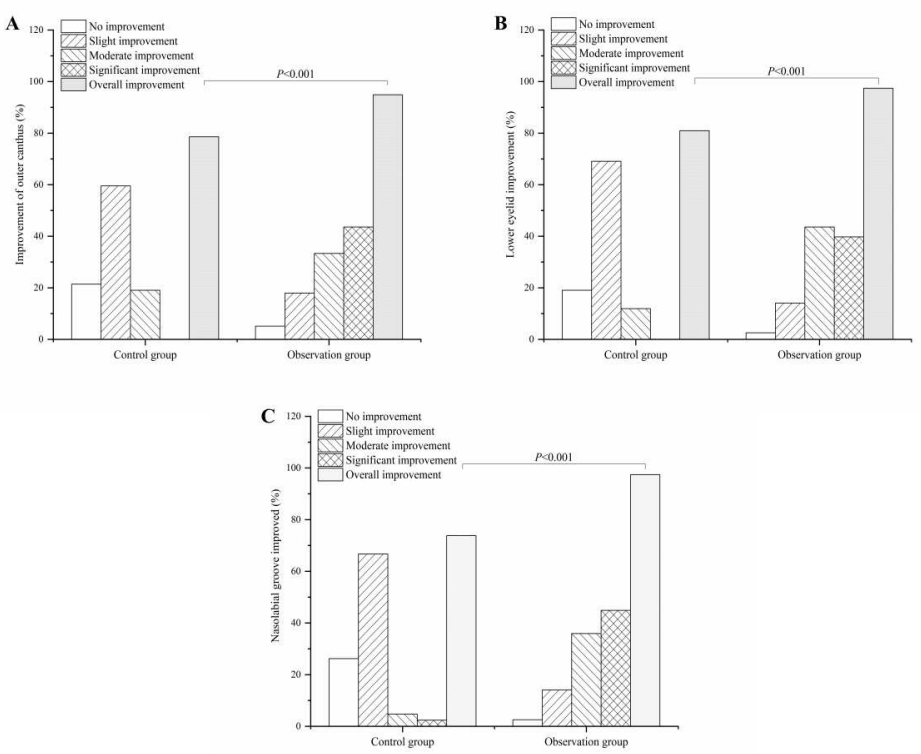
After the last treatment, the total improvement rates of self-skin firmness, wrinkle improvement, skin texture and overall effect in the observation group were significantly higher than those in the control group (χ^2=12.420, 13.226, 11.729, 18.069, $P < 0.05$). (fig. 2)

Incidence of adverse reactions

The incidence of adverse reactions in observation group (3.85%) was lower than that in control group (7.14%), but there was no significant difference ($P > 0.05$). (table 3)

