Macrolane for Volume Restoration and Contouring of the Buttocks: Magnetic Resonance Imaging Study on Localization and Degradation

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Background: Macrolane is a biocompatible, biodegradable, injectable stabilized hyaluronic acid–based gel of nonanimal origin manufactured using the nonanimal stabilized hyaluronic acid technology. This was a substudy to evaluate localization, displacement, and degradation of the gel when used for volume restoration and shaping of the buttocks.

Methods: Subjects aged 20 years or older seeking buttock augmentation received a maximum volume of 400 ml per subject. Gel localization and degradation up to 24 months after treatment was assessed using magnetic resonance imaging. Subjects carried out a self-assessment of aesthetic improvement using the Global Esthetic Improvement Scale. Safety assessments included adverse event reporting, blood sampling for analysis of systemic inflammatory responses, and body temperature.

Results: Eight subjects received a mean of 163 ml of nonanimal stabilized hyaluronic acid gel per buttock. After 6, 12, and 24 months, respectively, 56, 36, and 24 percent of gel remained in the buttocks, located primarily in the subcutaneous fat. Sixty percent of subjects rated their buttocks as improved up to 24 months after treatment. Over the 24 months, there was no gel displacement outside of the buttocks area, and the aesthetic result was not affected by minor gel displacement within the buttocks. There were no major inflammatory reactions or significant adverse events.

Conclusions: These data demonstrate that nonanimal stabilized hyaluronic acid gel degraded as expected in the buttocks, with minimal displacement. The treatment was well tolerated, and subjects' and investigators' perceptions of aesthetic augmentation of the buttocks remained high, even if only small volumes of the gel remained. (*Plast. Reconstr. Surg.* 132: 522e, 2013.)

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Reshaping of the buttocks is one of the fastest growing areas in aesthetic surgery, showing a 41 percent increase from 2009 to 2010 in the United States.[1] Reasons for buttock augmentation are varied but generally relate to the fact that the morphology of the buttock can change shape with aging and weight gain.[2] In addition, the buttock has long been recognized as an important secondary sexual characteristic, with a hip-to-waist ratio of 0.7 considered ideal.[3]

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Buttock contour surgery was pioneered in 1964 by Pitanguy,[4] who altered gluteal shape by the resection of tissue in the gluteal fold. Since then, gluteal implants, autologous fat grafting, and flap surgery have been developed to improve gluteal ptosis and/or small volume.[5] However, these traditional methods for buttock augmentation are all major surgical procedures, and they often require general anesthesia and/or produce scarring. Consequently, many people are now looking for a minimally invasive procedure. Injectable fillers based on hyaluronic acid demonstrate many of the properties of an ideal filler, as they are easy to use, biocompatible, nontoxic, and easily removed if needed (through the action of hyaluronidase or excision).[6,7]

Macrolane (Q-Med AB, Uppsala, Sweden) is a biocompatible, biodegradable, injectable stabilized hyaluronic acid of nonanimal origin manufactured using the nonanimal stabilized hyaluronic acid technology. The gel's biodegradable nature means that treatment effects are not permanent, allowing for continuous assessment and retreatment as the body ages. Although nonanimal stabilized hyaluronic acid gel is no longer marketed for the breast because of an ongoing debate regarding issues with radiologic imaging, numerous studies have found that the injection of the gel for breast and facial aesthetic procedures is effective and well tolerated.[8–14]

Magnetic resonance imaging can be used to distinguish between muscle and fat in tissue and has been used in the past to determine degradation rates and localization of fat after autologous fat grafting of the buttocks.[15,16] Magnetic resonance imaging has also been used to visualize nonanimal stabilized hyaluronic acid gel within the breasts.[11] Magnetic resonance imaging is therefore a useful tool for determining the gel's localization and degradation rates after injection into the buttocks. This was a substudy of eight subjects taking part in a multicenter trial of use of the gel for enhancement of the buttocks (unpublished data). The primary objective of the substudy was to use magnetic resonance imaging as a means of assessing the localization, potential displacement, and degradation of nonanimal stabilized hyaluronic acid gel when injected into the buttocks for volume restoration and contouring.

