Hyaluronic Acid Gel Distribution Pattern in Periocular Area With High-Resolution Ultrasound Imaging

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Abstract
Background: High-resolution ultrasound (HRUS) is a useful tool in defining anatomic and dynamic soft tissue relationships in the periocular area. It also allows visualization of hyaluronic acid (HA) gel within the soft tissue.

Objectives: The authors investigate the difference in the distribution pattern between 2 HA fillers in the periocular tissue using HRUS.

Methods: The charts of 10 patients who underwent periocular injection using HA gel filler and were subsequently examined with HRUS were reviewed. Half of the patients (n = 5) were treated with Restylane-L (Medicis Aesthetics, Inc, Scottsdale, Arizona) and the remaining 5 with Belotero Balance (Merz Aesthetics, Inc, San Mateo, California). Ultrasonographic evaluation (Logiq p6; GE Healthcare, Waukesha, Washington) was performed before and immediately after HA filler injection.

Results: The HA appears as a hypoechoic image within the soft tissue plane on HRUS. Restylane-L filler formed a localized hypoechoic image within the tissue, with some spread into bubbles or pearl-like configuration. Belotero Balance spread more widely into the tissue plane and diffused into an elongated or spindle-shaped hypoechoic image.

Conclusions: Our preliminary data suggest that HA gel fillers with differing production technologies show distinct spread and distribution patterns in the periocular tissues on HRUS examination.

Keywords
hyaluronic acid, high-resolution ultrasound, filler, periocular hollow, ultrasound, Belotero Balance, Restylane-LT, cosmetic medicine, oculoplastics

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The medical charts of 10 patients who underwent periocular injection using HA gel filler and were subsequently examined with HRUS were reviewed. The study was conducted in accordance with the institutional review board at the authors’ academic hospital. Each patient underwent injection of HA filler in the inferior orbital hollow by a single experienced injector (R.A.G.) with a 30-gauge needle, performed along or 2 to 6 mm below the infraorbital rim. All injections were delivered in the suborbicularis plane using a combination of direct serial puncture and retrograde linear threading techniques. Five patients underwent treatment with Restylane-L (Medicis Aesthetics, Inc, Scottsdale, Arizona) and 5 with Belotero Balance (Merz Aesthetics, Inc, San Mateo, California). Small aliquots of filler (0.01-0.05 mL) were placed, and the skin surface was manually molded with a cotton tip to smooth the contour of filler when necessary.

Ultrasonographic evaluation (Logiq p6; GE Healthcare, Waukesha, Wisconsin) was performed before and immediately after HA filler injection by a single operator (ASG) using a 15-MHz probe at a rate of 50 frames per second. Imaging was performed with the patient in a seated position, with eyelids closed, through methylcellulose medium. The probe was placed perpendicular to the area of interest (Figure 2): medial, central, or lateral, which correspond to the infraorbital area nasal to medial limbus, at the pupil, and temporal to the lateral limbus, respectively. Three static images in each area were acquired before and after the HA filler had been placed.

Pre- and posttreatment injection images were reviewed and representative images from the infraorbital region that matched most closely were selected. Selection criteria included demonstration of the dermis, subcutaneous tissue, and maxilla bone perpendicular arrangement over the region of interest; adequate clarity of the images; and demonstration of HA filler centrally within the frame.

The images were reviewed in a systematic manner. Features related to the shape and tissue distribution of HA gel filler were defined. Relationships to regional bony and soft tissue structures were also recorded. Observations were compared among investigators, and consensus concerning feature characteristics was reached.

Each treatment group consisted of 4 women and 1 man. The median age was 57 years (range, 37-84 years) for the Belotero Balance and 61 years (range, 47-80 years) for the Restylane-L. The average injection volume of HA gel filler was 1.0 mL (0.5 mL on each side) in all patients. On HRUS, HA gel fillers appeared as anechoic or hypoechoic spaces underneath the orbicularis muscle plane. Both Restylane-L (Figure 3A) and Belotero Balance (Figure 3B) formed distinct borders between the HA filler and surrounding soft tissue. Restylane-L filler formed localized hypoechoic lobular spaces within the tissue, with some tendency to spread in a vertical direction and with some diffusion to form a bubble or pearl-like configuration (Figure 4A-D). Belotero Balance, on the other hand, tended to spread more widely within the same tissue plane. It diffused in a horizontal fashion, giving rise to an elongated or spindle-shaped configuration (Figure 5A-D).

Two patients developed edema approximately 2 weeks after HA gel injection (1 patient each who received Belotero Balance and Restylane-L). Ultrasonography demonstrated diffuse hypoechoic and anechoic areas in the orbitomalar area, which represented the edema and HA gel filler, respectively. The distribution pattern of the 2 HA gel fillers was distinctive even when embedded within the edema.

The current commercially available HA fillers are mostly derived from nonanimal stabilized HA produced by
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Biotechnological processes using *Streptococcus* species bio-fermentation. The HA are cross-linked using 1,4 butanediol diglycidyl ether (BDDE), producing intermolecular bonds for enhanced stability of the HA matrix. Commercial products differ in the concentration and percentage cross-linking, as well as in the chemical processing technologies in which BDDE bonds are formed. These differences create variations in the rheological properties of each HA filler and thus their clinical behavior.

