Soft Tissue Filler Properties Can Be Altered by a Small-Diameter Needle

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BACKGROUND Small-bore needles reduce the complications associated with soft tissue filler injection. Gel particles must be sized appropriately to pass through fine-bore needles with an acceptable extrusion force. However, most soft tissue filler particles are larger than the inner diameter of the needle. The authors hypothesized that the physical properties of these particles change as the gel passes through the needle.

OBJECTIVE The authors aimed to investigate whether the predesigned physical and rheological properties of the filler change after passage through the small-bore needle.

METHODS AND MATERIALS Particle sizes of 4 hyaluronic acid (HA) fillers were analyzed using a particle size analyzer. Five soft tissue fillers with different particle sizes were subjected to rheological characterization. All tests were performed using fillers with and without a 30-G needle.

RESULTS Monophasic HA fillers with smaller particle sizes exhibited small changes between particle sizes but no differences in rheological properties. Biphasic HA fillers with larger particle sizes exhibited remarkable changes in particle size and rheological properties. Calcium fillers exhibited changes in rheological properties.

CONCLUSION Injection through small-bore needles can alter the physical properties and rheological equilibrium of soft tissue fillers. The authors suggest avoiding small-bore needles as they may affect the rheological equilibrium and clinical performance of fillers.

W. Lee has been an investigator, speaker, and consultant for JETEMA Co., Ltd., South Korea. One of the hyaluronic acid fillers, e.p.t.q. s 500 lidocaine was sponsored by JETEMA Korea.

Soft tissue filler injection is the second most commonly performed cosmetic surgical procedure.[1] It is considered an easy procedure because its effect is immediately visible after injection. However, the incidence of complications is increasing as the popularity of the procedure also increases. Skin necrosis and blindness from vascular compromise after soft tissue filler injection are among the serious complications of this procedure.[2] Unfortunately, the mechanism and treatment of vascular compromise have not been entirely identified, despite several previous studies that aimed to prevent complications.[2–6]

Among preventive measures, the diameter of the injection needle remains a controversial issue. Multiple studies have recommended the use of small-bore needles.[5,6] Although small-bore needles can reduce the risk of vascular confrontation, the chance of a vascular embolism may increase once a needle tip enters an artery. By contrast, the use of needles or cannulas larger than the inner diameter of the blood vessel

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increases the chances of damage to the vessel but eliminates the possibility that the needle would enter the artery.[7] The decreased pressure resulting from the use of a small-bore needle or cannula does not reduce the injection pressure to below the systemic arterial pressure.[8] Furthermore, the initiation of an injection requires a greater magnitude of pressure than that required to maintain the flow. A smaller internal needle diameter requires a higher initial pressure to overcome resistance to flow, which results in the transmission of a higher initial pressure to the surrounding tissues.[8,9]

Previously published measurements of hyaluronic acid (HA) gel particle size have confirmed that the gel particle sizes used in clinical practice are larger than needle sizes.[10] However, no previous publication has directly measured potential changes in particle size and distribution that may occur when a filler is passed through a small-diameter needle. The physiochemical structure of a filler and associated rheological characteristics are important because they can help determine the behaviors of these substances during and after the respective applications. In this study, the authors hypothesized that the rheological equilibrium of a filler would change as it passes through a needle. This study therefore aimed to investigate whether the predesigned physical properties and rheological properties of a filler change after passage through a small-bore needle.

Materials and Methods

Materials

A total of 5 fillers with different particle size were analyzed. Fillers A (e.p.t.q. s 500 lidocaine, JETEMA Co., Ltd., Seoul, South Korea) and B (Chaeum Style No. 3, Hugel Biophamaceuticals Co., Ltd., Seoul, South Korea) were monophasic HA fillers, whereas fillers C and D were biphasic HA fillers. Filler E was a calcium hydroxyapatite filler. At least 4 mL of fillers was required to measure all variables. No financial support was received, and unless stated otherwise, the soft tissue fillers discussed in this article were directly purchased from commercial sources.

