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Single-Session Off-Label Administration of Poly-L-Lactic Acid Microspheres (Juläine™) Across Multiple Facial and Cervical Subunits: An Independent Case Report

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Abstract

Background: Injectable Poly-L-Lactic Acid (PLLA) is a collagen biostimulator used in aesthetic medicine. PLLA-LASYNPRO™ (Juläine™, Nordberg Medical AB, Stockholm, Sweden), a spherical-microsphere formulation of PLLA, holds CE-mark approval restricted to correction of shallow to deep nasolabial folds. The safety and clinical outcome of extended-area application of this formulation have not been reported.

Objective: To describe the tolerability and qualitative clinical observations following single-session administration of PLLA-LASYNPRO™ across multiple facial and cervical subunits including higher-risk regions (forehead, temples, infraorbital, perioral, neck) in an adult patient with age-related loss of skin firmness, hydration and surface evenness.

Methods: One patient received a single session. Five vials of Juläine™ (150 mg PLLA each) were each reconstituted in 5 mL bacteriostatic saline and delivered *via* 25G blunt-tip cannulae (38 mm/50 mm) with area-specific techniques. Outcome was assessed by standardized photography and clinical review at baseline and 14 weeks.

Results: Qualitative visual assessment by the treating investigators suggested changes in skin texture and firmness and overall facial and cervical skin quality 14 weeks after the treatment. Adverse events were limited to transient oedema (3 days) and tenderness (2 days); no erythema, nodules, granulomas or vascular events occurred.

Conclusion: Single-session delivery of PLLA-LASYNPRO™ across multiple on-label and off-label facial and cervical areas was well tolerated and produced a clinically perceptible 14-week improvement. The procedure was performed by highly experienced clinicians and should not be uncritically replicated. Findings warrant confirmation in structured prospective studies.

Keywords: Regeneration; Skin quality; Poly-L-lactic acid; PLLA; Biostimulator; Forehead; Periocular; Perioral; Neck; Off-label

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Introduction

Injectable Poly-L-Lactic Acid (PLLA) is an absorbable biostimulator that induces gradual neocollagenesis through a regulated host response to deposited polymer particles [1,2]. The first-generation product (Sculptra®, Galderma) received European marketing authorization in 1999 and FDA approval for HIV-associated facial lipoatrophy in 2004, with subsequent expansion to nasolabial fold correction in immunocompetent adults in 2009 [3,4]. Since then, PLLA has been applied "off-label" to additional areas including cheeks, neck, décolletage, hands, buttocks and thighs [5-7].

Two features have historically limited PLLA deployment in thin-skinned, hyperdynamic or vascularly complex regions such as the forehead, temples, periorbital area, perioral region and neck: the irregular, flake-like morphology of first-generation particles (major axis ~2 µm to 150 µm) [8], and the tendency of these particles to aggregate in Carboxymethylcellulose (CMC) suspension both associated with papules, non-inflammatory nodules and, rarely, foreign-body granulomas [9,10]. Serious vascular events, including visual loss following injection to the periorbital and temporal

regions, have also been reported for PLLA and related biostimulators [11].

PLLA-LASYNPRO™ (Juläine™, Nordberg Medical AB, Stockholm, Sweden) is a PLLA formulation based on smooth, spherical microspheres (approximately 20 µm to 50 µm) suspended in sodium carboxymethylcellulose and non-pyrogenic mannitol [12,13]. Whether these physicochemical differences translate into clinically meaningful safety advantages in off-label areas remains unproven and is not tested by this single case. Physicochemical and reconstitution characteristics of PLLA-LASYNPRO™ under standard handling conditions have been described previously [13]. Preclinical work has described M2-macrophage mediated regenerative signaling in response to PLLA particles [2,14,15]. The CE-marked indication of Juläine™ is limited to correction of shallow to deep nasolabial folds [12]. We report the safety and 14-week aesthetic outcome of a single-session, multi-area administration of PLLA-LASYNPRO™ encompassing several regions outside the registered indication.