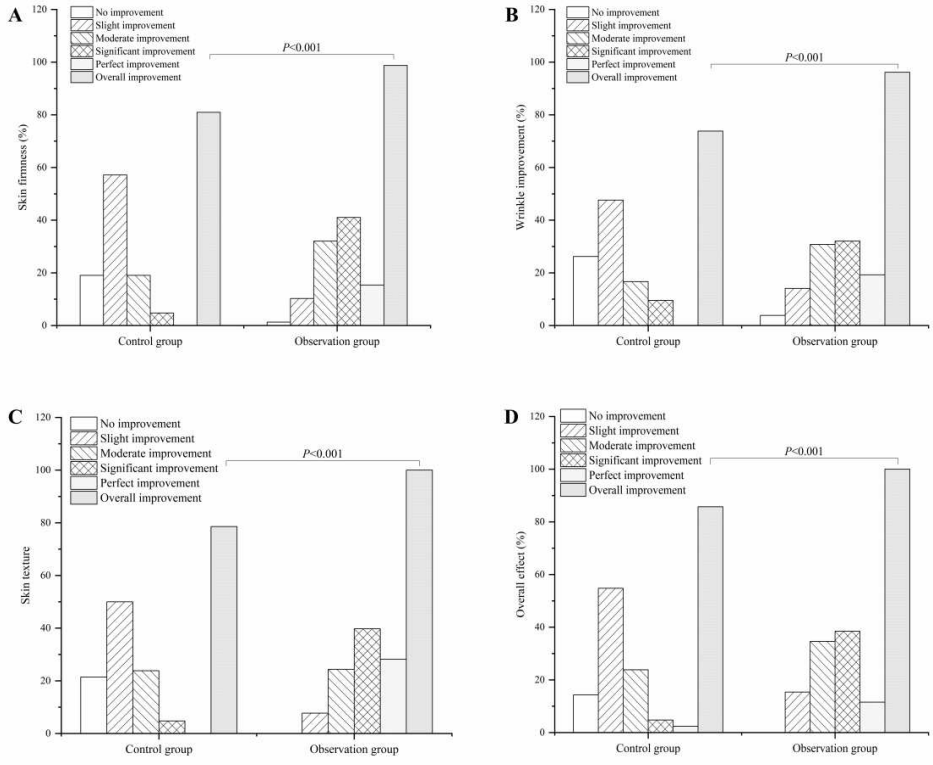
DISCUSSION

Skin relaxation is a natural physiological process with age. The main causes include decreased collagen, degradation of elastic fibers, water loss, thinning of fat layers and muscle relaxation (Freytag *et al*., 2022). Facial rejuvenation treatment is an important topic in the field of modern medical cosmetology, especially for the treatment of age-related sagging skin.



(Fig. A: Improvement of outer canthus; Fig. B: Lower eyelid improvement; Fig. C: Nasolabial groove improved)

Fig. 1: Comparison of improvement of outer canthus, lower eyelid wrinkles and nasolabial furrows between the two groups



(Fig. A: Skin firmness; Fig. B: Wrinkle improvement; Fig. C: Skin texture; Fig. D: Overall effect)

Fig.2: Comparison of self-perception evaluation of patients in the two groups

Table 1: Comparison of overall facial aesthetic improvement between the two groups [n (%)]

Groups	Level 1	Level 2	Level 3	Level 4	Level 5	Overall improvement (Level 1 to 3) rate
Control group(n=42)	0	3 (7.14)	15 (35.71)	22 (52.38)	2 (4.76)	18 (42.86)
Observation group(n=78)	19 (24.36)	32 (41.03)	21 (26.92)	5 (6.41)	1 (1.28)	72 (92.31)
χ^2						35.604
P						＜0.001

Table 2: Comparison of skin status test results between the two groups [min, ($\bar{x} \pm s$)]

Index		Control group(n=42)	Observation group(n=78)	t	P
Skin elasticity	Pre-treatment	29.89±3.87	28.70±4.23	1.513	0.133
	Post-treatment	43.73±5.93*	63.79±7.60*	14.836	＜0.001
Moisture content	Pre-treatment	23.52±3.95	24.35±3.64	1.156	0.250
	Post-treatment	32.70±3.85*	45.73±7.41*	10.635	＜0.001
Oil secretion	Pre-treatment	64.57±9.25	66.71±8.30	1.294	0.198
	Post-treatment	54.52±6.72*	44.04±5.36*	9.331	＜0.001
Dark spot	Pre-treatment	70.56±8.47	68.75±10.18	0.983	0.328
	Post-treatment	63.63±9.73*	48.87±7.15*	9.475	＜0.001
Complexion	Pre-treatment	29.28±4.11	29.10±3.98	0.234	0.816
	Post-treatment	40.34±5.42*	55.19±7.72*	11.073	＜0.001
Pore	Pre-treatment	25.99±3.85	25.43±4.05	0.735	0.464
	Post-treatment	37.58±4.64*	56.46±8.37*	13.525	＜0.001

Note: Compared with before treatment, *P＜0.05.

Table 3: Comparison of the incidence of adverse reactions between the two groups [n (%)]

Group	Allergy	Redness/Bruising	Itching	Dryness/Peeling	Totality
Control group(n=42)	1 (2.38)	0	1 (2.38)	1 (2.38)	3 (7.14)
Observation group(n=78)	1 (1.28)	1 (1.28)	1 (1.28)	0	3 (3.85)
χ^2					0.625
P					0.429

