



## Soft Tissue Fillers – For Wrinkles, Folds and Volume Augmentation



by  
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### Background

The search for an ideal soft tissue filler to correct various facial folds and wrinkles has gone on for years. At the turn of the last century Injectable Paraffin was tried but quickly found to be unacceptable.<sup>1</sup> A refined form of liquid silicone was introduced in the 1960's and for the next 30 years various forms of injectable silicone were used with few reported complications. Unfortunately, numerous complications arose from the use of adulterated or impure silicones and as a result injectable silicones were abandoned.<sup>2</sup> Autologous fat, another soft tissue filler, has been around for decades. In more recent years it has increased in popularity primarily due to improved harvesting techniques.<sup>3,4</sup> The longevity of contour correction following autologous fat is somewhat variable and appears to be dependant on several factors including: techniques used, amount of fat injected, location of recipient site, and type of defect being treated.

In the early 1980's, after extensive trials, injectable bovine collagen was introduced (Zyderm®, Zyplast®) and has become a gold standard against which other newly introduced injectables are assessed.<sup>5</sup> They are easily administered, safe, and effective in short-term soft tissue augmentation. However, the possibility of allergic reactions to bovine collagen and the limited duration of effect have stimulated the continued research for more ideal fillers.<sup>6</sup> In more recent years other collagen products to appear include: autologous injectable human collagen, (Autologen

– Collagenesis Inc., Beverly MA) which is processed from surgically excised skin.<sup>7</sup> If the patient does not have enough excess skin available, Dermologen™ Injectable Human Collagen is available from the same company and is manufactured from cadaver skin. Isologen® (Isologen Technologies Inc., Parammus NJ) is a living system of cultured and expanded autologous fibroblasts. Tissue from a non sun exposed skin area is obtained using a 3mm punch, and from there the collagen is harvested and grown in culture. The process is labor-intensive, time consuming and requires that the patient wait for the tissue to be grown.<sup>8,9</sup> Other tissue fillers popularized in recent years throughout Europe and now in Canada include: injectable hyaluronic acid derivatives (Restylane™, Hylaform®, Rofilan®), dextran beads suspended in hyaluronic acid (Reviderm®) and polymethylmethacrylate micro spheres suspended in bovine collagen (Artecoll™).

### Hyaluronic Derivatives

Hyaluronic acid is a basic building block of the dermis. It is a naturally occurring glycosaminoglycan that is a component of all connective tissue. It exhibits no species or tissue specificity as the chemical structure of this polysaccharide is uniform throughout nature. There is no potential for immunologic reactions to hyaluronic acid in humans. In the skin hyaluronic acid molecules bind water and create volume. The amount of hyaluronic acid in the skin decreases with age and its loss results in reduced dermal hydration and increased skin wrinkling.

**Restylane™** (Q-Med, Uppsala, Sweden) is a hyaluronic acid soft tissue filler that is made of hyaluronic acid biosynthetically produced through a bacterial fermentation process. The concentration of stabilized hyaluronic acid is 20 mg/ml. Three forms of the product are presently available (Restylane Fine Lines™, Restylane™, Perlane™) with a fourth on the horizon (Perlane Plus™). Each is designed to be injected at different layers in the skin (Figure 1). The clinical difference between the products is the size of

the gel particle. Restylane Fine Lines™ has 200,000 gel particles per ml and is used for fine superficial wrinkles. Restylane™ has 100,000 gel particles per ml and is used for larger wrinkles (ex. glabellar furrows, nasolabial lines, lip augmentation) (Figures 2, 3, 4). Perlane™ (8,000 gel particles per ml) is used for deeper folds (nasolabial) and volume augmentation (lips). Perlane Plus™, the thickest product will have 4,000 gel particles per ml. The products are designed to last between 9 and 12 months. Since there is no species or tissue specificity there is no potential for immunologic reactions to the hyaluronic acid. Skin testing is therefore not required. Local injection related reactions occasionally occur and may include: transient erythema, pain, itching, and tenderness.

**Hylaform®** (Biomatrix Inc., Ridgefield NJ, distributed in Canada by McGhan Medical, Toronto, Ontario) is another hyaluronic acid soft tissue filler similar to Restylane™. The concentration of hyaluronic acid is 6 mg per ml and is extracted from rooster combs. To date, there have been no reported instances of immunologic reactions to any residual avian products.<sup>10</sup> Hylaform is similar to the Restylane™ and used in similar wrinkle areas (glabella, nasolabial folds, marionette lines, lip augmentation, etc.). The duration of effect is less than Restylane™ (6 mos vs. 9-12) but is individually dependant.

**Rofilan®** is another hyaluronic acid derivative (Rofil Medical International, the Netherlands, distributed in Canada by Canderm Pharma Inc., St-Laurent, Quebec) that, like Restylane™ is manufactured from a bacterial fermentation process. The concentration of hyaluronic acid is 20 mg/ml. It was recently taken off the market in Canada as its duration of action was far shorter (3 months) than expected.