Juläine™ is CE-marked for shallow to deep nasolabial fold correction only. All other anatomical areas described in this report represent off-label use. This report documents an independent clinical observation and does not constitute guidance, recommendation, or endorsement for expanded-area administration.

Materials and Methods

Patient and ethical considerations. A 52-year-old female patient (Fitzpatrick skin type II) with age-related loss of facial and cervical skin firmness, hydration and surface evenness was treated in a single outpatient session. The multi-area, single-session approach was patient-requested and driven by a specific clinical need to address multiple ageing-related concerns in one intervention. The procedure was conducted in accordance with the Declaration of Helsinki (2013 revision) and Good Clinical Practice principles (ICH E6). Written informed consent for the procedure and for publication of clinical images was obtained and is held on file. As this report describes an isolated clinical case and not a structured investigation, formal Ethics Committee approval was not sought, consistent with local requirements for individual case reports.

Juläine™ (Nordberg Medical AB, Stockholm, Sweden) is a CE-marked injectable implant containing, per vial, 150 mg of PLLA microspheres, 45 mg of sodium carboxymethylcellulose and 145 mg of non-pyrogenic mannitol [12]. The microspheres are smooth, spherical and of homogeneous size (approximately 20 µm to 50 µm in diameter) [13].

Reconstitution. Each vial was reconstituted separately with 5 mL of bacteriostatic 0.9% sodium chloride, inverted gently to obtain a homogeneous milky-white suspension and used immediately after reconstitution, consistent with published handling data for PLLA-LASYNPRO™ [13].

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Treatment protocol

A total of five vials (750 mg PLLA) was administered in one session across the following areas, with 2.5 mL delivered per side.

(a) infraorbital region, superficial subcutaneous plane along the inferior orbital rim - 1 vial, 25G × 38 mm blunt-tip cannula; (b) upper face, temple and forehead (deep and superficial planes) - 1 vial, 25G × 38 mm cannula; (c) cheeks, three-zone fan technique (zygomatic, mid-malar and submalar), superficial plane - 1 vial, 25G × 50 mm cannula; (d) infraoral, upper lip and marionette lines (superficial plane) - 1 vial, 25G × 50 mm cannula; (e) neck (superficial plane) -1 vial, 25G × 50 mm cannula.

Blunt-tip cannulae were used exclusively. No needle or cannula of gauge finer than 25G was used in any area, as finer gauges elevate the risk of inadvertent intradermal, subfascial or intramuscular deposition of PLLA suspension planes in which the tissue response may differ from the intended subcutaneous behaviour and in which nodule formation and exaggerated inflammatory reactions are more likely. All operators (J.v.L, S.K, P.K) have substantial cumulative clinical experience with injectable biostimulators; the extended multi-area protocol used here was chosen on the basis of that experience and the physicochemical properties of PLLA-LASYNPRO™, and should not be replicated by operators without equivalent expertise. The rationale and residual risks including the reported risk of vascular compromise in the periorbital and temporal regions [11] were discussed with the patient in advance.

Outcome assessment

Standardized clinical photographs were obtained at baseline (day 0) and at 14 weeks' post-treatment under identical lighting, framing and patient positioning. Image acquisition was performed using a VECTRA® H2 handheld 3D facial imaging system (Canfield Scientific, Inc., Parsippany, NJ, USA), which provides three-dimensional stereophotogrammetric capture of the face and neck together with two-dimensional close-up photography of selected subunits. The same operator, imaging protocol and device settings were used at both time-points. Aesthetic outcome was evaluated by visual comparison of paired images. Adverse events oedema, erythema, ecchymosis, tenderness, nodules, vascular and visual symptoms were monitored by patient self-report (daily diary for the first 14 days and on demand thereafter) and by investigator review at 14 weeks. No validated numerical scales (e.g., WSRS, GAIS) or instrumental measurements were applied; the assessment is therefore qualitative.