Methods

Particle Size Analysis

The particle sizes of the 4 commercial HA soft tissue fillers were evaluated using laser diffraction. The gel particle sizes in the soft tissue fillers were measured using a laser scattering particle size distribution analyzer (EQUMDQC LA960, Horiba, Japan). Particle size measurements were taken in a constant temperature room at 20°C (±2°). Particle size was calculated on a volume basis. The fillers were dispersed in a saline solution, and particle size and distribution were determined. Premanufactured particle sizes were evaluated. As the state of the gel changes after measurement, the gel size after passing through a 30-G needle, which is commonly used to inject fillers in clinical practice, was evaluated with each new filler.

The mean particle size is not clinically representative of deformation and must be interpreted in consideration of size distribution. A three-point specification featuring $D_{v0.1}$, $D_{v0.5}$, and $D_{v0.9}$ is considered complete and appropriate for most particulate materials. $D_{v0.5}$ is the median for volume distribution. $D_{v0.9}$ describes the diameter where 90% of the distribution has a smaller particle size and 10% has a smaller particle size. $D_{v0.1}$ has the diameter where 10% of distribution has a smaller particle size and 90% has a larger particle size. The authors compared the degree of change in $D_{v0.1}$, $D_{v0.5}$, and $D_{v0.9}$ from before to after passage through a needle in this experimental setting.

Hyaluronic acid gel particles were also analyzed using a light microscope (ECLIPSE Ni-U, Nikon, Japan). Hyaluronic acid fillers were stained with methylene blue and subsequently diluted with distilled water at a ratio of 1:50. The fillers were finally smeared on slide glasses and examined at ×40 magnification. They were injected at a velocity of 12 mm/min.

Rheological Test

The rheological properties of the above-described 4 HA soft tissue fillers and one calcium hydroxyapatite filler were evaluated. Rheological characterization was performed using an automated controlled stress rheometer (Discovery hr2, TA, Korea) with a parallel

plate diameter of 40 mm and temperature of 25°C. The experiments were performed within the linear viscoelastic range. The elastic (G′) and viscous (G″) moduli were determined using a frequency sweep test. The G′ values measured for each gel at a frequency of 0.1 Hz were compared. Each filler was placed on the plate of the rheometer and analyzed before passage through a needle. Thereafter, each new filler was passed through a 30-G needle and analyzed.

Results

Particle Size and Microscopic Findings

Changes in particle size and distribution are shown in Table 1. $D_{v0.5}$ of filler A exhibited a change of less than 9.8%. The relatively large particle-sized monophasic filler B exhibited a 24.5% change in $D_{v0.5}$ after passage through the 30-G needle. The $D_{v0.5}$ of filler C decreased by more than 58.8%, while that of filler D decreased by more than 49.4%. The $D_{v0.1}$ of fillers A and B exhibited a change of 10.1% and 18.9%, respectively, while that of fillers C and D decreased by 7.2% and 7.6%. $D_{v0.9}$ changed by 8.8% in filler A and 27.6% in filler B, whereas $D_{v0.9}$ changed by approximately 56.2% in filler C and by 43.4% in filler D. These results indicate that the effect of passing through a needle on particle sizes was stronger in biphasic fillers than in monophasic fillers. These results demonstrate that the extent of particle size changes in biphasic fillers is remarkable in the $D_{v0.5}$ to $D_{v0.9}$ diameter range compared with $D_{v0.1}$ diameter.

Microscopic analysis of fillers A and B revealed a slight difference between the originally manufactured product and the sample after passage through the 30-G needle (Figure 1). Microscopic analysis of fillers C and D revealed large differences between the pre-manufactured products and samples after passage through the 30-G needle (Figure 2).

