J O C D | 4 8 1 | B
Journal Name | Manuscript No.
Dispatch: 7.1.10 | Journal: JOCD | CE: Krishna Sarma
Author Received: | No. of pages: 5 | PE: Shivachandran

Original Contribution

Longevity of effects of hyaluronic acid plus lidocaine facial filler

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Summary

Background A new hyaluronic acid filler containing pre-incorporated 0.3% lidocaine reduces pain and enhances patient comfort. *In-vitro* studies confirm functional equivalence with non-lidocaine-containing products, but only limited data is available on the long-term effects of lidocaine on filler performance in the clinical setting.
Aims To investigate whether inclusion of lidocaine impacts the longevity of hyaluronic acid fillers.
Patients/Methods 60 patients with moderate–severe bilateral naso-labial folds received 24 mg/mL hyaluronic acid with pre-incorporated lidocaine or an equivalent product without lidocaine and were followed-up for up to 76 weeks.
Results Significantly better results were found in favor of HA gel with pre-incorporated lidocaine for physician assessment of injection pain and patient pain assessment after injection (both $P < 0.001$). Long-term follow-up of patients after almost a year showed that 91% (52/57) patients had no evidence of facial asymmetry and investigators confirmed lidocaine had no effect on filler longevity. High levels of patient satisfaction and prolonged benefits due to persistence of the product were noted, with those patients needing additional treatment requiring 'top-up' rather than full re-treatment.
Conclusions The addition of 0.3% lidocaine does not affect product longevity and the small volume required for 'touch-up' also suggests that longevity is maintained.

Keywords: facial filler, hyaluronic acid, Juvéderm® ULTRA, lidocaine, longevity

Introduction

Facial folds and wrinkles can be treated with reversible, non-invasive techniques, such as hyaluronic acid (HA) fillers, which smooth out wrinkles and re-contour sunken areas, producing a more natural, youthful, healthy appearance.[1,2] HA facial fillers integrate with surrounding tissue to restore skin moisture, elasticity and tone.[2] Their major benefits of biocompatibility, stability *in-vivo*, safety, effectiveness, good tolerance and versatility have led to their extensive use in the USA and increased popularity in Europe over the past decade.[3]

However, facial filler injections are often associated with patient pain and discomfort, resulting in the need for adjunctive topical or regional anesthesia which can prolong or complicate the procedure.[4,5] Currently there are no standardized guidelines for use of anesthetics with facial filler treatments, with variations between practices regarding choice of anesthetic and area treated.[6]

A new HA range (Juvéderm® ULTRA range) comprising a smooth, cohesive gel with uniform consistency, even flow characteristics and extended duration of clinical effects [3,7,8] has been developed to correct moderate to severe wrinkles and folds for up to 1 year. Each product contains pre-incorporated 0.3% lidocaine (3 mg/mL) to facilitate ease of injection, reduce pain and

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Accepted for publication September 27, 2009

enhance patient comfort.[9,10] Extensive physical and chemical characterization of this new lidocaine-containing HA filler range *vs.* non-lidocaine containing products has been conducted *in-vitro*, and clinical studies have been carried out evaluating the new product *in-vivo*. This paper aims to confirm the *in-vitro* results by investigating whether pre-incorporated lidocaine impacts the longevity of HA facial fillers *in-vivo*, through long-term follow-up of patients injected with HA gel containing pre-incorporated lidocaine *vs.* HA gel without pre-incorporated lidocaine. The reported results of these evaluations are specific to this new range of HA fillers with pre-incorporated lidocaine and cannot be directly extrapolated to other HA fillers.

Materials and methods

This study comprised long-term follow-up of 60 patients with moderate to severe naso-labial folds (NLFs) who were initially enrolled into a prospective, multicenter, randomized, double-blind study across three European centers from June–September 2007.[9,11] All patients provided written informed consent prior to commencement of any study procedures. Patients were randomized to receive 24 mg/mL HA gel containing pre-incorporated lidocaine (Juvéderm® ULTRA 3) on one side of the face, and HA gel without lidocaine (Surgiderm®) on the other. All patients were treated with an average 0.62 mL per side. Pain severity and ease of injection were assessed by both injecting physicians and patients. A visual analogue scale ('0': no pain to '10': extreme pain) was used for patient pain assessment and adverse events were recorded for the study duration.

A long-term study was then conducted to confirm the *in-vitro* results and to investigate whether lidocaine has any impact on the longevity of the product, through follow-up of the patients from the primary trial. Retrospective patient note analysis was conducted and patients were reassessed for asymmetry upon their return to the clinic for routine follow-up, possible re-treatment or additional treatment (e.g. with botulinum toxin).