PATIENTS AND METHODS

This was a prospective, open-label, noncomparative study performed using subjects aged 20 years or older in Stockholm, Sweden. Exclusion criteria included active skin disease or inflammation, scar tissue on the area to be treated, body mass index less than 20, skin fold thickness less than 2 cm (measured using calipers over the subcutaneous layer), excessive skin laxity (>50 percent stretch of the skin), premalignant tumors near the area to be treated, liposuction or other procedures in the area during the previous 6 months, tumors, and subjects seeking corrections for other body parts between the umbilicus and the knees. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local independent ethics committee (Regionala etikprövningsnämnden i Stockholm).

Before injection of the product, the skin was sterilized with 70% alcohol, and local anesthesia (0.5% lidocaine with epinephrine; 40 ml per buttock) was used at the planned incision and injection site. A 16-gauge tumescent cannula was used for subcutaneous infiltration of the anesthetic. All subjects received prophylactic intravenous flucloxacillin (2 g) for 10 to 20 minutes before the start of the procedure. A maximum of 400 ml of Macrolane VRF30 per subject was injected into the subcutaneous fatty tissue (supramuscularly) through a 5-mm incision. The nonanimal stabilized hyaluronic acid gel was injected with a multiple tunneling technique, similar to that used for fat grafting, using a 15-cm, 12-gauge cannula with a blunt tip. An optional touchup treatment could be performed within 8 weeks after initial treatment if required. Subjects were advised to avoid strenuous activity, including constant pressure in the treated area for a 2- to 3-week period after treatment.

Magnetic resonance imaging was performed on all subjects in the prone position 1 to 5 days, 6 months (±14 days), 12 months (±28 days), and 24 months (±28 days) after treatment. Imaging was performed with a 1.0-T (Siemens Harmony; Siemens, Munich, Germany) or 1.5-T (Siemens Symphony) superconductive system using surface coils. Sagittal short TI inversion recovery and proton density images were acquired with a slice thickness of 5 mm covering all of the implant. Transverse images with a minimal gap and 2-mm thickness were acquired covering all of the implant. The 2-mm transverse images were used for volume measurements of the implant. The first subject underwent an extended magnetic resonance imaging examination (1 to 2 hours instead of 30 minutes) to evaluate the optimal settings to clearly differentiate the gel from the surrounding tissues, the gluteus maximus muscle, and the fat tissue. Scans were evaluated to determine the

localization, possible displacement, and remaining volume of the study product.

Standardized photographs of the subjects were taken by the investigator before treatment and 1 month (3 to 6 weeks), 6 months (±14 days), 12 months (±28 days), 18 months (±28 days), and 24 months (±28 days) after treatment. Eighteen-month data are not presented. Based on these photographs, subjects and investigators independently assessed the aesthetic improvement of the buttocks using the five-point Global Esthetic Improvement Scale (i.e., worse, no change, improved, much improved, or very much improved).

Systemic inflammatory responses to the injection procedure and nonanimal stabilized hyaluronic acid gel were assessed with serum C-reactive protein, serum interleukin-6, plasma procalcitonin, white blood cell count, and blood differential measurements from blood samples taken 0 and 48 hours before treatment, 6 and 48 hours after treatment, and 1 month after the first treatment. Subjects also measured their body temperature in the morning at home during the 2 days before treatment, on the day of treatment, and for 3 days after treatment. Safety was also assessed by adverse event reporting by the investigator and subject at each study visit. Expected treatment-related events included redness, swelling, tenderness, pain, bruising, and itching.

RESULTS

Demographic Data

A total of eight subjects were included in this substudy and treated with nonanimal stabilized hyaluronic acid gel injections into the buttocks. The mean age of the subjects was 45 years, and seven of eight subjects were women. Table 1 lists the subject demographics. A mean volume of 162.5 ± 22.5 ml of gel was injected per buttock. Of the eight subjects, seven underwent magnetic resonance imaging at 12 months and five at 24 months; of the three subjects who did not undergo the 24-month imaging, two were lost to follow-up after attending the 18-month visit. No subjects required touch-up treatment after the initial treatment or pretreatment medication before magnetic resonance imaging examination.

