

Investigation of Physical Properties of a Polycaprolactone Dermal Filler when Mixed with Lidocaine and Lidocaine/Epinephrine

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ABSTRACT

Introduction: In esthetic treatments with dermal fillers, increasing numbers of physicians are using the technique of mixing an anesthetic agent into the dermal filler before treatment to increase the comfort of the patients. This study aimed at evaluating the effects on the physical properties of a polycaprolactone (PCL)-based dermal filler after mixing with lidocaine.

Methods: A range of 2.0% lidocaine and 2.0% lidocaine/epinephrine concentrations was mixed with the PCL dermal filler to evaluate the changes in dynamic viscosity and elasticity, extrusion force, pH, and needle jam rates. The number of passes back to forth for optimal

homogeneity of lidocaine and PCL dermal filler was determined.

Results: With 15 mixing strokes the lidocaine solution can effectively be mixed into dermal filler resulting in a homogenous blend. The viscosity, elasticity, and the extrusion force decrease with increasing lidocaine volume. The viscosity and elasticity of the dermal filler is sufficient to keep the PCL microspheres in suspension. There were no needle jams. The pH of the PCL dermal filler mixed with lidocaine solution is equivalent to that of the original dermal filler.

Conclusion: It is concluded that mixing of lidocaine into the PCL-based dermal filler can safely be performed without harmful changes in the physical properties of the original dermal filler.

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INTRODUCTION

Polycaprolactone (PCL)-1 dermal filler (Ellansé™; AQTIS Medical, Utrecht, the

Netherlands) is a soft tissue dermal filler based on PCL microspheres. The smooth and totally spherical-shaped PCL microspheres (25–50 μm) are homogeneously suspended in a tailor-made aqueous carboxymethylcellulose (CMC) gel carrier.

PCL and CMC individually have an excellent and established biocompatibility profile and have been used successfully in numerous Conformité Européenne marked and US Food and Drug Administration approved medical devices, such as dermal fillers, oral and maxillofacial surgery, wound dressing and controlled drug delivery [1–6].

PCL is a totally bioresorbable, nontoxic medical polymer and is attractive for use in medical devices because of its controlled and safe bioresorption process [7–11]. With ^3H -labeled PCL and C^{14} -labeled PCL implantation studies, it has been proved that PCL was completely excreted from the body [7, 8].

After treatment the CMC gel carrier is gradually resorbed by macrophages over a period of several weeks, during which the PCL microspheres will trigger a natural response of the human skin and stimulate a natural wound-healing process through neocollagenesis. The new collagen replaces the volume of the resorbed carrier. The microspheres are not phagocytosed because of their size and surface characteristics. The PCL microspheres are totally smooth and spherical shaped, which has been shown to be optimal for dermal fillers [12, 13]. The PCL dermal filler is indicated for deep dermal and subdermal implantation.

In 2007 Busso and Applebaum [14] published a report of their experiences in mixing a calcium hydroxylapatite-based dermal filler with lidocaine for use of the soft tissue filler in treatment of the hand. The result of mixing the two components is that the treatment is less painful to the patient than the conventional

hand injection, and is characterized by less swelling and bruising, with minimal posttreatment downtime.

Increasing numbers of physicians are adopting and using this technique for mixing the PCL dermal filler with standard 2.0% lidocaine-hydrochloride (HCl) solutions, up to 0.19 mL of lidocaine with a 1.1 mL syringe of PCL dermal filler. Mixing 0.19 mL of 2.0% lidocaine solution with 1.1 mL of PCL dermal filler yields a 0.3% lidocaine concentration. This concentration is equivalent to that found in other soft tissue fillers, such as Restylane and Juvederm [15, 16]. The authors suggest that adding up to 0.3% of the anesthetic agent lidocaine to the PCL-based filler will not substantially affect its characteristics, confirming the usability of this mixture in clinical practice.

MATERIALS AND METHODS

Study Purpose and Design

In this study the characterization of the physical properties of PCL dermal filler mixed with plain 2.0% lidocaine-HCl solutions and combined 2.0% lidocaine-HCl and epinephrine under various mixing condition is investigated.

A range of lidocaine and lidocaine with epinephrine concentrations was mixed with the PLC dermal filler to evaluate the changes in dynamic viscosity and elasticity, extrusion force, pH, and needle jam rates. Investigators also evaluated the mixtures at the front, middle, and back of each mixed syringe as a measure of mixing efficiency.