Data were analyzed using descriptive statistical techniques and all analyses were of an exploratory nature.

Results

In-vitro data

Extensive physical and chemical characterization of the new HA filler range with pre-incorporated lidocaine *vs.* non-lidocaine containing products determined functional equivalence between the two products (Table 1). Spectroscopic analysis (FT-IR and NMR) showed an identical imprint between the two products, thereby confirming that pre-incorporated lidocaine does not affect the molecular structure of the HA network. Furthermore, all release specifications for both products were the same, thus demonstrating functional equivalence.

Table 1 Results of chemical/physical characterization of HA gel incorporating lidocaine and without lidocaine

Chemical/physical test	HA injectable gel incorporating lidocaine and without lidocaine
Spectroscopic analysis	
FT-IR	Both product lines proved to be equivalent
UV-VIS	
NMR	
NaHA concentration	Equal
Characterization of pH	Equal
Characterization of osmolarity	Equal
Characterization of extrusion force	Equal
Protein analysis	<5 ppm
Characterization of heavy metals	Below detection limits
Characterization of residual cross-linker	<2 ppm
Susceptibility to degradation	
Enzymatic	Degradation mechanisms remain intact in both product lines
Free radical	
Rheological characterization	Equal

Source: Allergan Medical Internal Document.

In-vitro studies also established that addition of lidocaine does not affect product characteristics, HA content, or physical properties. Despite their sensitivity to degradation, no significant drop in rheology (flow and deformation of the gel under stress) or extrusion force was noted, thus confirming that lidocaine does not degrade HA or the gel network (Figs 1 and 2). Degradation of the HA network by lidocaine would also result in the generation of small HA fragments, identifiable by scientifically validated methods such as size exclusion chromatography with multi-angle light scattering (SEC-MALS). However, no such fragments were detected in the Juvéderm line of dermal fillers (Source: Allergan Internal Document).

Stability testing for HA gel pre-incorporated with lidocaine demonstrated that neither the gel network nor the lidocaine degraded in the syringe. Similarly, extensive real-time and accelerated stability data validated an expiry date of up to 2 years when the product is stored between 2–25 °C. Therefore, addition of lidocaine does not affect product longevity. Other product properties,

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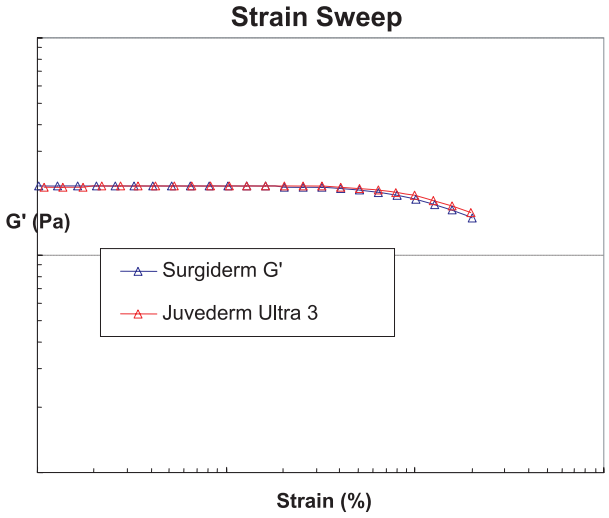

Figure 1 Rheology (flow and deformation of the gel under stress).

COLOR

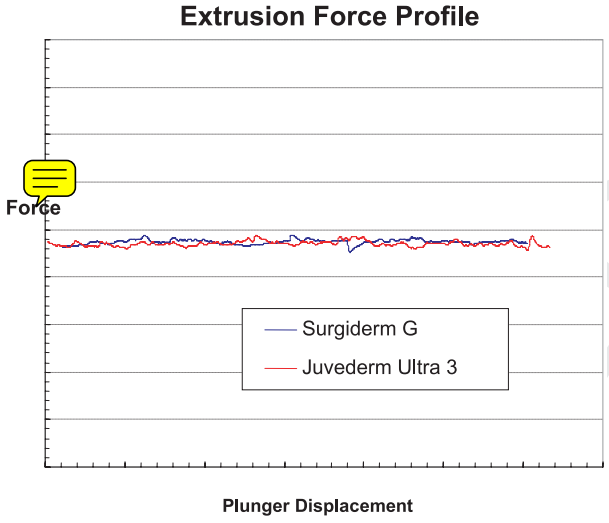

Figure 2 Extrusion force (force required to make gel flow).

including appearance, pH, NaHA content, sterility and osmolarity, were all unaffected by the presence of lidocaine (Source: Allergan Medical Internal Document).