Rheological Test Results

The rheological characteristics of the fillers evaluated in this study are shown in Table 2. The monophasic fillers A and B showed no remarkable

TABLE 1. Summary of the Size and Distribution Test Results

	Character	Conc. (mg/mL)	Size Before Passing Through a 30-G Needle						Size After Passing Through a 30-G Needle					
			Range	Mean	SD	$D_{v0.1}$	$D_{v0.5}$	$D_{v0.9}$	Range	Mean	SD	$D_{v0.1}$	$D_{v0.5}$	$D_{v0.9}$
A	Monophasic	24	152.43–1,531.91	471.83	204.37	258.93	430.47	735.93	133.10–1,337.48	428.20	188.13	232.97	388.37	671.77
B	Monophasic	20	116.21–1,754.61	480.76	250.96	218.26	428.23	807.16	88.58–1,167.72	358.50	172.11	177.21	323.42	584.09
C	Biphasic	20	101.46–4,537.43	1,161.35	728.91	248.58	1,073.95	2,110.99	116.21–2009.69	531.60	311.51	231.61	442.98	922.67
D	Biphasic	20	88.58–2,636.47	785.48	404.66	211.87	797.85	1,257.52	101.46–1,531.91	436.39	214.77	195.68	403.74	711.40

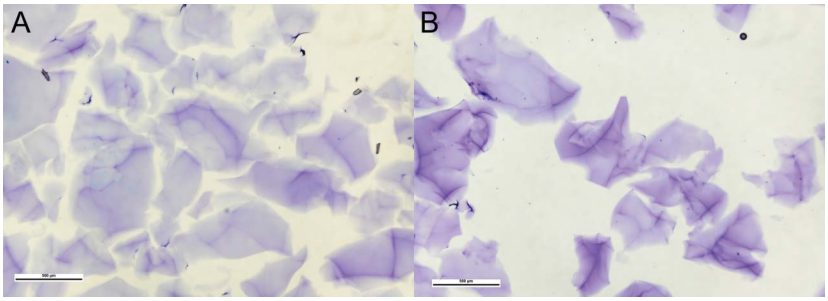

Figure 1. Microscopic observations of the premanufactured filler A (left) and the samples after passage through a 30-G needle (right). The mean particle size of filler A decreased from 471 to 428 μm/mL.

differences in rheological properties (Figures 3 and 4). The rheological properties of filler C passed through the 30-G needle exhibited changes in terms of becoming less elastic and less extensible than those of the premanufactured filler (Figure 5). The authors observed marked alterations in the states of rheological equilibrium in filler D with large particle sizes (Figure 6). Viscoelastic properties of biphasic fillers changed more markedly, indicating that the intensity of filler rheological changes during passage through a 30-G needle might be dependent on particle size. The calcium filler product also exhibited differences during rheological testing (Figure 7).

The coefficients of variation were calculated based on 3 replicative measurements from 2 filler samples (to account for variations arising from the instrumentation used). A value less than 5% was considered satisfactory. The coefficient of variation with respect to particle size was 9.62%. Additional coefficients of variation were 3.31% for the storage modulus, 2.98% for the loss modulus, and 3.30% for complex viscosity.

Discussion

In this study, the authors observed changes in gel particle size after passing the gels through the needle. Furthermore, the physical properties of the fillers changed after passing through the needle. However, the magnitude of deformation and degree of changes in physical properties were unpredictable. The authors assumed that changes in physical parameters that determine the rheological properties of the filler, such as particle size, can cause deviations in clinical performance.

Hyaluronic acid fillers are classified into 2 categories based on the cross-linking method used during manufacturing: monophasic or biphasic. Biphasic fillers exist over a broad spectrum of relatively larger HA particle sizes. Non-crosslinked HA acts as a carrier to allow larger-sized HA gel particles to be more easily injected through a fine needle into the soft tissue. By contrast, monophasic fillers consist of HA gel particles that exhibit a narrow size spectrum after being subjected to the grinding process. More crosslinks must be produced due to the process of manufacturing monophasic fillers, and thus, monophasic fillers

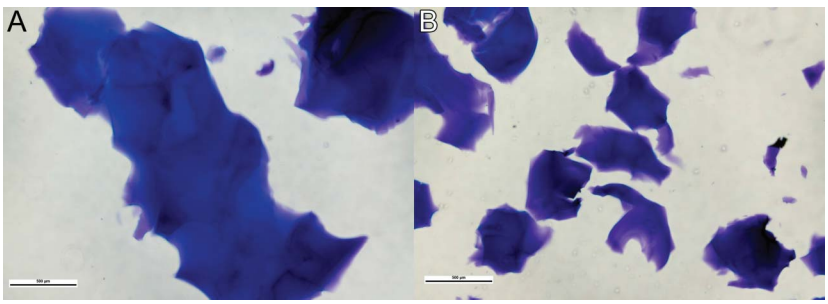

Figure 2. Microscopic observations of the premanufactured filler D (left) and the samples after passage through a 30-G needle (right). The mean particle size of filler D decreased from 785 to 436 μm/mL.