Materials and Equipment

For this study 1.1 mL syringes of the PCL-1 dermal filler were used. The usage of the PCL

dermal filler in this study is representative of the entire product line as all the relevant product characteristics are identical throughout the entire product range. Testing was performed on three different commercial lots.

The 2.0% lidocaine solution was composed of anhydrous lidocaine-HCl (20 mg/mL) (Xylocaine 2.0%; Astra Zeneca BV, Zoetermeer, the Netherlands). The 2.0% lidocaine solution with epinephrine was composed of anhydrous lidocaine-HCl (20 mg/mL), epinephrine (5 µg/mL) (Xylocaine 2.0% with epinephrine; Astra Zeneca BV).

A rheometer (Haake RS-6000; Thermo Electron GmbH, Karlsruhe, Germany) was used to measure the dynamic viscosity and elasticity of the media. Rheology was evaluated with a titanium rotor, with a gap of 0.105 mm and tau (τ) of 5 Pa, over a frequency sweep of 0.1–10 Hz evaluated at 0.6 Hz. Extrusion force was measured by a material tester (model H1Ks; Tinius Olsen, Ltd., Salfords, Surrey, UK). Extrusion force was evaluated through a 27G $\frac{3}{4}$ inch needle with an extension rate of 1 mL/min.

Media pH was measured using a pH meter with a probe (pH340I, and Sentix 41 probe, respectively; WTW, Weilheim, Germany). The pH was obtained by completely coating the glass bulb of the pH probe with media. The female-to-female Luer lock connectors used to connect the mixing and media syringes were from Baxa (rapid fill connector, ref. 13901; Bracknell, Berkshire, UK).

Procedures

For the PCL-1 dermal filler, 1.1 mL syringes were mixed with one of four volumes of 2.0% lidocaine or 2.0% lidocaine with epinephrine solution: 0.05 mL (0.09% final lidocaine-HCl); 0.10 mL (0.17% final lidocaine-HCl); 0.14 mL



Fig. 1 Polycaprolactone-based dermal filler mixed with lidocaine, using a female-to-female Luer lock connector

(0.23% final lidocaine-HCl); 0.19 mL (0.30% final lidocaine-HCl).

One milliliter mixing syringes (Beckton Dickinson, Franklin Lakes, New Jersey, USA) were used to withdraw the lidocaine solution from the 20 mL vial via a 21G $\frac{5}{8}$ inch needle. The push rod of the mixing syringe was drawn back to make sure all the lidocaine solution was cleared from the needle and afterwards depressed to remove all excess air. Next, the mixing syringe with lidocaine was firmly connected to a syringe of PCL dermal filler using a female-to-female Luer lock connector (Fig. 1).

Lidocaine and PCL dermal filler were mixed by alternately depressing the plungers on the mixing and media syringes. Each mixing stroke was composed of one complete compression of the dermal filler syringe push rod, followed by one complete compression of the mixing syringe push rod. Push rods were compressed firmly and quickly, at approximately two compressions per second.

Following mixing, the mixing syringe and Luer lock connector were removed and discarded, and the lidocaine/dermal filler mixture was recapped with the original media

syringe cap. The dermal filler-lidocaine blends were tested between 15 min and 120 min after mixing with lidocaine.

RESULTS

Number of Passes Between Syringes Sufficient for Blending of Lidocaine with PCL Dermal Filler

The extrusion force was used to determine the number of passes between syringes needed for

sufficient blending of lidocaine with the PCL dermal filler. With adequate mixing of the components the difference in viscosity across all regions of the syringe is minimal and the extrusion force profile is uniform from the front to the back of the syringe.

The difference in viscosity from the front to the back increased with increasing volume of lidocaine, suggesting that larger volumes of lidocaine required more mixing than small volumes. It also reflects a greater magnitude of change in physical properties with increasing concentration of lidocaine.