Table 1. Summary of Demographic Characteristics

Baseline Characteristics	Value
No. of patients	8
Mean age ± SD, yr	45.3 ± 7.4
Sex, n (%)	
Female	7 (88)
Male	1 (12)
Mean weight ± SD, kg	63.0 ± 8.6
Mean height ± SD, cm	166.5 ± 6.8
Mean BMI ± SD, kg/m^2	22.7 ± 2.3
Mean skin-fold thickness ± SD, mm	3.9 ± 0.7
Mean skin laxity ± SD, %	29.5 ± 10.4

BMI, body mass index.

Magnetic Resonance Imaging Assessment

On magnetic resonance imaging scans, nonanimal stabilized hyaluronic acid gel was visible in a globular subcutaneous pattern, with some gel in a feather-like pattern inside the gluteal muscle and with signal intensity close to that of water. Representative scans from three subjects at 1 to 5 days and 6, 12, and 24 months after treatment are shown in Figure 1. Posttreatment scans 1 to 5 days after injection demonstrated that more than 60 percent of the gel was located in the deep subcutaneous fat in six of the subjects (Fig. 2). The remaining gel was generally located intramuscularly. By 6 and 12 months after treatment, seven and six subjects, respectively, had more than 60 percent of the gel located in the subcutaneous fat (Fig. 2). After 24 months, three of five subjects had more than 60 percent of the gel located in the subcutaneous fat, whereas over time, gel placed intramuscularly tended to degrade more than gel placed in the subcutaneous fat (Fig. 1, *below*). At 6, 12, and 24 months after treatment, respectively, means of 56 percent (183.5 ml), 36 percent (118.7 ml), and 24 percent (86.7 ml) of the gel remained in the buttocks, although the degradation rate was highly variable between subjects (Fig. 3). The degradation rate between buttocks was similar, allowing for an even appearance at all time points (Fig. 3).

At the 6-month visit, parts of the nonanimal stabilized hyaluronic acid gel implant had changed position in five subjects (62.5 percent) since the initial examination. Changes in position included local displacement of the product in the superior, medial, and/or lateral direction; and coalescence of product to form fewer but larger deposits. There were no further changes in the position of the gel at 12 and 24 months after initial treatment. No subject experienced displacement of the product outside of the buttock area, and this was also not clinically apparent or diagnosed by the investigator.

Safety Data

None of the treatment-related adverse events were unexpected or serious. Laboratory assessments showed that serum C-reactive protein was