TABLE 2. Summary of the Rheological Test Results

	Rheology Before Passing Through a 30-G Needle			*Rheology After Passing Through a 30-G Needle*		
Filler	*G′ (Pa)*	*G″ (Pa)*	*Complex Viscosity (Pa. s)*	*G′ (Pa)*	*G″ (Pa)*	*Complex Viscosity (Pa. s)*
A	282.02	48.03	455.33	291.18	46.47	467.29
B	250.99	29.98	402.31	262.38	34.47	421.18
C	739.86	246.16	1,240.99	623.65	274.92	1,084.74
D	753.63	169.03	1,229.24	492.17	181.36	834.81
E	1,084.02	640.54	2,003.96	640.02	447.01	1,252.95

necessarily contain a higher content of crosslinking agent.[11]

Multiple studies have recommended the use of small-bore needles (27 G and 30 G).[5,6] Previous publications claimed that using a needle or cannula with a smaller diameter could reduce the risk of vascular confrontation. In practice, small-bore needles are preferred because their use can reduce undesired side effects, such as pain, bruising, bleeding, and edema, and may help the physician to perform a more delicate injection. Although small-bore needles have several clinical advantages, some clinical aspects should be considered when using a filler with a large particle size. As larger gel particles are more difficult to push through a small-bore needle, it will be more difficult to extrude a filler with a large average particle size. The extrusion force applied to the filler can be increased by increasing the average particle size. Therefore, doctors may experience resistance while injecting fillers containing larger gel particles, especially when small-bore needles are used.

The ability of a particle to withstand deformation and pass through the needle appears to be attributable to the thixotropic properties of the gel, even if the particle is larger than the inner diameter of the needle. Thixotropic properties enable the filler to remain a solid in the syringe, change to a liquid under pressure (i.e., while passing through the needle), and resolidify after passing through the needle.[12] However, the inner diameter of a 30-G needle is 0.16 mm. This suggests that large particles beyond the linear viscoelastic range may be so deformed during their passage through the needle that they cannot be restored. Filler C had a mean particle size of 1,161.35 ± 728.91 μm/mL, suggesting the presence of some particles larger than 1,800 μm (1.8 mm). These larger particles can cause interrupted or sporadic flow of the product through the needle.

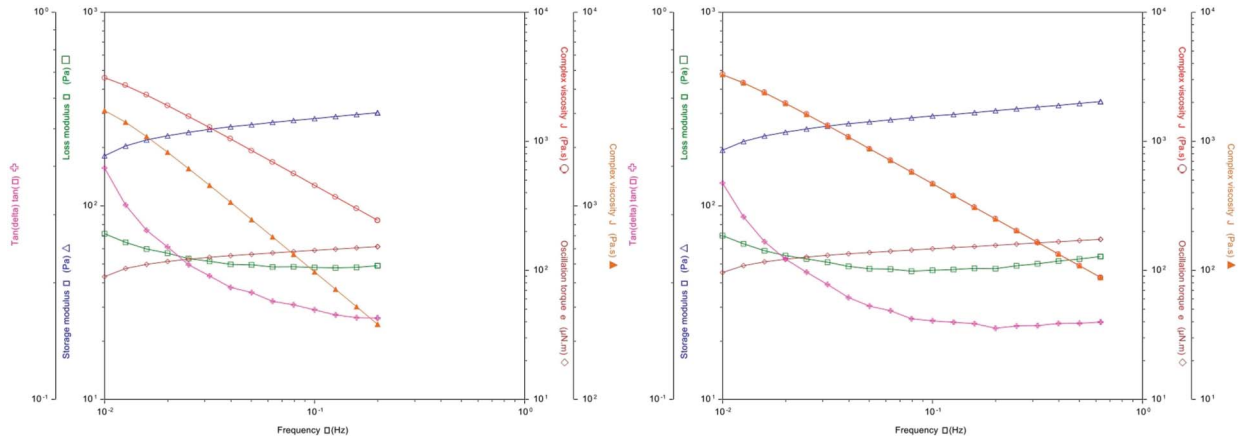

Figure 3. The rheological test results of filler A are shown. Rheological findings of the premanufactured product (left) and the product after passage through a 30-G needle (right). Note that no noticeable differences are visible between the premanufactured products and the samples after passage through a 30-G needle. The storage modulus, loss modulus, complex viscosity, and TanΔ are indicated by blue, green, orange, and pink lines, respectively.