Recent *in-vitro* kinetic studies showed that the lidocaine contained in the new product range is rapidly released from the gel following injection and then it is metabolized, leaving the remaining product exactly equivalent to the non-lidocaine containing HA gel implant, leading to equivalent product performance and longevity. Following lidocaine absorption, its elimination half-life is typically 1.5–2 h (Source: Allergan Medical Internal Document).

Double-blind *in-vivo* study

Sixty patients with moderate to severe symmetrical NLFs were enrolled (56 females, 4 males), with a mean age of 50.4 years (range 35–74 years). All patients were successfully injected with both products (one on each side of the face), with 95% of injections considered easy or very easy. Significantly better results were found in favor of HA gel with pre-incorporated lidocaine regarding physician assessment of injection pain and mean patient pain assessment (both $P < 0.001$). Comparable mild to moderate adverse events were reported for both products.[11]

Long-term follow-up data

Investigators followed-up patients to a maximum of 76 weeks (average treatment interval and long-term follow-up: 47.2 weeks [329.3 days]). Data were available for 95% (57) patients (three patients did not return to clinic). Patients returned to clinic for a variety of reasons (re-treatment, routine scheduled follow-up or additional treatment) and investigators remained blinded to treatment allocation during this reassessment visit.

Overall, 91% (52/57) of patients showed no clinical evidence of asymmetry in NLF volume at long-term follow-up. Of the five patients noted with asymmetry, one had evidence of increased volume loss on the side treated with HA gel with pre-incorporated lidocaine, while four showed evidence of increased volume loss on the side treated with HA gel alone. Investigators indicated that addition of lidocaine did not affect HA gel longevity in 52 patients (91%), while they were uncertain in those 5 patients (9%) with evidence of facial asymmetry.

Thirty-three patients (57.9%) received re-treatment and 24 patients (42.1%) received no additional treatment when they returned to the clinic (Table 2). The average volume of HA gel injected into either the right or left NLFs at follow-up if required was 0.23 mL, thereby demonstrating the persistence of the product with only 'top-up' rather than full re-treatment being needed (Fig. 3). The amount needed per side was identical in most cases, demonstrating that the efficacy of both products over time was similar.

No additional AEs were reported in the follow-up period.

Discussion

This new range of HA dermal fillers including pre-incorporated lidocaine offers prolonged duration of clinical improvement and an excellent safety profile.[12,13]

Table 2 Volume of facial filler re-injected at long-term follow-up

Right and left NLF (mL)	Number of patients
0.3 + 0.3	11
0.4 + 0.4	5
0.25 + 0.25	5
0.6 + 0.6	2
0.8 + 0.8	2
0.55 + 0.55	1
0.2 + 0.2	1
0.7 + 0.8	1
0.8 + 0.4	1
0.7 + 0.65	1
0.45 + 0.5	1
0.2 + 0.4	1
0.[illegible]0.25	[illegible]
Mean: 0.23 + 0.23	3[illegible]

Furthermore, the incorporation of 0.3% lidocaine facilitates the injection procedure, significantly reducing pain and enhancing patient comfort.[8,11]

This study investigated whether the favorable *in-vitro* results obtained for HA plus lidocaine could be replicated *in-vivo* by determining whether lidocaine has any impact on the longevity of HA gel through long-term follow-up of patients injected both with HA alone and with the HA gel containing pre-incorporated lidocaine. The results showed that HA gel with pre-incorporated lidocaine did not result in asymmetry of NLFs compared with HA alone and that even after a year post-treatment, only half the patients required additional treatment. Of the patients who needed re-treatment, only 'top-up' treatment was needed rather than full re-treatment, demonstrating the longevity of effect.

In a prospective study by Wahl, 3566 patients who had previously received facial fillers for NLFs were re-treated using the new HA gel filler with pre-incorporated lidocaine.[14] Injectors' and patients' evaluation of comfort and esthetic results found that the HA filler with pre-incorporated lidocaine provided a more comfortable injection experience and improved esthetic result for most patients compared with other dermal fillers used previously.[14]

In conclusion, HA gel with pre-incorporated lidocaine is highly effective in meeting a wide range of patients' needs since it results in significant cosmetic improvements by providing a natural, smooth, long-lasting look. Furthermore, the addition of lidocaine results in a more comfortable, gentle injection experience according to both investigator and patient assessments. Longevity of the product is evident from the results of this study since patients returning to the clinic demonstrated extremely high levels of patient satisfaction and no evidence of facial asymmetry, even after more than 12 months post-treatment. Prolonged benefits were conferred as a result of persistence of the product, with only approximately one-third of patients requiring additional 'touch-up' treatment, rather than full re-treatment. Thus, it can be concluded that the addition of 0.3% lidocaine does not affect the longevity of this highly effective new product range of dermal fillers.