Results and Discussion

Unblinded qualitative assessment by the treating investigators (J.v.L, S.K, P.K) at 14 weeks is reported below.

Safety

The single-session extended-area administration was well tolerated. Post-procedural findings were limited to mild oedema at the injection sites, substantially resolving within 3 days, and tenderness resolving within 2 days. The patient reported feeling presentable in social settings by postoperative day 5 and resumed work on postoperative day 7, by which time injection-site oedema had almost completely subsided. No erythema was observed at any time point. Up to and including the 14-week review, there were no subcutaneous papules or nodules including in the perioral, temporal, forehead and infraorbital regions traditionally considered susceptible to PLLA-related nodule formation [9,10] and no granulomas, hypersensitivity reactions, pigmentary alterations, contour irregularities, or vascular or visual events were recorded.

Aesthetic outcome

At 14 weeks, visual comparison of the paired photographs

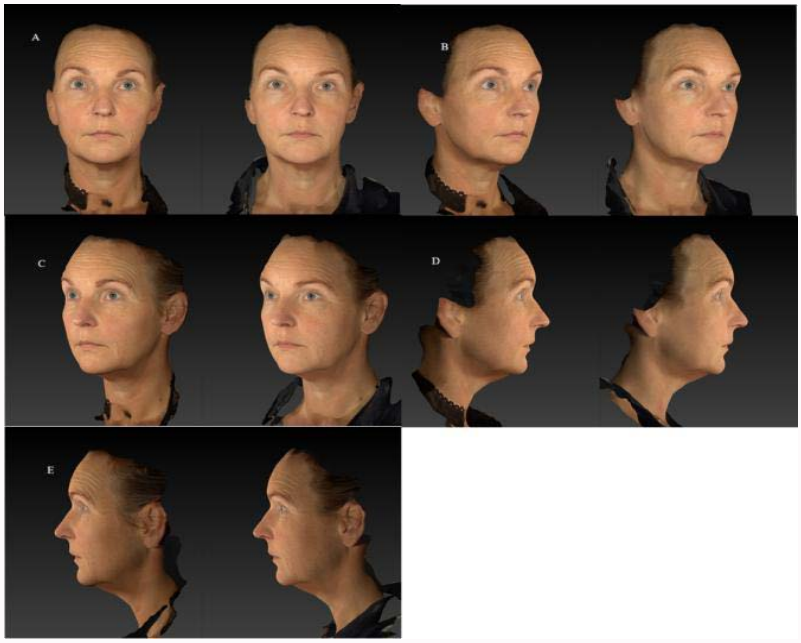

Figure 1: Wide-field clinical views of the patient at baseline (left panel of each pair) and at 14 weeks (right panel) following a single-session administration of PLLA-LASYNPRO™ (Juläine™) across the infraorbital region, upper face (temple and forehead), cheeks, perioral region and neck. Images were acquired with a VECTRA® H2 3D facial imaging system (Canfield Scientific, Inc., Parsippany, NJ, USA) under standardised lighting, framing and patient positioning. Peripheral black artefacts are inherent to the three-dimensional capture envelope and do not represent tissue changes.

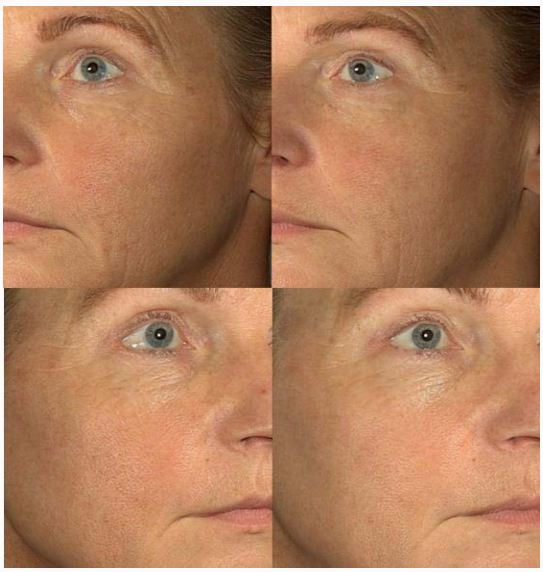

Figure 2: Periorbital and malar close-up photographs at baseline (left panel of each pair) and at 14 weeks (right panel), acquired with the same VECTRA® H2 3D facial imaging system (Canfield Scientific, Inc.) under identical lighting and framing at both time-points.