Back in 1999, PLLA was licensed and put on the market in Europe as a new filler "newfill", while Sculptra was also certified to treat skin wrinkles, scars, skin aging and other symptoms *(Munia et al*., 2022). PLLA is widely used in facial rejuvenation treatments due to its injectable properties and slow degradation into carbon dioxide and water in soft tissues (Wu *et al*., 2024). Sculptra was approved by the U.S. Food and Drug Administration (FDA) in August 2004 after a fast-track review for the treatment of human immunodeficiency virus-associated facial fat atrophy. Subsequent studies have further shown that Sculptra can significantly increase the thickness of the skin and the amount of tissue in the fat atrophy area of the face and restore the fat atrophy area to its original state, with good safety (Fabi & Bråsäter, 2023; Haddad *et al*., 2024).In China, Shanghai Xinsheng Medical Products Co., Ltd. produces "Meso De" injection PLLA, which has the same material, structure and composition as Sculptra. It is mainly used for the correction of subcutaneous facial fat and skin collagen loss and the elimination of facial wrinkles and has passed the registration test of China Drug and Biological Products Identification Institute. Several clinical trials have investigated the effect of PLLA in the treatment of facial rejuvenation (*Lin & Lin, 2022; Xu et al*., 2024). Previous studies have shown that patients receiving PLLA injection filler therapy have significant differences in skin improvement between weeks 4 and 24 compared with the control group and have long-term efficacy and safety (*Sarubi et al*., 2022).

Current studies have shown that RA has multiple anti-aging mechanisms. On the one hand, it can reduce the degradation of collagen by inhibiting the activity of collagenase, which helps to maintain the normal structure and elasticity of the skin; On the other hand, RA can also reduce UV damage to the skin and prevent photoaging (*Kang et al*., *2022*). RA, as a clinically approved anti-aging product, has been widely used in dermatology and medical cosmetology fields. Its safety and efficacy are supported by numerous studies. However, the use of RA

also requires attention to its potential side effects, such as dry skin, redness, peeling, etc., so it needs to be used under the guidance of a professional physician (Eichenfield *et al*., 2021). Although PLLA and RA have each shown significant efficacy in the treatment of facial rejuvenation, there has been relatively little research on the synergies between the two. In theory, PLLA increases dermal thickness by stimulating collagen production, while RA improves skin elasticity and texture by promoting elastin synthesis and skin cell regeneration. When used in combination, the two may produce better anti-aging effects.

This study is a clinical retrospective study and subjects meeting the inclusion criteria will be divided into two groups according to the different treatments received by the patients: PLLA combined with RA treatment group (observation group) and RA treatment group alone (control group). Through the evaluation and follow-up before treatment and after the last treatment and by means of skin histology and imaging analysis, the improvement of facial skin relaxation, wrinkles, elasticity, gloss and fineness of the two groups of subjects was compared and the synergistic mechanism of PLLA and RA combined application was discussed. The results showed that after the end of the last treatment, the total improvement rates of outer canthus, lower eyelid wrinkles, nasolabial wrinkles (WSRS) and middle face overall aesthetics (GAIS) in the observation group were significantly higher than those in the control group. In addition, the scores of skin elasticity, moisture content, skin color and pores were significantly higher than those of the control group. The scores of oil secretion and dark spot were significantly lower than those of control group. The improvement rate of self-skin firmness, wrinkle improvement, skin texture and overall effect in observation group was significantly higher than that in control group. Follow-up results showed that the incidence of adverse reactions in the observation group was lower than that in the control group, but there was no significant difference.

Analysis of the results of this study

When PLLA is injected into the skin, its particles are gradually coated by macrophages and lymphocytes, triggering a mild subclinical inflammatory response in the skin. This response is a natural repair mechanism of the body that stimulates fibroblasts to produce new collagen, mainly type I and Type III collagen. Type I collagen is the most abundant type of collagen in the skin, which increases skin's fineness and elasticity (*Chen et al*., *2023*). Type III collagen is mainly distributed between the epidermis and dermis and acts as a subcutaneous scaffold, which is related to the formation of static wrinkles in the superficial layer of the face (Shahrajabian & Sun, 2024). At the same time, PLLA also enhances the activity of proline hydroxylase, which helps provide energy for collagen synthesis. As a result, PLLA is able to rapidly enhance the support structure and thickness of the skin, significantly improving the elasticity and firmness of the skin in the short term (Su *et al*., 2024). RA accelerates skin renewal by regulating epidermal cell proliferation and differentiation and stratum corneum metabolism and helps reduce pigmentation, thereby improving skin roughness and fine lines, uneven skin tone and dark spots. At the same time, RA can also promote the recovery of skin barrier function and the improvement of moisturizing ability, so as to balance the secretion of oil on the skin surface, reduce the accumulation of oil and improve the problem of oily skin (Motamedi *et al*., 2022; Reynolds *et al*., 2024).When RA is used in combination with PLLA, the multiple functions of RA provide a better environment for the collagen generated by PLLA, making the generation and distribution of collagen more uniform, promoting the repair and regeneration of skin tissue and realizing its anti-aging effect (Lee *et al*., 2022). That is, this complementarity makes the combination of the two likely to have a better therapeutic effect. In addition, the combined application of PLLA and RA may produce synergies through some common mechanisms. For example, both may improve skin condition by affecting mitochondrial function and oxidative stress levels. The injection of PLLA can promote the metabolic activity of fibroblasts and increase the number and function of mitochondria, thus improving the antioxidant capacity of the skin (Sarubi *et al*., 2023).RA regulates intracellular REDOX balance and reduces the production of reactive oxygen species, thereby reducing oxidative stress in the skin (Abed *et al*., 2023). Therefore, the combined application of the two can also further improve the aging state of the skin by co-regulating mitochondrial function and oxidative stress levels.