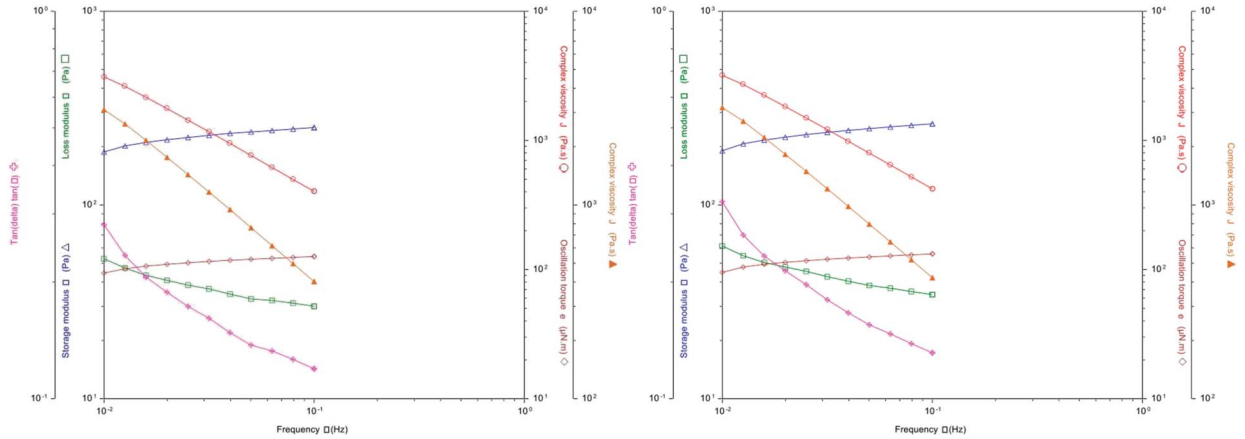

Figure 4. The rheological test results of filler B. Rheological findings of the premanufactured product (left) and the product after passage through a 30-G needle (right). Although differences in the particle sizes are observed, no noticeable differences in the rheological test results were observed between the premanufactured products and the samples passed through a 30-G needle. The storage modulus, loss modulus, complex viscosity, and TanΔ are indicated by blue, green, orange, and pink lines, respectively.

Although the authors presume that large particles could cause "stop-and-go" flow through a small-bore needle, the authors did not consider the possibility of a change in the physical property that might affect the clinical performance of the filler, such as the lifting capacity and longevity. In this study, the authors confirmed the changes in gel particle sizes after passage through a small-bore needle by comparing the particle sizes and rheological parameters. These changes may cause the injected filler to disappear more rapidly than expected and/or a decrease in the elevation of soft tissue at an earlier time point than expected.

Theoretically, a comparison of the particle size with the inner diameter of the needle reveals a change in particle size distribution of the filler due to damage from passage through a 30-G needle. Although the authors noticed changes in particle size in the monophasic fillers, the rheological characterization of samples after passage through needles revealed no remarkable differences in this experiment. The median particle size for filler A was 430 μm (0.43 mm). which was definitely greater than the 30-G inner diameter (0.16 mm). Filler B, with a median particle size of 0.42 mm, also did not exhibit definite differences in rheological characterization, despite changes in particle size. These results can be