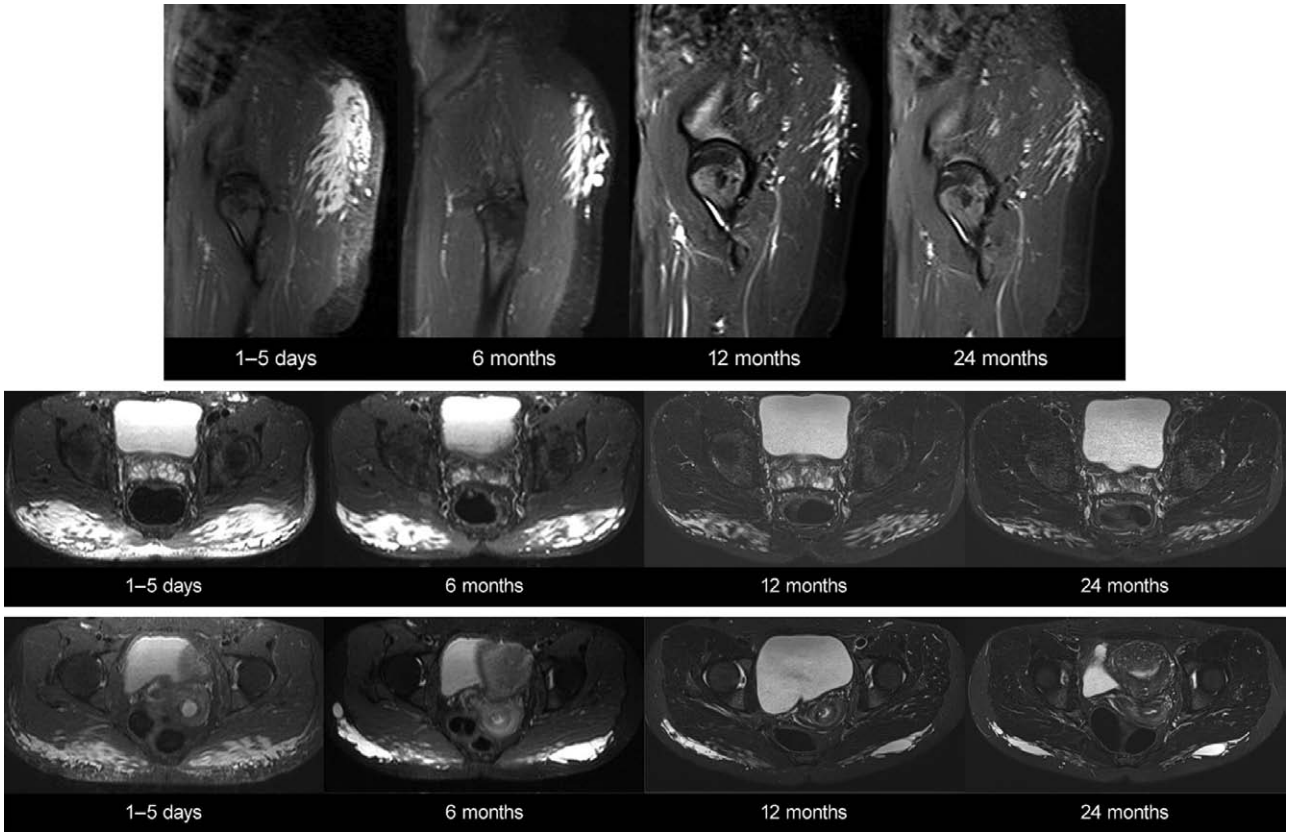

Fig. 1. Magnetic resonance imaging scans of nonanimal stabilized hyaluronic acid gel within the buttocks. (*Above*) Sagittal short TI inversion recovery images: some of the gel is inside the gluteal muscle in a feather-like distribution. The majority of the gel is in a globular subcutaneous pattern. (*Center*) Transverse short TI inversion recovery images. Nearly all of the gel is in the subcutaneous space, with continuous degradation. (*Below*) Transverse short TI inversion recovery images. More than 50 percent of the gel is inside the gluteal muscle in a feather-like distribution. The rest is in a globular subcutaneous pattern. The gel inside the muscle is degraded faster.

raised in two subjects 48 hours after administration of the product (131 mg/liter and 45 mg/liter; reference value, <3 mg/liter). No other clinical symptoms were evident, apart from mild itching in one of these subjects that did not require treatment. One subject had pyrexia (fever, 37.8°C) which lasted for 1 day after treatment. This subject also had a slightly raised white blood cell count but did not have an elevated serum C-reactive protein level.

Global Esthetic Improvement Scale Data

When compared with pretreatment photographs, all subjects rated their buttocks as improved or better (i.e., improved, much improved, or very much improved) 1 month after treatment (Fig. 4). By 6, 12, and 24 months after treatment, seven of eight (88 percent), five of seven (71 percent), and three of five (60 percent) subjects still considered their buttocks as improved. Investigator ratings of improvement were similar (Fig. 4). Representative examples of the aesthetic improvement achieved are shown in Figure 5.

DISCUSSION

Nonanimal stabilized hyaluronic acid gel is a biodegradable and biocompatible product used for body contouring and volume restoration. As expected, this study showed that the product degrades in the body over time.