Acknowledgments

Medical writing support for this paper was provided by Allergan.

Figure 3 Patient at baseline, 1 month and 16 months. Photograph: ©Hervé Raspaldo 2008 (Mrs VG).

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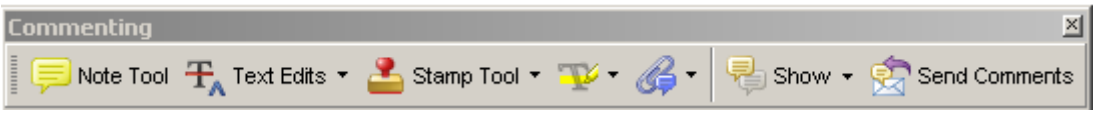

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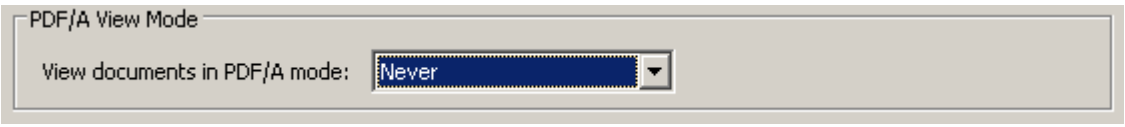

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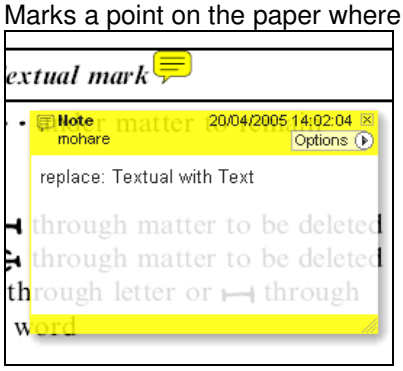

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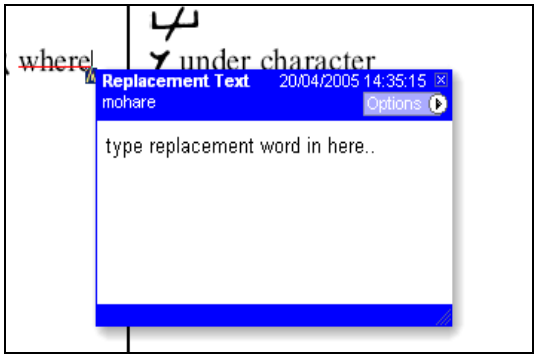

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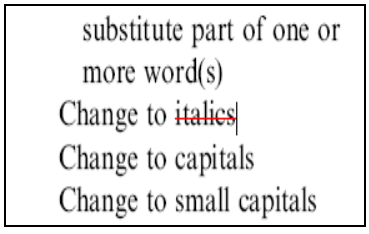

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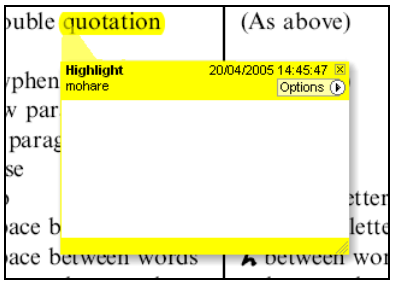

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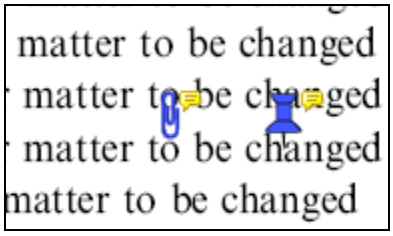

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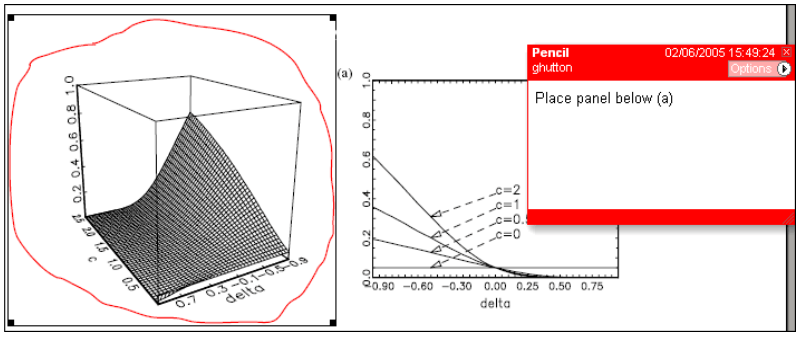

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