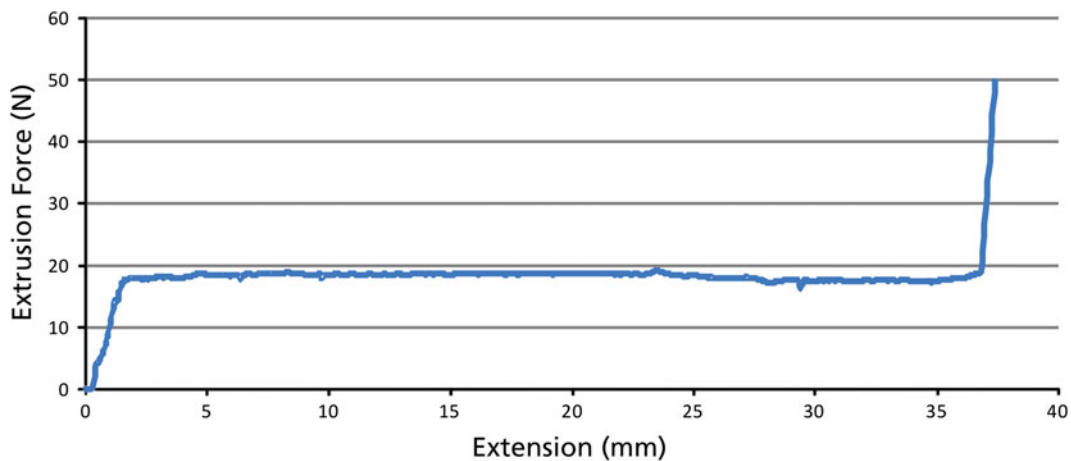


Fig. 2 Extrusion force profile of polycaprolactone dermal filler without lidocaine, 0 mixing strokes

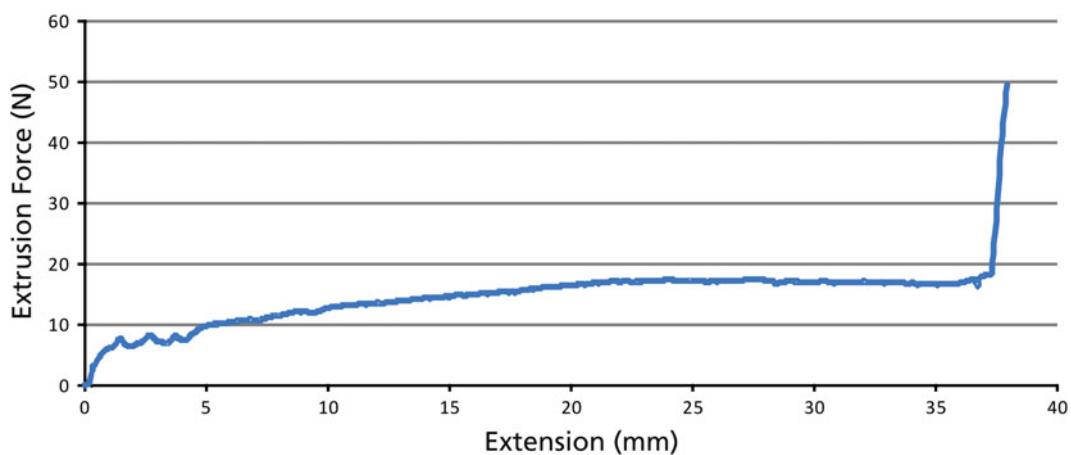


Fig. 3 Extrusion force profile of polycaprolactone dermal filler mixed with 0.19 mL lidocaine using a female-to-female Luer lock connector, five mixing strokes

Figure 2 shows the extrusion force of PCL dermal filler without lidocaine and zero mixing strokes, demonstrating a uniform profile from the front to the back.

Five mixing passes did not provide adequate mixing for any volume tested. The extrusion force profile of PCL dermal filler mixed with 0.19 mL lidocaine with five mixing strokes can be seen in Fig. 3, showing an increase in extrusion force from the front to the back of the syringe.

Ten mixing passes provided adequate mixing for 0.05 mL of lidocaine, but not for the other volumes. The extrusion force profile of PCL dermal filler mixed with 0.19 mL lidocaine with 10 mixing strokes, shown in Fig. 4, demonstrates a nonuniform extrusion profile reflecting the front-to-back inhomogeneity.

Following 15 mixing strokes, the extrusion force was uniform from the front to the back of the syringe for all lidocaine volumes tested, even at the maximum tested volume of lidocaine. Figure 5 shows the uniform extrusion profile of PCL dermal filler mixed with 0.19 mL lidocaine with 15 mixing strokes.