Restylane-L is an elastic HA gel with a particle size of approximately 250 µm. It is biphasic in nature, with selectively sized particles of cross-linked HA suspended within a non-cross-linked carrier. The total HA concentration is 20 mg/mL.

Figure 3. Sagittal section of high-resolution ultrasound images of (A) Restylane-L (Medicis Aesthetics, Inc, Scottsdale, Arizona) (outlined in blue) and (B) Belotero Balance (Merz Aesthetics, Inc, San Mateo, California) (outlined in orange) showing distinct borders between the hyaluronic acid filler and surrounding tissue.

Figure 4. Examples of high-resolution ultrasound images of Restylane-L (Medicis Aesthetics, Inc, Scottsdale, Arizona) forming a more localized area within the subdermal layer, with “spread” into pearls or bubbles (outlined in blue).
Belotero Balance is monophasic in nature and contains varying amounts of cross-linked high molecular weight and low molecular weight HA that are subject to 2 successive cross-linking processes, yielding a monophase polydensified HA gel filler. The total concentration of HA in Belotero Balance is 22.5 mg/mL.7

As previously described, both Restylane-L and Belotero Balance appear to form distinct borders between the HA filler and surrounding soft tissue.2,3 In this study, we were able to identify through HRUS that the distribution patterns for Restylane-L and Belotero Balance differ within the periocular dermal layers.

We find ultrasound evaluation helpful in our practice to monitor filler placement. On ultrasound, Restylane-L filler formed a more localized distribution within the tissue and had the tendency to spread in a vertical fashion and form a bubble or pearl-like pattern. Belotero Balance filler distributed more widely within the same tissue plane. It diffused in a horizontal fashion, giving rise to an elongated or spindle-shaped configuration. These findings correlate with our clinical experience that Belotero Balance injections to the subcutaneous tissue give a smoother effect, especially in thin-skinned patients (Figure 6). Restylane-L, on the other hand, may be more powerful in providing volume in the deeper subdermal layer (Figure 7). Clinical photographs showed approximately 50% of HA gel filler remaining at 7 months posttreatment (Figure 7). In our practice, a particular HA filler is chosen after detailed clinical examination, depending on patients’ specific needs. We have anecdotally observed successful treatment with both Restylane-L and Belotero Balance; however, long-term objective data are not available.

Two patients developed edema around the periorbital area approximately 2 weeks after Restylane-L and Belotero Balance injections. It is interesting to note that the distribution pattern of both Restylane-L and Belotero Balance remained consistent even when embedded within edema. Tyndall effect and malar edema are important side effects of HA fillers, but the precise mechanism of occurrence is unknown. Theoretically, Belotero may increase the risk of these problems, but in clinical practice, some practitioners believe that Belotero decreases the risk compared with other fillers. We hope that long-term studies will help provide a clearer picture of the advantages and disadvantages of the various HA gel fillers with different rheological and physical properties.
Flynn et al.9 reported findings consistent with our ultrasonographic observations. In their histologic sections comparing mono- and biphasic intradermal HA injections of the forearm and buttocks, they found that the biphasic gel (eg, Restylane-L) showed clumps of material and formed large spaces in the subcutaneous tissue. The material was found in pools that appeared to push against separated collagen bundles. Monophasic polydensified gel (eg, Belotero) demonstrated abundant HA volume separating the collagen fibers throughout the depth of the reticular dermis. Only 10% of the material was seen as pools, and the rest appeared as harmonious diffusion.

Magnetic resonance imaging (MRI) is another modality for visualization of HA gel in vivo. Gensanne et al.10 have shown that T2 images demonstrate the ability for in vivo visualization and characterization of filler agents and also tissue modifications. However, the ease of performing HRUS in the clinical setting is an advantage. In addition, the ability to demonstrate the eyelid dynamics is another advantage over MRI.

This study had a number of limitations. First, our study sample was small. Second, the single injector was not blinded; therefore, injector variability should be taken into account. Another drawback of this study was our inability to capture consistent representative HRUS images before and after HA injection. There are no unequivocal landmarks to ascertain that the comparative slices are in the identical location. However, all pre- and posttreatment images were reviewed, and comparative images that matched most closely with each other were selected.

CONCLUSIONS

Our preliminary data, using HRUS to evaluate HA filler pattern in vivo, suggest that HA gel fillers with differing production technologies show distinct diffusion and distribution patterns in the periorcular tissues. Understanding the dynamics of interaction between these HA fillers and the subcutaneous tissues can assist clinicians in the selection and application of these products for rejuvenation.

Disclosures

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Figure 7. (A, D) This 47-year old woman complained of a tired and hollowed appearance in her lower eyelids. The oblique views show a distinct depression over her inferomedial orbit. (B, E) Immediately after injection of Restylane-L (Medicis Aesthetics, Inc, Scottsdale, Arizona) into the deep subdermal plane (0.5 mL on each side). Restylane-L is a more powerful tool for providing volume in the deep subdermal layer. (C, F) Seven months posttreatment, the effects of Restylane-L persist in the lower eyelid. (G, H) High-resolution ultrasound images of the right lower eyelid show the location of Restylane-L (outlined in red) immediately after injection (G) and 7 months after injection (H).