

New Hyaluronic Acid Filler for Subdermal and Long-lasting Volume Restoration of the Face

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Abstract

Over the past few years, the focus in the field of aesthetic medicine has gradually shifted towards minimally invasive procedures. As more and more patients are refusing to take prolonged absences from their work, the use of filler materials, botulinum toxin A, peelings, laser, fat implantation and other minor surgical corrections has significantly increased. Minimally invasive volume restoration of the face through long-lasting resorbable fillers is nowadays more attractive and important to patients.

Keywords

Hyaluronic acid, minimally invasive filler procedures, subdermal volume restoration

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Using combinations of filler materials, botulinum toxin A, peelings, laser, fat implantation and other minor surgical corrections, it is possible to achieve optimal clinical results for individual patients over a period of two years. These methods can cumulatively achieve the same result that would have previously been achieved by surgical procedures. In the course of the ageing process the treatment stages that are necessary for each individual can be applied without creating an irrevocable outcome for the patient, which may occur when invasive surgical procedures are used.

It is necessary for the treating physician to master all of the new minimally invasive techniques in order to give patients optimal advice tailored to their specific needs. Physicians should never choose a technique just because they are proficient in it if the technique does not represent the optimal solution for a particular patient's needs.

Despite the fact that fat and fillers have now been in use for decades and despite many new developments in this sector, even minimally invasive methods can have side effects and contraindications that must be taken into account in specific cases and need to be fully explained to patients.

The use of permanent fillers such as polyacrylates has become increasingly controversial over the past few years due to the appearance of granulomas.

Hyaluronic acid is the gold standard for treatment, but in applications and clinical evaluations we found that the approximate effective duration with first- and second-generation hyaluronic acids (and even the numerous 'new hyaluronic acids' that have been developed in the past few years) was only three to four months. Nowadays, there are three different technologies for manufacturing hyaluronic

acids. According to the first method, a partly cross-linked portion of hyaluronic acid is suspended in a non-cross-linked hyaluronic acid (bi-phasic products such as Restylane, Perlane, Hylalform, etc.) in order to make the substance injectable. According to the second method, hyaluronic acid is first partly cross-linked (around 1–20%), and the final product, which is described as a mono-phasic product (Juvederm, Esthelis and Teosyal), is then sucked into a syringe. The latest development in the field of hyaluronic acids is a highly cross-linked hyaluronic acid (over 70%) that has no suspension at all and still has the best injectability features. The author has used one of these newly developed hyaluronic acids (Varioderm® Subdermal, Adoderm Company) for volume restoration on the face for more than two years. When injected properly, this hyaluronic acid has proved to be effective for a significantly longer period of time (12–18 months after one single injection). The only disadvantage was a slightly increased swelling tendency during the initial phase. There were no subsequent complications. In our view, this substance represents an interesting new development in the field of fillers.

Hyaluronic Acids – Natural Occurrence and Properties

Since the 1980s, hyaluronic acids have been widely used as a material for the manufacturing of implants. Hyaluronic acid is part of a class of substances that form the extracellular matrix of the skin. To a large extent, hyaluronic acid can bond to water.^{5,10,11} Hyaluronic acid affects the controlled permeability of cells; it separates various cells and compensates for the hydroxyl radicals formed during the inflammation process.^{2,3} High-molecular-weight hyaluronic acid has the property of being able to absorb more water with increasing degradation (isovolumic degradation).⁵ By using cross-linking technology, it is possible to produce a polymer with a higher molecular weight of between 5 and 6 million but with the same chemical structure.¹

Figure 1: Subcutaneous Hyaluronic Acid Implant Varioderm Subdermal Three Months After Injection (Rat 25, Group Three)