This study explored the synergistic effect of PLLA and RA on age-related skin relaxation in facial rejuvenation through a controlled clinical trial. The results showed that PLLA together with RA could significantly improve the total improvement rate of outer canthus, lower eyelid wrinkles and nasolabial wrinkles, improve the overall aesthetic effect of the middle face, improve skin elasticity, moisture content, skin color and pore state, reduce oil secretion and dark spot scores and significantly improve patients' self-perception evaluation and generally showed high safety and effectiveness. The above results depend on the synergistic mechanism of PLLA and RA, which is mainly reflected in promoting the synthesis of collagen and elastic fibers, regulating the proliferation and differentiation of skin cells and improving skin barrier function. These mechanisms work together to significantly improve the physiological state and appearance of the skin. Therefore, PLLA combined with RA therapy has high clinical significance and application value and is worthy of further research and application. In future studies, we will further explore the optimal dose and frequency of PLLA and RA, as well as the combined

application with other anti-aging techniques, to further improve treatment effectiveness and patient satisfaction. Long-term follow-up results can also be looked at to assess the durability and safety of treatment. Through these studies, we hope to provide more accurate and effective solutions for facial rejuvenation treatment, bringing beauty and confidence to more patients.

This study has some limitations. The sample size was relatively limited, which may bias the results and adversely affect the extrapolation of conclusions. Individual differences in patients' underlying diseases may also affect the generalisability of the findings. The reliability of the results of the synergy between PLLA and RA may be affected by the fact that there was no group set up to use PLLA alone. Therefore, further expansion of the sample size and development of precise assays are recommended to more fully assess the efficacy and synergistic effects of combination therapies.

CONCLUSION

In this study, we analysed the role of PLLA and RA on age-related skin laxity in facial rejuvenation treatment, with a view to providing a new reference basis for clinical treatment. The results showed that after the combined treatment, the skin condition of the patients was significantly improved and facial rejuvenation was promoted, along with a good safety profile, which is of high clinical application value. However, this study has a small sample size and a short follow-up period and failed to observe the long-term effectiveness of this method of treatment. Multi-centre, large-sample, high-quality clinical studies can be continued for verification in the later stage.

Consent to participate

We secured a signed informed consent form from every participant.

Ethical approval

This experiment was approved by Sin-An Cosmetic Clinic Hospital Ethics Committee. (No. 2022(036))

Author contribution

[Yan Xiang]: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.

[Xiufeng Ming]: Participated in collecting, assessing and interpreting the date. Made significant contributions to date interpretation and manuscript preparation.

[Yunxi Liu]: Provided substantial intellectual input during the drafting and revision of the manuscript.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

REFERENCES

Abed K, Foucher A, Bernard D, Tancrède-Bohin E and Cavusoglu N (2023). One-year longitudinal study of the stratum corneum proteome of retinol and all-trans-retinoic acid treated human skin: An orchestrated molecular event. *Sci. Rep.,* **13**(1): 11196.

Akita H, Sasaki R, Yokoyama Y, Negishi K and Matsunaga K (2014). The clinical experience and efficacy of bipolar radiofrequency with fractional photothermolysis for aged Asian skin. *Exp. Dermatol.,* **23**(Suppl 1): 37-42.

Althwanay A, AlEdani EM, Kaur H, Kasapoglu M, Yadavalli R, Nawaz S and Nath TS (2024). Efficacy of topical treatments in the management of mild-to-moderate acne vulgaris: A systematic review. *Cureus,* **16**(4): e57909.