In the current study, 36 percent of the gel remained in the buttocks at 12 months, which is consistent with results in the breast, where 25 to 36 percent of the gel remained 12 months after treatment, depending on submuscular and subglandular placement of the product.[11] As with gel used in the breasts, the degradation rate in the buttocks was variable; between 16 and 45 percent of the gel remained in the buttocks of those subjects undergoing magnetic resonance imaging at 24 months. These rates are comparable with one

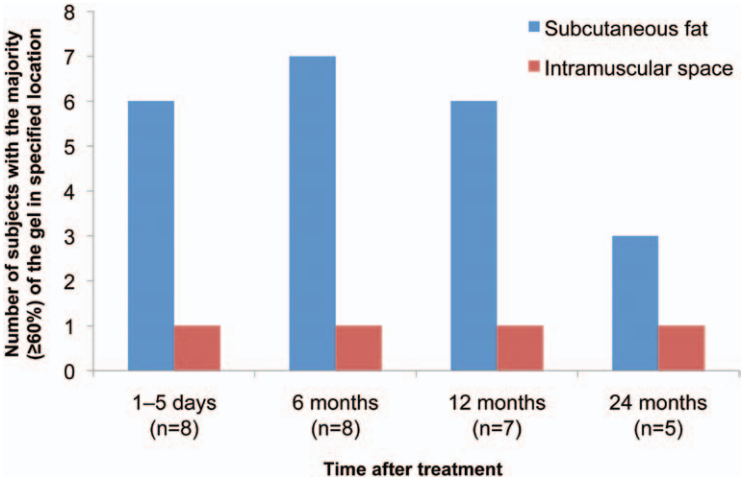

Fig. 2. Approximate volume and localization of nonanimal stabilized hyaluronic acid gel in the buttocks. *n*, number of subjects undergoing magnetic resonance imaging at visit.

previous 24-month imaging study of gel used for breast augmentation, where 19 percent of the gel was still present at the end of the study (Q-Med, unpublished data). The reasons for the observed between-subject variability in degradation are unknown; however, in the current study, higher rates of degradation were seen when the gel was placed intramuscularly compared with placement in the subcutaneous fat.

The aim was to place the gel supramuscularly; however, unintended intramuscular gel placement was noted on magnetic resonance imaging, especially in thin subjects. This may relate to the thin gluteal muscle fascia being difficult to localize by hand during implantation. In two subjects in this study, 40 percent or more of the gel was located in the muscle immediately after treatment. Intramuscular gel placement did not appear to affect the aesthetic result, as subjects with intramuscular placement still assessed their buttocks as improved.

To minimize the risk of inadvertent injection into blood vessels, nonanimal stabilized hyaluronic acid gel should be injected using a blunt cannula.[17] In addition, the gel should be injected only by physicians who have a thorough knowledge of the anatomy of the treatment site and who are experienced with injection techniques in the relevant area. Furthermore, special caution should be exercised when treating areas in close proximity to permanent implants or vulnerable structures such as nerves, vessels, and viscera.

The gel appeared on magnetic resonance imaging scans with a signal intensity close to that of water. The distribution of the gel within the tissue reflected the multiple tunneling technique used to inject the product, with multiple globular deposits dispersed throughout the deep

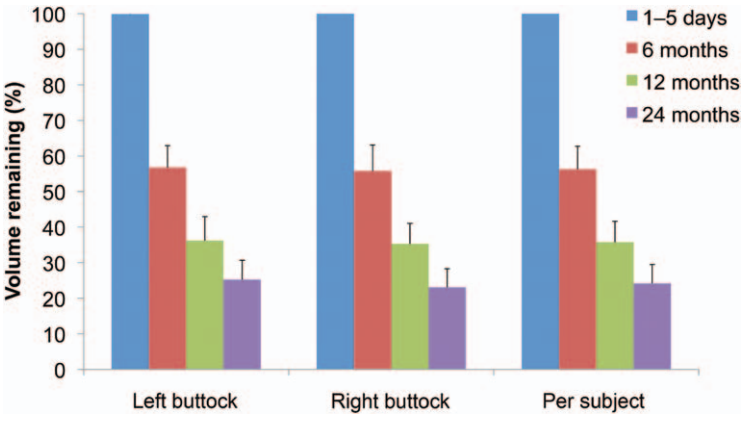

Fig. 3. Volume of nonanimal stabilized hyaluronic acid gel remaining per buttock and per subject up to 24 months after treatment.

