

Varioderm[®] - an innovative hyaluronic acid

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Introduction

Because more and more patients are refusing to take prolonged absences from work there has been a continual development in the field of aesthetic medicine towards minimally invasive interventions. These include the use of augmentation procedures, botulinum toxin A, peeling, laser systems, threads, minor operative corrections and the application of appropriate external treatments.

Using combinations of these methods optimum concepts can be developed for the individual patient over a period of several years. These can cumulatively achieve the same result as would previously have been achieved by large surgical operations. In the course of the aging process the treatment stages necessary for each specific individual need can be applied, without creating an irrevocable outcome for the patient, e.g. by using an invasive surgical procedure. Years of contact and mutual trust often develop through this between the patient and the doctor. It is particularly important for the physician active in the field of aesthetics to keep up-to-date with the continuing developments in individual techniques by means of advanced training. The patient can meet the aging process together with continually improving treatments. It is therefore necessary for the treating physician to master all the necessary techniques in order to give the patients the optimum advice for their own individual situations. In no way should a technique be used in which the doctor is proficient, but which does not represent the optimum solution for that particular patient's needs.

However, even minimally invasive methods can have side-effects and contraindications, which must be taken into account in individual cases and which need to be fully explained. Despite the fact that fillers have now been in use for decades and despite many new developments in this sector it seems that the ideal substance has still to be found.

Permanent fillers using polyacrylates have become increasingly controversial over the past few years due to the appearance of granulomas.

Bovine collagen and pure hyaluronic acid are largely free from problems regarding to the quantity used the frequency of complications. Clearly, an allergy test is necessary when bovine collagen is used. In the field of collagens there is an interesting new porcine collagen which appears to be lasting longer and for which an allergy test is not necessary.

The disadvantage of hyaluronic acid is that it is only effective for short or very short periods. In application tests with profilometric evaluations we saw that the approximate effective duration with first and second generation hyaluronic acids was only three to four months (figure 1). In the past few years there has therefore been an almost unmanageable number of 'new hyaluronic acids'. On

the one hand there was often no apparent advantage and on the other the risk from added ingredients was increased. With previously known hyaluronic acids a highly cross-linked portion was suspended in a non-cross-linked hyaluronic acid, in order to make the substance capable of being injected. The latest developments have made it possible to inject a highly cross-linked hyaluronic acid even without suspension. The author has now had the opportunity of using one of these hyaluronic acids (Varioderm®, from Adoderm GmbH company) for over a year. It has shown that when injected properly (27G needle) it is effective for a significantly longer period - 9 to 12 months after a single injection - the only disadvantage was a slightly increased tendency to swelling in the initial phase. Any subsequent complications could not be determined. In our view this substance represents an interesting new development in the field of fillers. For further quality evaluations multicenter studies with neutral methods of measurement are certainly necessary.

Hyaluronic acids – natural occurrence, chemical structure, properties and identification

Since the 1980s hyaluronic acids have been widely used as a material for the manufacture of implants. Hyaluronic acid is part of a class of substances which form the extracellular matrix of the skin. Hyaluronic acid can bond to water to a large extent [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].

Hyaluronic acid is a polysaccharide which consists of repeating disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine using a $\beta(1\rightarrow3)$ bond. Each disaccharide is joined to the next one via a $\beta(1\rightarrow4)$ bond. The linear polymer is also known as sodium hyaluronate [2,4,5,9]. By cross-linking technology, it is possible to produce a polymer with a higher molecular weight of from 5 to 6 million but with the same chemical structure [1].

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 the non-cross-linked polymer with a significantly higher molecular weight [8]. By sterilizing of cross-linked hyaluronic acid at 1.2 atmospheres at 100°C for 30 minutes the properties and chemical composition do not change [2,3]. The determination of molecular weight is a suitable way of characterizing the molecular weight.

Determination of endotoxins

Impurities are also to be expected from hyaluronic acid from bacterial fermentation. The determination of endotoxins is recommended. The maximum allowed value should be less than 0.05 IU/mg [12].

Protein content

The protein content of hyaluronic acid should be tested in order to rule out any immunological reactions.