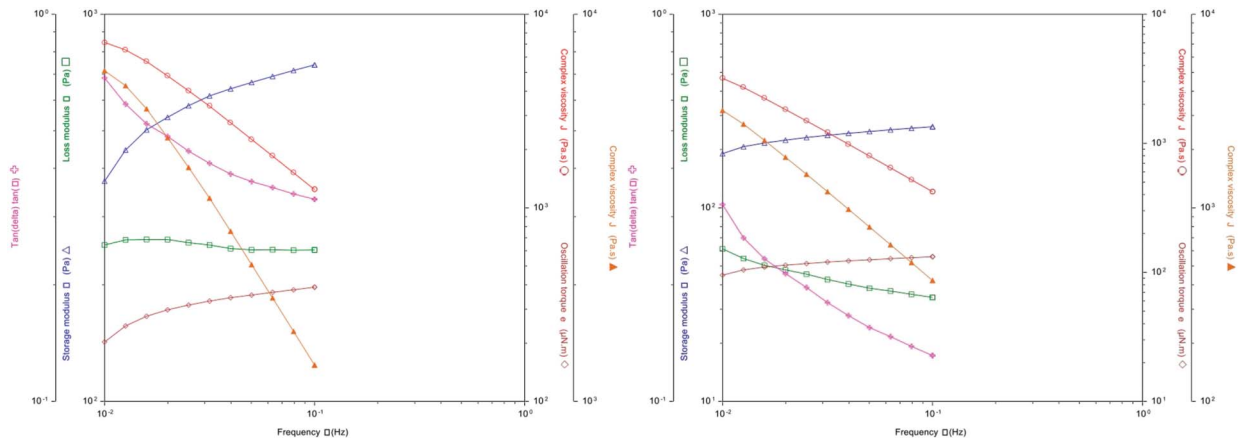

Figure 5. The rheologic test results of filler C. Rheological findings of the premanufactured product (A) and the product after passage through a 30-G needle (B). Significant differences were observed in the rheological test results between the premanufactured products and the samples passed through a 30-G needle. The storage modulus, loss modulus, complex viscosity, and TanΔ are indicated by blue, green, orange, and pink lines, respectively.

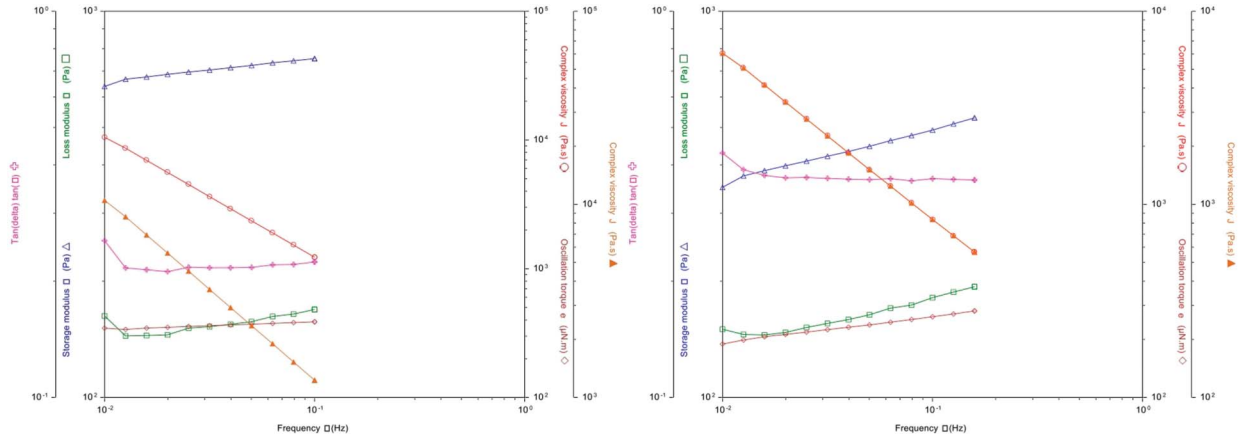

Figure 6. The rheologic test results of filler D. Rheological findings of the premanufactured product (A) and the product after passage through a 30-G needle (B). Significant differences were observed in the rheological test results between the premanufactured products and the samples after passage through a 30-G needle. The storage modulus, loss modulus, complex viscosity, and TanΔ are indicated by blue, green, orange, and pink lines, respectively.