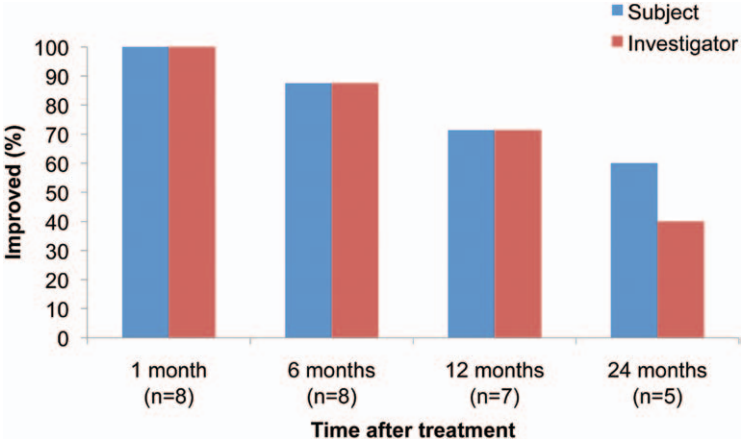

Fig. 4. Subjects' and investigators' perceptions of aesthetic improvement rated as improved, much improved, or very much improved up to 24 months after treatment by the Global Esthetic Improvement Scale.

subcutaneous tissue with a feathered pattern inside the gluteal muscle, comparable to scans obtained after autologous fat grafting.[15,16]

The highly variable nonanimal stabilized hyaluronic acid gel degradation rate between subjects in the current study is similar to degradation rates of fat after fat grafting. Using subjective assessments, the degradation rate after fat grafting can range from 25 to 90 percent in clinical studies.[18] Furthermore, in a recent survey of 508 plastic surgeons, the majority considered that the loss is greater than 50 percent 6 months after fat grafting.[18] A reason for this variable degradation after fat grafting is fat cell survival, which can be affected by fat processing, aspiration technique, body location, and site of injection.[6,19] Two studies