Dynamic Viscosity of PCL Dermal Filler Compared to PCL Dermal Filler with Lidocaine Mixtures with or without Epinephrine

The dynamic viscosity measures the way a fluid responds to stresses and strains. The dynamic viscosity of the PCL dermal filler decreased with increasing lidocaine concentration without or with epinephrine. Figure 6 shows the dynamic viscosity percentual difference of PCL dermal filler blended with 0.05 mL, 0.10 mL, 0.14 mL, and 0.19 mL 2.0% lidocaine solution mixed with 15 mixing strokes. No statistically significant viscosity differences were measured

for lidocaine solutions with or without epinephrine.

Even at 0.23 mL of lidocaine solution blended with the PCL dermal filler, the CMC gel viscosity/elasticity was sufficient enough to keep the PCL microspheres in suspension in time (not shown).

Extrusion Forces of PCL Dermal Filler Compared to PCL Dermal Filler with Lidocaine

The extrusion forces of the PCL dermal filler mixed with lidocaine were lower than those of the PCL dermal filler alone. The average extrusion force decreased with the increase in volume of lidocaine added to the 1.1 mL PCL dermal filler syringe.

In Fig. 7 the average extrusion forces of PCL dermal without lidocaine and PCL dermal filler blended with 0.05 mL, 0.10 mL, 0.14 mL, and 0.19 mL 2.0% lidocaine solution mixed with 15 mixing strokes are shown. The average extrusion force of PCL dermal filler without lidocaine through a 27G^{3/4} inch needle was 17.2 N and decreases to 13.0 N for PCL dermal filler mixed with 0.19 mL 2.0% lidocaine solution.

Differences in average extrusion force for PCL dermal filler mixed with lidocaine with and without epinephrine was not statistically significant for all volumes, suggesting that epinephrine had no effect on the extrusion force.

Incidence of Needle Jamming in PCL Dermal Filler Blended with Lidocaine with or without Epinephrine

Needle jamming may occur if there is a cluster of PCL microspheres in the CMC gel carrier.

No needle jams were observed in any of the extrusion tests, indicating optimal homogeneity

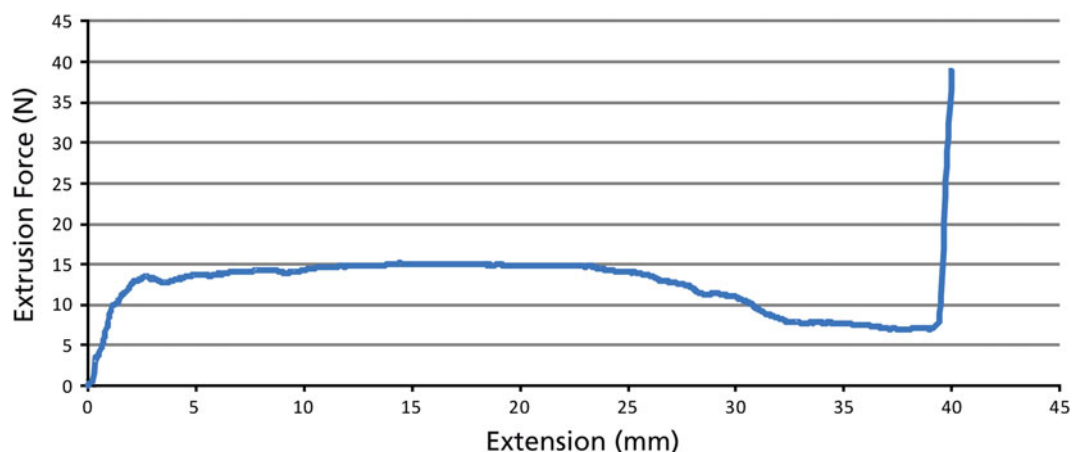


Fig. 4 Extrusion force profile of polycaprolactone dermal filler mixed with 0.19 mL lidocaine using a female-to-female Luer lock connector, 10 mixing strokes