Nucleid acids

The content of nucleid acids should be determined photometrically at 260nm (purines and pyrimidines absorbing wavelength).

The content of iron, heavy metals, bacteria and glycosaminoglycan sulphate should be determined. All tests should be performed on not sterilized products. Thermal sterilization is possible. It is expected that hyaluronic acid will contain

fragments of low molecular weight, which must be detected because they can cause inflammatory reactions [9].

Biocompatibility

When used as a filler it was proven that there was no sensitizing resulting from the use of hyaluronic acid products of non-animal origin [4]. An immunological reaction is not to be expected when using hyaluronic acid preparations which have been prepared using bacterial fermentation [4]. Pathological changes and acute or chronic sensitivity has been observed after the use of cross linked hyaluronic acid with no systemic effects [5]. In [6,7] animal experiments have confirmed the blood compatibility of hyaluronic acid cross linked by divinyl sulfone. Animal experiments in [13] with rats, rabbits, monkeys and guinea pigs over a period of 33 months showed that cross-linked hyaluronic acid is biocompatible (non-inflammatory, non-toxic, non-immunizing). The immunological compatibility of the cross-linked acid is demonstrated mainly by the fact that the glycosaminoglycan chains contained within its basic structure remain unchanged after chemical modification (cross-linking with divinyl sulfone) [13].

Biodegradation

The degrading process of cross-linked hyaluronic acid (cross-linked with divinyl sulfone) 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. These are the enzymatic splitting by hyaluronidase which happens to only a small extent and the much more vigorous decomposition by hydroxyl radicals which serve as a source of active oxidation. Enzymatic decomposition takes place 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. 20% of the applied quantity of cross-linked hyaluronic is decomposed within 10 days; the decomposition of the remaining gel takes 100 days and longer. The oxidation of hydroxyl radicals proceeds significantly faster in inflamed tissue. Decomposition can be detected by lowering the viscosity. The decomposition reactions of the cross-linked hyaluronic acid are significantly slowed by the blocking of the access to the interior of the matrix compared with the non-cross-linked material [2,3]. Cross-linked hyaluronic acid is metabolized in the liver into CO₂ and water [5,10].

The production process for Varioderm®

Sodium hyaluronate obtained by biofermentation is dissolved in water and cross-linked using divinyl sulfone until a degree of cross-linking of between 70 and 90% cross-linking 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 divinyl sulfone (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 to ethyl bridges. Sodium hyaluronate and divinyl sulfone 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 on 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 to the initial mixture, is subsequently made into particles and stabilized, to facilitate the filling of the syringes without the need for any dilution. This described as a monophasic particle technology (MPT).

Varioderm® - product overview

The Varioderm® range of products consists of four different products: Varioderm® Fine Line, Varioderm®, Varioderm® Plus and Varioderm® Subdermal.

Varioderm® Fine Line

Varioderm® Fine Line consists of 6 mg/ml of cross-linked hyaluronic acid. It is intended for the treatment of superficial folds such as crows' feet and perioral folds. The injection is introduced without any problems into the superficial dermis by means of a 30G needle using a linear or multipuncture technique, or a combination of both these techniques.

Varioderm®

The first CE-certified product from the Varioderm range of products consists of cross-linked hyaluronic acid (12mg/ml). It is intended for the treatment of moderate to deep folds for the whole of the face. The injection is carried out using a 27G needle in the middle and deep dermis (not in the superficial dermis!)

Varioderm® Plus

Varioderm® Plus consists of cross-linked hyaluronic acid (18mg/ml). It is intended for the treatment of deep folds and is placed in the lower dermis with a 27G needle.

Varioderm® Subdermal

Varioderm® Subdermal consists of cross-linked hyaluronic acid (27mg/ml). It is intended for the treatment of very deep folds, volume augmentation and for the contours of the face. It is carried out by placing a 26G needle into the subcutis by means of a criss-cross technique or a multipuncture technique, or by a combination of both these techniques.

Clinical use

The new filler Varioderm® was used from April 2006 to June 2007 in the forms described above. In total 34 patients were treated with very different indications (figure 2).