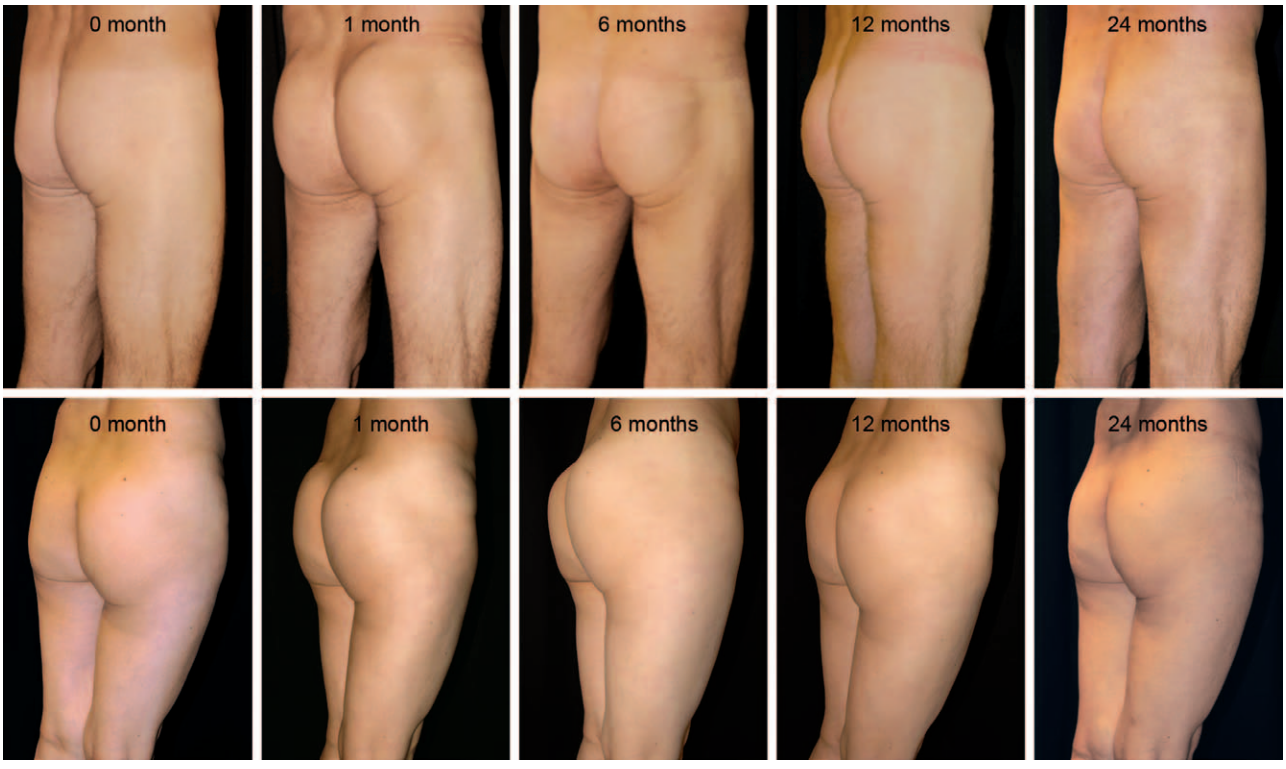

Fig. 5. Aesthetic improvement up to 24 months after receiving nonanimal stabilized hyaluronic acid gel for buttock augmentation. At 6, 12, and 24 months after treatment, respectively, means of 56, 36, and 24 percent of the gel remained in the buttocks across all subjects.

have used magnetic resonance imaging as a more objective measurement to assess degradation after fat grafting and found degradation rates of 24 to 36 percent and 49 percent at 3 months after treatment.[16,20] For nonanimal stabilized hyaluronic acid gel, the degradation rate was similar for each buttock, allowing for an even buttock appearance over time.

Although some subjects had magnetic resonance imaging–confirmed position changes in the product during the first 6 months, this did not affect the aesthetic result, which was rated as improved, much improved, or very much improved in seven of the eight subjects (88 percent) 6 months after treatment. No further changes in the position of the gel were noted at 12 and 24 months after treatment even though the improvement scores decreased slightly.

In the larger multicenter study, injection of nonanimal stabilized hyaluronic acid gel in the buttocks was well tolerated up to 24 months after treatment (unpublished data). In this substudy, although there was an increase in C-reactive protein in two subjects 48 hours after treatment, this was not accompanied by any clinical symptoms, apart from mild itching in one subject, which resolved without treatment. All subjects in this substudy had received prophylactic intravenous antibiotics before injection.

As with autologous gluteal fat grafting, subjects may choose to have a touchup procedure to maintain the result. Indeed, the positive results of fat grafting in the breasts are contingent on the subject receiving small volumes over multiple treatments.[21]

This study had some limitations. The sample size was small, as magnetic resonance imaging follow-up could be performed for subjects at only a single center. In addition, the Global Esthetic Improvement Scale is based on subject and investigator perceptions of improvement. However, photographs of aesthetic improvement have been provided from two representative patients to allow for an objective assessment of the result.

This initial pilot study demonstrated the feasibility of using up to 400 ml of nonanimal stabilized hyaluronic acid gel for buttock augmentation. There were no technical or health problems related to the treatment procedure. As expected for this biodegradable product, the gel degraded over the period of study; interestingly, the majority of subjects still assessed their buttocks as improved 2 years after treatment despite the fact that, on average, only 24 percent of the product remained in the buttocks. In addition, there was minimal product movement over the course of the 2 years.

CONCLUSIONS

These data demonstrate that nonanimal stabilized hyaluronic acid gel degraded as expected in the buttocks and there was minimal displacement of the gel. The treatment was well tolerated and could effectively create an aesthetic augmentation of the buttocks. Subjects' and investigators' perceptions of aesthetic improvement remained high, even if only small volumes of gel remained.

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