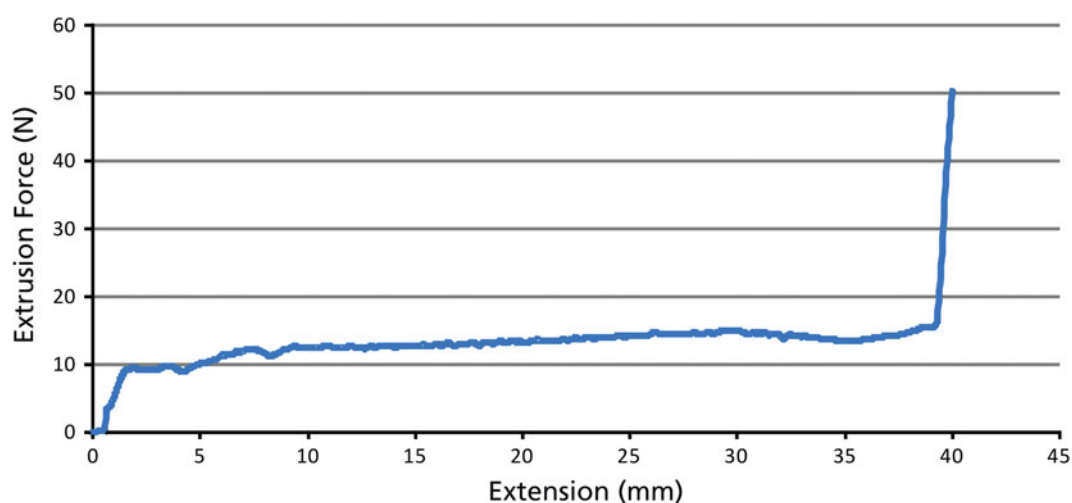


Fig. 5 Extrusion force profile of polycaprolactone dermal filler mixed with 0.19 mL lidocaine using a female-to-female Luer lock connector, 15 mixing strokes

and suspension of the PCL microspheres in the CMC gel carrier after mixing with lidocaine with or without epinephrine.

Elasticity and pH of PCL Dermal Filler Blended with Lidocaine Compared to PCL Dermal Filler without Lidocaine

The tan delta (δ) values (the tangent of the ratio loss modulus [G''] over the storage modulus [G']) provides a quantitative tool to evaluate the relative elasticity of the media. The elasticity of PCL dermal

filler decreased with increasing concentrations of lidocaine solution. Figure 8 shows the elasticity percentage difference of PCL dermal filler blended with various volumes of 2.0% lidocaine with and without epinephrine mixed with 15 strokes. The PCL dermal filler blends were less elastic than PCL dermal filler without lidocaine solution. No statistically significant elasticity differences were measured for lidocaine solutions with or without epinephrine.

The pH was between 7.1 and 7.2 for all tested samples.

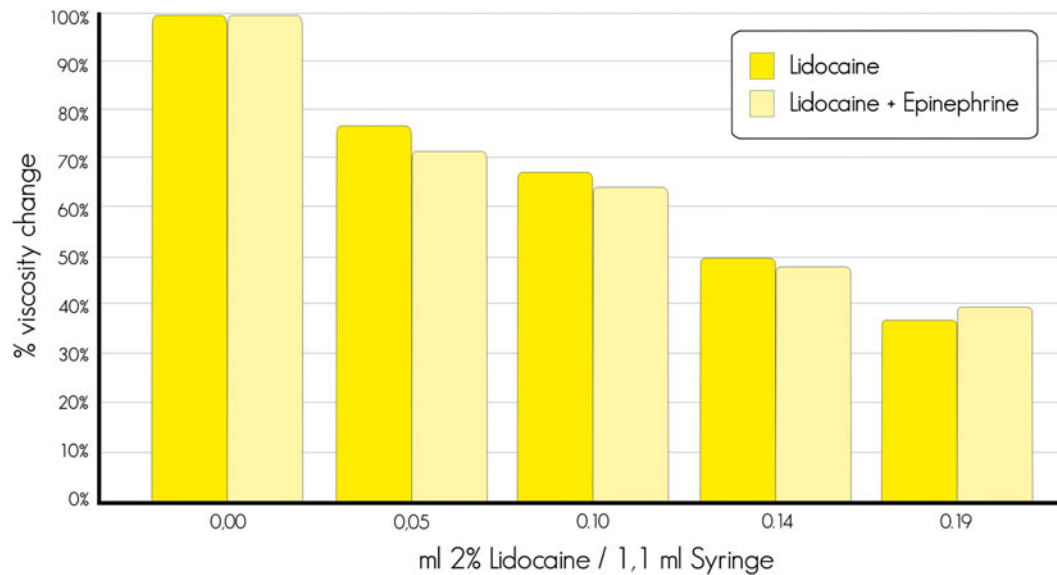


Fig. 6 Dynamic viscosity procentual difference of polycaprolactone dermal filler mixed with various volumes of 2.0% lidocaine with and without epinephrine (15 mixing strokes, 0.6 Hz)