Injection depths

With the preparation Varioderm® Subdermal the depths were subcutaneous and deep dermis. A 26G needle was used as an injection cannula. The subcutaneous injection of Varioderm® was mostly carried out for the treatment of deep nasolabial and marionette folds. The injection pressure was acceptable and acute reactions such as swellings, reddening and pain were either minimal or not present. A pronounced volume effect and good adaptation to the tissue were obvious, so that even very pronounced wrinkles could be augmented. No complications were noticeable either short-term or at check-ups after three, six and nine months.

The treatment effect generally lasted for nine months.

In the area of the middle dermis and the treatment of lips, the injection of Varioderm® was carried out using a 30G needle. The injection was also technically straightforward. A slightly increased local inflammation reaction was noticed, which was more pronounced in particular cases, especially when the lips were being augmented. Medium-term complications only occurred with one single patient. Four weeks after the treatment of nasolabial folds, inflamed nodular changes to the skin appeared, which receded after hyaluronidase had been injected for two sessions. It was noticeable with this patient that many previous treatments had been carried out. It was therefore decided not to use permanent fillers. Otherwise treatment with Varioderm® showed a high degree of safety. The augmentation effect did not last for as long as with Varioderm® subcutaneously, but the patients treated still showed a clear augmentation after six months (figure 3).

Varioderm® Fineline was injected superficially (upper dermis) using a 30G needle. While there was a stronger local reaction, Varioderm® Fineline was also used for the augmentation of the lips. It was noticeable here that in comparison to other fine line preparations there was a distinctly increased injection pressure.

Some patients initially showed an increased inflammation reaction but this disappeared completely within one to two hours. The adaptation to the tissue was very good and suitable treatment of wrinkles was possible in the perioral and in the periocular region. The effects of the treatment lasted for approximately four to five months.

Summary

With over 60 preparations available, the market for hyaluronic acids is cluttered and for the individual user it can be quite difficult to easily comprehend. In particular it is frequently difficult for the doctor to recognize whether a 'new' hyaluronic acid has really been produced by a new production technique or whether the name or the firm has simply been changed. The permanent fillers, particularly the acrylates are increasingly being viewed critically by leading users because of the risk of granulomas. The development of hyaluronic acids with long-lasting effects and a good safety profile is therefore an important element in the field of fillers. According to the specifications mentioned previously hyaluronic acids are deemed to be very safe. Here skin nodules and hardening generally appear due to incorrect injection techniques; histologically there are no granulomas. Treatment can be performed by the intranodal injection of hyaluronidase. The use of steroids with a corresponding risk of atrophy is not necessary. Overall with Varioderm[®] there is a new hyaluronic acid that could be tested with a good volume effect, good adaptation to the tissue, long-lasting augmentation and a good safety profile (figure 4). From this it can be assumed that an effect lasting for more than 12 months can to some extent be achieved; the single case involving the development of inflamed nodular changes is in our view, most likely the result of some previous treatment or other.

The new manufacturing process for Varioderm[®] is interesting with its extremely high degree of cross-linking. This produces an injection with an acceptable needle pressure without the need for suspension in a non-cross-linked hyaluronic acid.

Side-effects such as 'blue lines', which we have seen with first and second generation hyaluronic acids have not been described in the previous use of Varioderm[®]. In particular with sensitive patients the initial quantities should be chosen conservatively; if necessary repeat the injection because in individual cases unusually strong acute reactions can occur. Again in the labial area the injection volume should be small at the first session (0.5ml). In the case of swelling the author recommends the use of Varioderm[®] Fineline.

In our view the duration of effective treatment with previous preparations has until now been disappointing and to an extent the material could start to slip. It will be seen if the use of Varioderm[®] Subdermal is of any advantage here. Multicenter studies under standardized conditions should take place for the purpose of objective assessment. Such tests have already been initiated by the manufacturers.

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Literature

[Already in English apart from]

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Figure 1: Photographs of a younger patient before and after injection with Varioderm 1ml (9 months)

Figure 2: In total 34 patients were treated with very different indications

Figure 3: After 6 months a clear augmentation effect was noticeable

Figure 4: The good safety profile of Varioderm®

Figure 5: Injection with 1.5ml in the nasolabial and marionette folds

Figure 6: Profilometry: before the injection, directly after the injection, three months after the injection and six months after the injection.