Bhatnagar S, Dave K and Venuganti VVK (2017). Microneedles in the clinic. *J. Control. Release,* **260**: 164-182.

Chen L, Zeng Z and Li W (2023). Poly (acrylic acid)-Assisted intrafibrillar mineralization of type i collagen: A review. *Macromol. Rapid Commun.,* **44**(9): e2200827.

Christen MO (2022). Collagen stimulators in body applications: A review focused on poly-l-lactic acid (PLLA). *Clin. Cosmet. Investig. Dermatol.,* **15**: 997-1019.

Contini M, Hollander MHJ, Vissink A, Schepers RH, Jansma J and Schortinghuis J (2023). A systematic review of the efficacy of microfocused ultrasound for facial skin tightening. *Int. J. Environ. Res. Public Health,* **20**(2): 1522.

Day DJ, Littler CM, Swift RW and Gottlieb S (2004). The wrinkle severity rating scale: A validation study. *Am. J. Clin. Dermatol.,* **5**(1): 49-52.

Dong Y, Zhang Y, Yu H, Zhou L, Zhang Y, Wang H, Hu Z, Luo S (2024). Poly-l-lactic acid microspheres delay aging of epidermal stem cells in rat skin. *Front Immunol.,* **15**: 1394530.

Eichenfield DZ, Sprague J and Eichenfield LF (2021). Management of acne vulgaris: A review. *JAMA,* **326**(20): 2055-2067.

Fabi S and Brasater D (2025). Letter to the Editor on: Safety and efficacy of poly-L-lactic acid filler (Gana V vs. Sculptra) injection for correction of the nasolabial fold: A double-blind, non-inferiority, randomized, split-face controlled trial. *Aesthetic Plast Surg.*, **49**(3): 988-990.

Fisher SM, Borab Z, Weir D and Rohrich RJ (2024). The emerging role of biostimulators as an adjunct in facial rejuvenation: A systematic review. *J. Plast. Reconstr. Aesthet. Surg.,* **92**: 118-129.

Freytag L, Alfertshofer MG, Frank K, Moellhoff N, Helm S, Redaelli A, Voropai D, Hernandez CA, Green JB and Cotofana S (2022). Understanding facial aging through facial biomechanics: A clinically applicable guide for

improved outcomes. *Facial Plast. Surg. Clin. North Am.,* **30**(2): 125-133.

Griffiths TW, Watson REB and Langton AK (2023). Skin ageing and topical rejuvenation strategies. *Br. J. Dermatol.,* **189**(Suppl 1): 17-23.

Haddad A, Avelar L, Fabi SG, Sarubi J, Somenek M, Coimbra DD, Palm M, Durairaj KK, Somji M, Vasconcelos-Berg R, Hanseok L, Morlet-Brown K, Huang J, Fitzgerald R, Hexsel D, Mao C, Weinberg F, Prygova I and Bråsäter D (2025). Injectable poly-l-lactic acid for body aesthetic treatments: An international consensus on evidence assessment and practical recommendations. *Aesthetic. Plast. Surg.*, **49**(5): 1507-1517.

Kang S, Lee H, Jun SH, Park SG and Kang NG (2022). Enhancement of efficacy of retinoids through enhancing retinoid-induced rar activity and inhibiting hydroxylation of retinoic acid and its clinical efficacy on photo-aging. *Pharmaceutics,* **14**(11): 2412.

Lee WR, Huang TH, Hu S, Alalaiwe A, Wang PW, Lo PC, Fang JY and Yang SC (2022). Laser-assisted nanoparticle delivery to promote skin absorption and penetration depth of retinoic acid with the aim for treating photoaging. *Int. J. Pharm.,* **627**: 122162.

Lin JY and Lin CY (2022). Nonsurgical lower eyelid rejuvenation using injectable poly-d,l-lactic acid in Asian patients. *J. Cosmet. Dermatol.,* **21**(10): 4328-4331.

McCarthy AD, Hartmann C, Durkin A, Shahriar S, Khalifian S and Xie J (2024). A morphological analysis of calcium hydroxylapatite and poly-l-lactic acid biostimulator particles. *Skin Res. Technol.,* **30**(6): e13764.

Milosheska D and Roškar R (2022). Use of retinoids in topical antiaging treatments: A focused review of clinical evidence for conventional and nanoformulations. *Adv. Ther.,* **39**(12): 5351-5375.