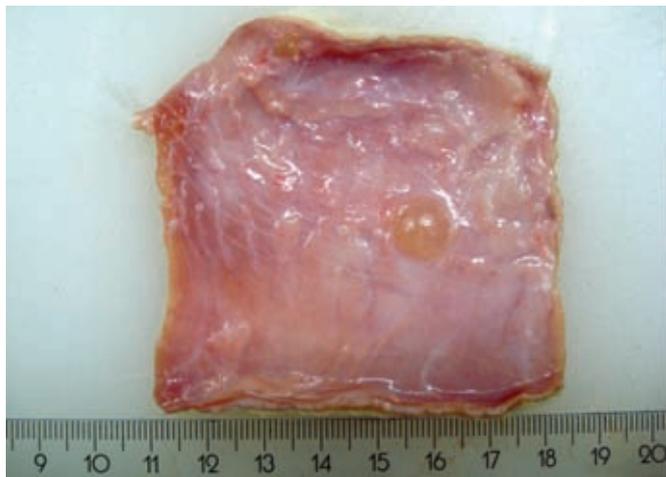
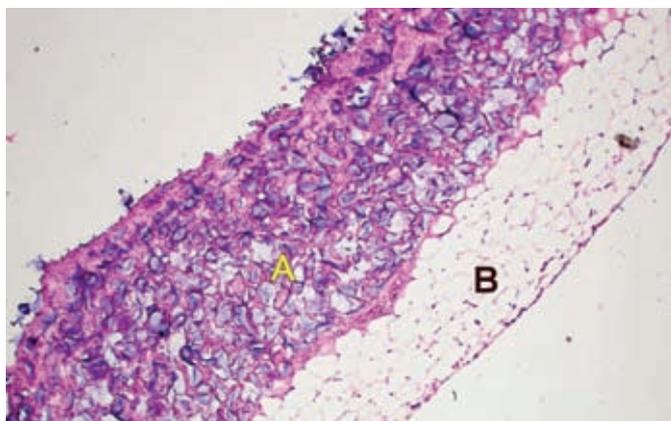
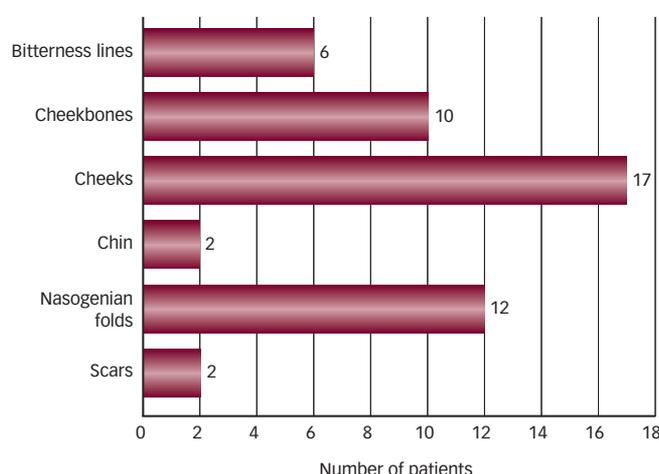


Figure 2: Cross-section of Hyaluronic Acid Gel Implant at Low Magnification (Rat 25, Group Three)



The capsule (A) consists of a mesh-like connective tissue and includes many small encapsulated gel particles (stained blue). On the bottom right is subcutaneous fat tissue (B).

Figure 3: 39 Patients Were Treated with Different Indications



The viscosity and elasticity of hyaluronic acid are affected by the number of bonds and rings in the molecular chains. Cross-linked hyaluronic acid has a significantly higher elasticity than non-cross-linked polymer with a significantly higher molecular weight.⁸

Sterilisation of cross-linked hyaluronic acid at 121°C for 15 minutes does not change its properties or chemical composition.^{2,3}

Impurities can also be expected in hyaluronic acid due to bacterial fermentation. The determination of endotoxins is necessary. The maximum allowed value should be less than 0.5IU/mg.¹²

The protein content of hyaluronic acid should be tested in order to rule out any immunological reactions. The content of nucleic acids should be determined photometrically at 260nm (purines and pyrimidines absorbing wave light).

Biocompatibility

When used as a filler, hyaluronic acid products of non-animal origin have been proved not to have any sensitising effect.⁴ An immunological reaction is not to be expected when using hyaluronic acid preparations that have been produced by means of bacterial fermentation.⁴ Pathological changes and acute or chronic sensitivity have been observed after the use of cross-linked hyaluronic acid, with no systemic effects.⁵ Animal experiments have confirmed that hyaluronic acid cross-linked by divinyl sulphone (DVS) is compatible with blood.^{6,7} Animal experiments with rats, rabbits, monkeys and guinea pigs conducted over a period of 33 months showed that cross-linked hyaluronic acid is biocompatible (non-inflammatory, non-toxic, non-immunising).¹³ The immunological compatibility of the cross-linked acid has been demonstrated mainly by the fact that the glycosaminoglycan chains contained within its basic structure remain unchanged after chemical modification (cross-linking with DVS).¹³

The biocompatibility of Varioderm Subdermal has also been extensively tested using the following test procedures according to European Directive and ISO standard 10993: sensitisation, irritation,

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acute systemic toxicity, genotoxicity, mutagenicity and systemic effect after subcutaneous implantation with three to six months of follow-up. All results are similar to the above previous findings with the DVS cross-linked hyaluronic acids, demonstrating the biocompatibility (non-inflammatory, non-toxic, non-mutagenic and non-genotoxic) of Varioderm Subdermal.¹⁵ Figure 1 demonstrates the durability in the subdermis after three months as encapsulated hyaluronic acid does not migrate. In Figure 2, histological image at low magnification shows the capsule of the gel inclusion consisting of a meshwork of connective tissue septa (reddish), which includes many little gel zones (stained blue). Low-inflammation cells are located in the connective tissue septa around the gel zones and in the border zone towards the lumen of the big gel zone on the top left side. The gel was leaked from the big gel zone during preparation.