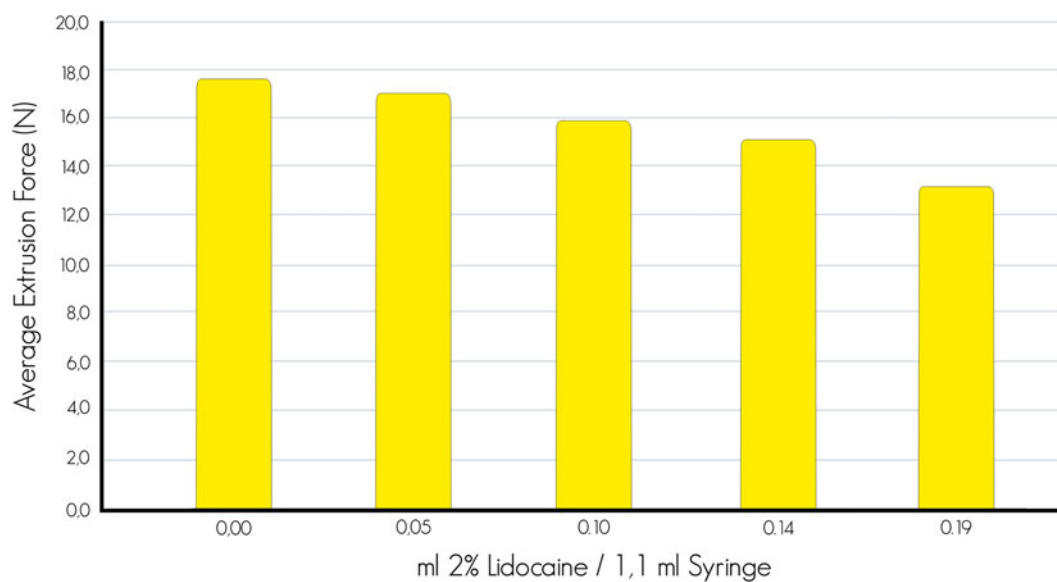


Fig. 7 Average extrusion force of polycaprolactone dermal filler mixed with various volumes of 2.0% lidocaine (15 mixing strokes)

DISCUSSION

Hand mixing lidocaine or lidocaine with epinephrine with the PCL dermal filler causes no significant changes to the physical properties of the original formulation. With 15

back-and-forth passes the anesthetic agent(s) can adequately be mixed into the gel resulting in a homogenous blend. The viscosity/elasticity of the gel in the PCL dermal filler mixed with 2.0% lidocaine with or without epinephrine is sufficient to keep the PCL