explained as follows. Monophasic fillers contain relatively small-sized particles over a narrow spectrum and a large amount of crosslinking agent.[13] Accordingly, monophasic fillers are highly cohesive.[10] This relatively small, narrow spectrum of filler particles and strong cohesiveness allow the monophasic filler particle to easily pass through the needle and maintain appropriate rheological properties. Even if the particle is broken, the rheological properties of a filler with a large amount of crosslinking will not change. However, most biphasic filler particles did not contain high levels of crosslinking. Accordingly, when using a small-bore needle, the particles may be disrupted, leading to greater changes in the rheological properties. In addition, the particle size analyzer used in this study was based on laser scattering, which analyzes the particle size using hydration. As HA gel has a very high affinity for water, hydrated HA filler particles would appear larger than the original gel particles.[14]

In clinical practice, the manufacturer provides information regarding physical properties. It is not possible to account for the particle sizes of all types of premanufactured filler products. The particle size in an HA gel must be controlled to reduce the extrusion force and associated side effects (e.g., pain and bleeding) during injection. Therefore, the gels must be engineered to pass through a needle at an appropriate

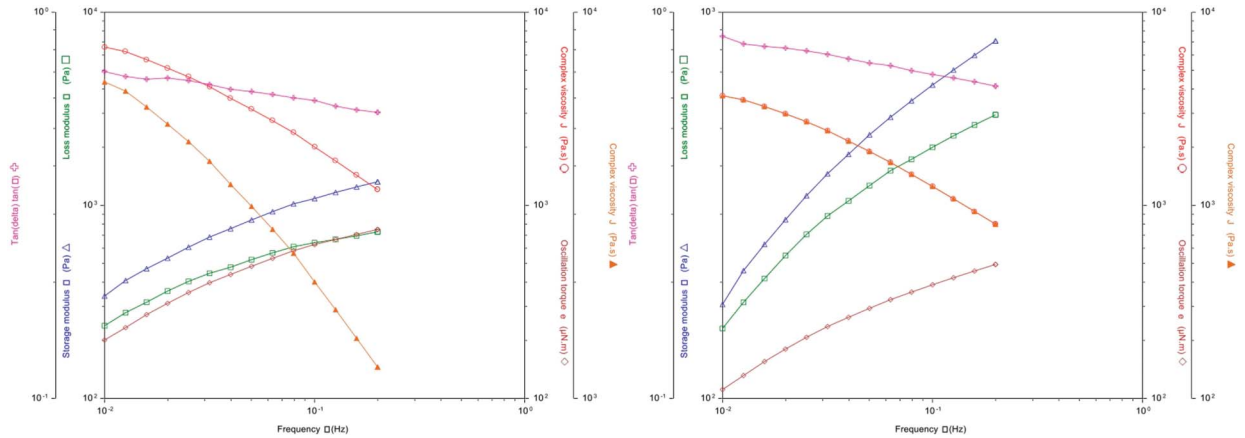

Figure 7. The rheological test of the calcium filler revealed differences between the premanufactured products (left) and those subjected to passage through a 30-G needle (right). The storage modulus, loss modulus, complex viscosity, and TanΔ are indicated by blue, green, orange, and pink lines, respectively.

rate and with the desired extrusion force. The resulting gel particle sizes are related to the extent of cross-linking and the molecular weight, as highly cross-linked HA gels associated with higher G′ values will be denser and more compact. When the authors use fillers specifically indicated for deeper soft tissue layers, the authors should avoid using a small-bore needle to inject the filler. Furthermore, manufacturers should provide recommendations regarding the minimal needle size required to minimize changes in the physical properties of the fillers.

To maximize changes in the filler after passage through the needle, the authors designed their experiment to compare the prefilled gel particles with gel particles that had been passed through a 30-G needle, which is considered to have a small diameter among the needles used for filler treatment. This experimental design is considered a limitation of this study. It seems necessary to compare the particle sizes and changes in rheological characteristics after passage through 25-G and 27-G needles, which are also used widely for filler treatment in clinical settings.

Conclusion

The authors recommend avoiding the use of small-bore needles with fillers containing large-sized gel particles, given the potential effects on particle size and rheological equilibrium. These changes may consequently affect the clinical performance of the gels, including the longevity and lifting capacity.

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