Figure 4: Durability and Filling Effect of Varioderm Products

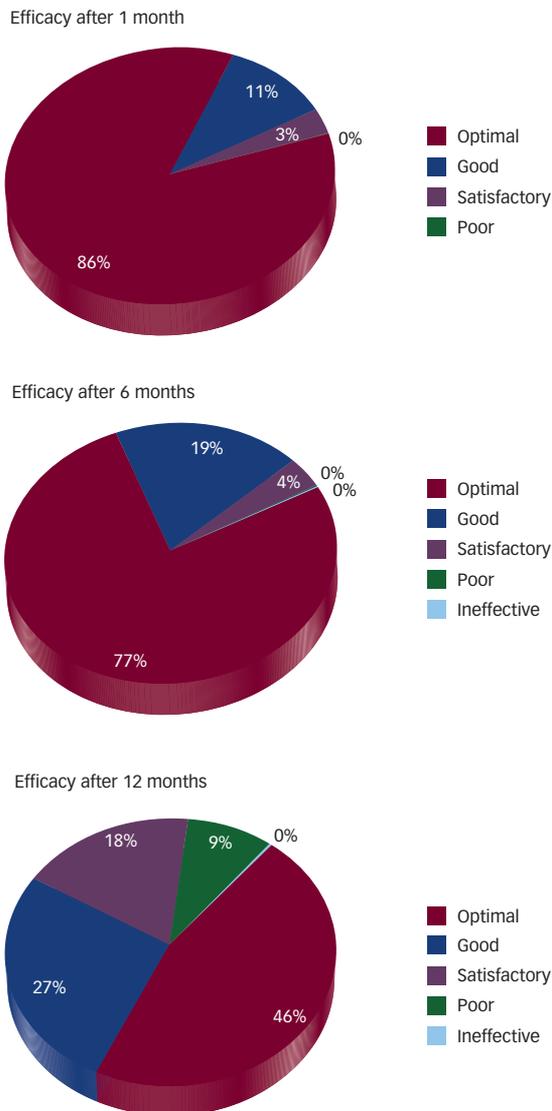


Figure 5: Cheek Augmentation and Marionette Lines of a Patient Before and After Injection with Varioderm Subdermal 1ml (Before and After 12 Months)



Figure 6: Injection with Varioderm Subdermal 2ml in the Naso-labial Folds (Before and After Nine Months)



Figure 7: Varioderm Subdermal 2.5ml Deep Naso-labial and Marionette Folds (Before and After 12 Months)



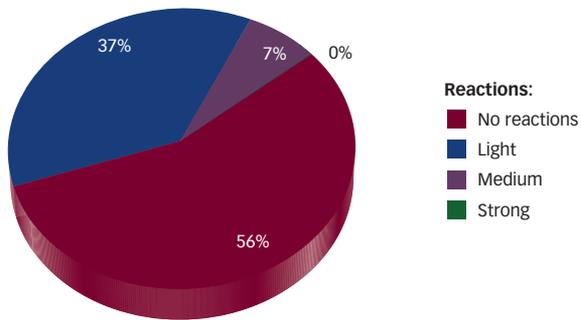
Biodegradation

The degrading process of cross-linked hyaluronic acid (cross-linked with DVS) takes place from the surface of the material. At the same time there is a steady but slower decomposition within the polymer matrix. The material decomposes by two different mechanisms: enzymatic splitting by means of hyaluronidase, which happens only to a small extent, and the much more vigorous decomposition by hydroxyl radicals, which serve as a source of active oxidation. Enzymatic decomposition occurs very slowly. Viscous hyaluronic acids in a physiological common salt solution are broken down subcutaneously within a few days if the hyaluronidase cannot penetrate the gel. Twenty per cent of the applied quantity of cross-linked hyaluronic acid is decomposed within 10 days; the decomposition of the remaining gel takes ≥ 100 days. The oxidation of hydroxyl radicals proceeds significantly faster in inflamed tissue. Degradation can be detected by lowering the viscosity. The degradation reactions of the cross-linked hyaluronic acid are slowed down significantly by the blocking of access to the interior of the matrix compared with the non-cross-linked material.^{2,3} Cross-linked hyaluronic acid is metabolised in the liver into CO₂ and water.^{5,10}