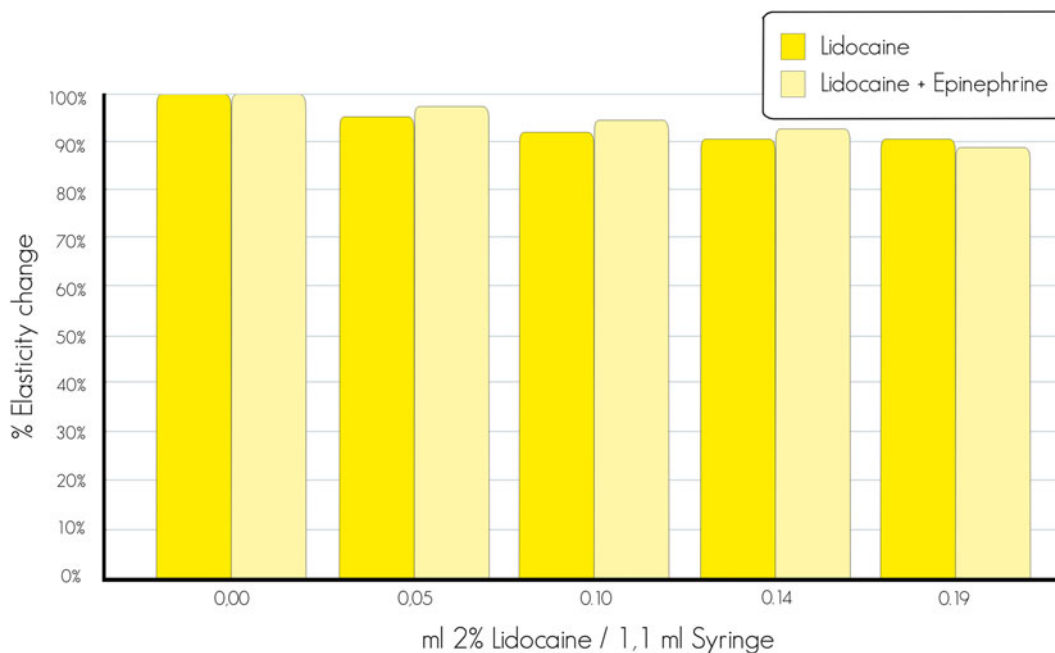


Fig. 8 Elasticity of PCL dermal filler mixed with various volumes of 2.0% lidocaine with and without epinephrine (15 mixing strokes)

microspheres in suspension even after 24 h. There were no needle jams, indicating that the PCL microspheres were homogeneously suspended in the gel, even after mixing the dermal filler with the anesthetic agent. The pH values of the PCL dermal filler mixed with lidocaine with or without epinephrine are equivalent to those of the original dermal filler. The viscosity, elasticity, and the extrusion force of the dermal filler decrease with increasing lidocaine content. There was no statistically significant change in physical properties for lidocaine solutions with or without epinephrine. The changes in physical properties are identical for the entire product range.

Mixing a lidocaine solution with the dermal filler obviates the need for nerve blocks or local infiltration, thereby reducing the treatment times and prevents tissue distortion that may be caused by injecting local anesthetics. This may also positively affect the patients' treatment experience and satisfaction. In addition,

previous studies have shown that the addition of lidocaine to collagen-based dermal fillers resulted in less swelling and bruising [17], potentially due to the antihistaminergic effect of lidocaine on mast cells [18]. Similar findings have been reported for hyaluronic acid-based dermal fillers mixed with lidocaine, also showing a reduction in swelling, erythema, and bruising [16, 19–21]. As lidocaine is suggested to decrease these side effects, this is also expected for the PCL-based dermal filler mixed with lidocaine.

The limitations of this study are that it does not investigate the influence of lidocaine and epinephrine on the clinical safety and performance of the PCL dermal filler, and the influence of the clinical anesthetic effect of lidocaine after mixing with the PCL dermal filler.

This study does not address a potential interaction of lidocaine or epinephrine with the components of the PCL dermal filler and its potential influence on anesthetic efficacy. It is expected that, because of its hydrophilicity,

lidocaine will be situated in the aqueous (hydrophilic) CMC gel carrier. Predicted on the hydrophobicity of the nonporous PCL microspheres [22] no affinity is expected between lidocaine and PCL microspheres, and there will be no driving force of the lidocaine to migrate into the PCL microspheres.

This is supported by a study describing the release profile of lidocaine from PCL threads [23]. PCL pellets were compounded with lidocaine and then extruded to obtain highly loaded threads. The lidocaine release profile showed a rapid release in the first hours and completed in a few days, indicating that there is no affinity or reaction between the PCL matrix and lidocaine.

It is not expected that lidocaine will bind or react with the CMC carrier, but is free to move and yield the desired anesthetic effect. CMC is a known time-release agent for lidocaine [24], and there are several commercial medical products available based on CMC gel and lidocaine as an anesthetic agent.

This study does not address the effect of the premixed anesthetic on the clinical efficacy of the PCL dermal filler. Physicians have reported no decrease in clinical efficacy after mixing the PCL dermal filler with lidocaine with or without epinephrine, as has also been reported for hyaluronic acid-based dermal fillers containing lidocaine (for review, see Smith and Cockerham [21]). Planned (pre)clinical studies with lidocaine premixed before treatment and lidocaine incorporated in the PCL dermal filler syringe itself are aimed at confirming this.

CONCLUSION

The advantages of mixing lidocaine with PCL dermal filler before treatment are lower viscosity and elasticity, lower extrusion force, providing a greater ease of molding, increased

patient comfort, reduced need for nerve blocks and infiltration anesthesia, which may be attractive for both physicians and patients.

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Conflict of interest. Dr. de Melo is an advisor of AQTIS Medical, and has received consultancy and speaking fees from the company. Dr. Marijnissen-Hofsté is an employee of AQTIS Medical.

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