Motamedi M, Chehade A, Sanghera R and Grewal P (2022). A Clinician's guide to topical retinoids. *J. Cutan. Med. Surg.,* **26**(1): 71-78.

Munia C, Parada M and de Alvarenga Morais MH (2022). Changes in facial morphology using Poly-L-lactic acid application according to vector technique: A case series. *J. Clin. Aesthet. Dermatol.,* **15**(7): 38-42.

Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M and Smith S (2003). A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol. Surg.,* **29**(6): 588-595.

Nie C, Li Y, Li R, Yan Y, Zhang D, Li T, Li Z, Sun Y, Zhen H, Ding J, Wan Z, Gong J, Shi Y, Huang Z, Wu Y, Cai K, Zong Y, Wang Z, Wang R, Jian M, Jin X, Wang J, Yang H, Han JJ, Zhang X, Franceschi C, Kennedy BK and Xu X (2022). Distinct biological ages of organs and systems identified from a multi-omics study. *Cell Rep.,* **38**(10): 110459.

Reynolds RV, Yeung H, Cheng CE, Cook-Bolden F, Desai SR, Druby KM, Freeman EE, Keri JE, Stein Gold LF, Tan JKL, Tollefson MM, Weiss JS, Wu PA, Zaenglein AL, Han JM and Barbieri JS (2024). Guidelines of care for the management of acne vulgaris. *J. Am. Acad. Dermatol.,* **90**(5): 1001-1006.

Sarubi J, Avelar LET, Nero MPD, Kamamoto C and Morais M (2022). Facial rejuvenation on the use of injectable poly-L-lactic acid and hyaluronic acid: Combined technique. *J. Cosmet. Dermatol.,* **21**(10): 5261-5263.

Sarubi J, Guarnieri C, Del Nero MP, Kamamoto C, Honda M, Saito F and Haddad A (2023). Targeted and individualized gluteal Poly-L-Lactic acid injection for optimal aesthetic results in the gluteal region. *J. Clin. Aesthet. Dermatol.,* **16**(6): 30-36.

Shahrajabian MH and Sun W (2024). Mechanism of action of collagen and epidermal growth factor: A review on theory and research methods. *Mini Rev. Med. Chem.,* **24**(4): 453-477.

Su D, Yang W, He T, Wu J, Zou M, Liu X, Li R, Wang S, Lai C and Wang J (2024). Clinical applications of a novel poly-L-lactic acid microsphere and hyaluronic acid suspension for facial depression filling and rejuvenation. *J. Cosmet. Dermatol.,* **23**(11): 3508-3516.

Urdiales-Gálvez F, Braz A and Cavallini M (2023). Facial rejuvenation with the new hybrid filler HArmonyCa™: Clinical and aesthetic outcomes assessed by 2D and 3D photographs, ultrasound and elastography. *J. Cosmet. Dermatol.,* **22**(8): 2186-2197.

Wu X, Cen Q, Wang X, Xiong P, Wu X and Lin X (2024). Microneedling radiofrequency enhances poly-l-lactic acid penetration that effectively improves facial skin laxity without lipolysis. *Plast. Reconstr. Surg.,* **154**(6): 1189-1197.

Wu X, Zhang Z, Zhu J, Lu S, Chen C, Wu X, Wang X and Zhao Z (2022). Can microneedle fractional radiofrequency system treatment impair the skin barrier function in Chinese patients? A prospective clinical trial. *Dermatol. Ther. (Heidelb),* **12**(10): 2371-2382.

Wu Y, Kurosaka H, Wang Q, Inubushi T, Nakatsugawa K, Kikuchi M, Ohara H, Tsujimoto T, Natsuyama S, Shida Y, Sandell LL, Trainor PA and Yamashiro T (2022). Retinoic acid deficiency underlies the etiology of midfacial defects. *J. Dent. Res.,* **101**(6): 686-694.

Xu Q, Sun X, Yang W, Bai Y and Tan X (2024). Comprehensive systematic review of Poly-L-lactic acid in facial clinical application. *Aesthetic. Plast. Surg.*, **48**(23): 5115-5135.

Ziai K and Wright HV (2022). Carbon dioxide laser rejuvenation of the facial skin. *Facial Plast. Surg. Clin. North Am.,* **30**(3): 331-346.