The Production Process for Varioderm Subdermal

Sodium hyaluronate obtained by biofermentation is dissolved in water and cross-linked using DVS until a degree of cross-linking of more than 70% is achieved; the degree of cross-linking is always monitored for each batch. The DVS is subsequently completely washed away. This cross-linked sodium hyaluronate is the reaction product with DVS (C₂H₃-SO₂-C₂H₃). The hydroxyl groups of the disaccharide from D-glucuronic acid and N-acetyl-D-glucosamine are cross-linked to each other by sulfonyl bis ethyl bridges. Sodium hyaluronate and DVS form a continuous network and an aqueous gel during the reaction. The properties of the cross-linked hyaluronic acid depend not only on the relative number of DVS bridges, but also on the cross-linking positions in the hyaluronate chains and their spatial arrangements with each other. These can all be affected by the reaction parameters. The highly concentrated and cross-linked hyaluronic acid, which has a significantly higher viscosity compared with the initial mixture, is subsequently made into particles and stabilised to facilitate the filling of the syringes without the need for any dilution. This is described as a monophasic particle technology (MPT).

Figure 8: Good Safety Profile of Varioderm Subdermal



Clinical Experience

Varioderm Subdermal was used between April 2006 and December 2008. In total 39 patients were treated with different indications (see *Figure 3*). The product that was used consisted of 27mg/ml cross-linked Varioderm Subdermal, which is the highest concentration of dermal filler available currently on the worldwide filler market.

Varioderm Subdermal was injected in subcutaneous tissue and the deep dermis using a 26G needle. Subcutaneous injections of Varioderm Subdermal were mostly used for the treatment of deep naso-labial and marionette folds, cheeks and cheekbones. The injection pressure was acceptable, and acute reactions such as swelling, reddening and pain were either minimal or did not occur. A pronounced volume effect and good adaptation to the tissue were observed, so that even very pronounced folds could be corrected. No complications were noticed either in the short term or during check-ups after three, six, nine and 12 months, with treatment effects lasting for 12–18 months (see *Figure 4*).

Conclusion

With over 70 preparations available, the market for hyaluronic acids is cluttered; for the individual user, it can be quite difficult to comprehend. Frequently, it is difficult for doctors to find out whether a 'new' hyaluronic acid has really been produced by means of a new production technique or whether the name or the firm has simply been changed. Only two other hyaluronic acid fillers (besides Varioderm Subdermal) are useful for deep folds and subdermal volume augmentation, but they are much more difficult and traumatic to implant (with 16G needles) as local anaesthesia and small incision is needed. A further problem is the dislocation and migration of the

filler from the injected area. Varioderm Subdermal fulfils our expectations from the injectability (26G needle and very easy to inject). Permanent fillers, in particular acrylates, are increasingly being viewed critically by leading users because of the risk of granulomas. Therefore, the development of this hyaluronic acid with long-lasting effects and a good safety profile plays an important role in the field of fillers. According to the specifications mentioned above, hyaluronic acids are deemed to be very safe. Short-term skin nodules and hardening generally appear to be due to the injection techniques used and the product volume injected; a histology study demonstrated the absence of granuloma. Foreign-body reactions with long-term nodules may rarely occur when hyaluronic acid fillers are applied. Treatment of such nodules can be performed by intra-nodal injection of hyaluronidase.¹⁶ There is no need to use corticosteroids, which are associated with the risk of atrophy.

The immunological compatibility of the cross-linked acid has been demonstrated mainly by the fact that the glycosaminoglycan chains contained within its basic structure remain unchanged after chemical modification.

Overall, Varioderm Subdermal is a new hyaluronic acid that has been tested and has shown a good volume effect, good adaptation to the tissue and long-lasting augmentation (see *Figures 5–7*). This suggests that an effect lasting for more than 12–18 months can be achieved in some cases with a good safety profile (see *Figure 8*). The new manufacturing process for Varioderm Subdermal is interesting, allowing an extremely high degree of cross-linking. Suspension in a non-cross-linked hyaluronic acid solution is not necessary, as injection is performed with an acceptable needle pressure.

In our view, the duration of effective treatment has been disappointing with previous preparations for subcutaneous indications, and the material was somewhat difficult to inject and tended to start slipping. The new product, Varioderm Subdermal, showed significant advantages in this respect. For further qualitative evaluation, more studies using neutral methods of measurement are needed.¹⁴ ■

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