showed generalized improvement in skin quality across all treated subunits. A reduction in visible rhytides was clinically apparent in three regions in particular: (i) the forehead, with attenuation of horizontal rhytides on frontal and oblique views (Figure 1A-1C); (ii) the periorbital area, with reduction of lateral canthal ('crow's feet') lines and smoother infraorbital skin texture visible in both wide-field and close-up views (Figure 1A, 1B, 1C, Figure 2A, 2B); and (iii) the anterior and lateral neck, with reduction of horizontal cervical rhytides and a more defined cervicomental transition (Figure 1D, 1E). In the periorbital close-ups, perceived dermal thickness and light-reflective quality were increased bilaterally (Figure 2A, 2B). Improvement was apparent within the registered indication (perioral region, nasolabial fold territory) as well as in off-label regions. The 14-week time-point is consistent with the expected kinetics of PLLA-mediated neocollagenesis, which develops progressively over weeks to months [1,2,16].

Rationale for extended-area use

The decision rested on the physicochemical profile documented *in vitro* [13] and on operator experience. Micro-aggregation of CMC-suspended PLLA particles has been implicated in non-inflammatory nodule formation [9,10]. No comparative advantage is claimed.

Mechanistic context

Recent preclinical work supports a predominantly regenerative response to PLLA, characterized by M2 macrophage polarization and increased collagen I and III synthesis in aged skin models [14,15]. A lactate-driven histone lactylation (H4K12la) feedback loop in macrophages has been proposed as an additional regenerative signaling pathway [17]. These mechanisms are presented as context only; no tissue sampling or biomarker analysis was performed, and no mechanistic link to the clinical course is claimed.

Safety considerations specific to off-label areas

Risks associated with PLLA injection in anatomically complex regions are not zero, regardless of the formulation used. The periorbital and temporal regions deserve particular caution: at least two cases of visual loss following PLLA injection in these areas have been reported, and similar events have been described for related biostimulators [11]. Minimum safety requirements for extended-area PLLA administration in these territories are, in our view: exclusive use of blunt-tip cannulae no finer than 25G, strictly superficial placement in thin-skinned and dynamic subunits, a single vial per

anatomical territory, and performance by operators with documented biostimulator experience.

Limitations

This is a single case treated in a single session at a single center, with 14-week follow-up. Outcome was assessed qualitatively, without validated scales (WSRS, GAIS, Fabi-Bolton), without instrumental measurement of dermal thickness, elasticity or hydration, and without blinded evaluators. Nodules of PLLA origin may appear beyond 14 weeks, meaning the safety observations cannot be considered conclusive for late-onset events [9,10]. This report was prepared independently by the authors without sponsor involvement, and no generalization to clinical practice should be made.

Conclusion

This report describes the independent clinical course of a single patient who received a single session of PLLA-LASYNPRO™ across multiple facial and cervical subunits outside the approved indication. At 14 weeks, the procedure was tolerated without acute adverse events, and unblinded investigator assessment suggested changes in skin quality. These observations are purely descriptive and do not establish efficacy, safety, or non-inferiority relative to other PLLA formulations. The approach used blunt-tip cannulae ≥ 25G, superficial placement, and multi-area delivery was chosen on the basis of operator experience and should not be uncritically replicated. Given that PLLA-associated nodules may appear after 6 months; the 14-week follow-up is insufficient for definitive safety conclusions. Confirmation through prospective, controlled studies with adequate statistical power, validated instruments, and longer follow-up is required.

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