All of the hyaluronic acid fillers are supplied as clear colorless transparent gels packaged in a disposable syringe. The amount supplied per syringe varies slightly as do the costs. Although topical anaesthesia with EMLA may be used in some areas (crows feet, forehead) local nerve blocks (lidocaine 2%) especially when augmenting lips, is beneficial for pain relief during injections.

### Hyaluronic acid and Dextran beads

**Reviderm®** (Rofil Medical International, the Netherlands, distributed in Canada by Canderm Pharma, St-Laurent, Quebec) is a soft tissue filler composed of *hyaluronic acid (60%) mixed with dextran beads (40%)*. It is manufactured from non-animal products. No skin testing is required. The dextran micro beads range in size from 40-60 microns and are evenly suspended in the hyaluronic acid gel. Reviderm® is biocompatible and biodegradable yet long lasting (12-24 months according to the distributor) because of the stimulation of new collagen within the dermis. There is a macrophage response to the product by 30 days accompanied by fibroblast proliferation and new collagen

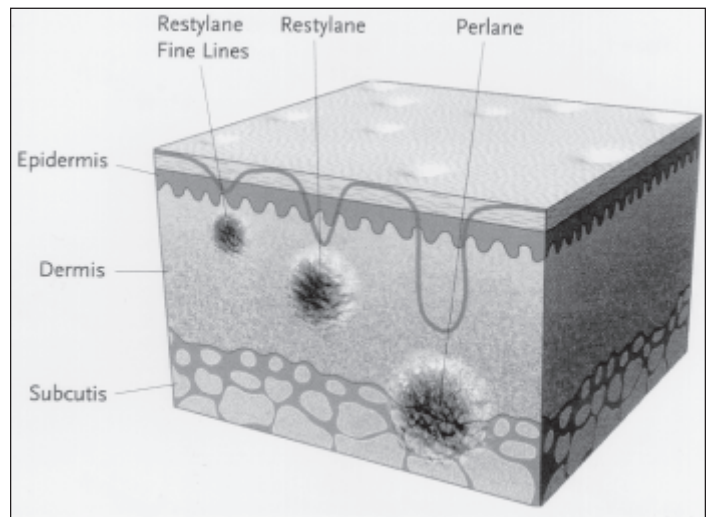


Figure 1 – Levels of injection for hyaluronic acid products.

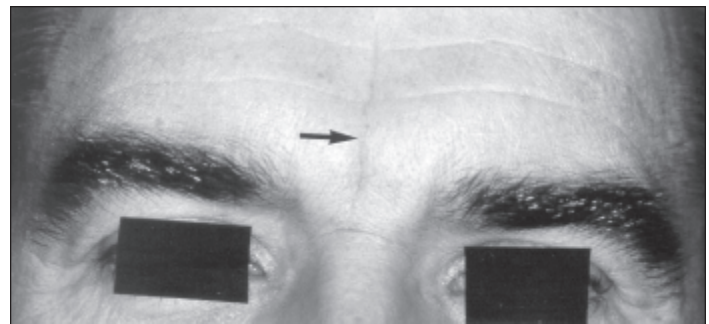


Figure 2a – Prominent vertical forehead line (arrow).

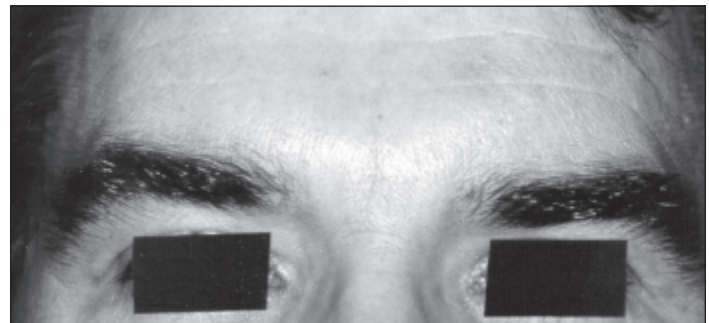


Figure 2b – Post Restylane™ injection.

formation. With time the product is metabolized and completely gone from the tissue. Reviderm® is designed to be injected deep within the dermis (similar to Perlane and Artecoll®) and may be used in the treatment of nasolabial folds, glabella furrows, perioral lines as well as other facial wrinkles. Long term studies are not available in Canada with this product and its duration of action beyond 9 months requires confirmation.

## Polymethylmethacrylate microspheres suspended in bovine collagen

**Artecoll®** (Rofil Medical International, the Netherlands, distributed in Canada by Canderm Pharma Inc., St-Laurent, Quebec) consists of homogenous polymethylmethacrylate (PMMA) microspheres evenly suspended in a solution of partially denatured 3.5% bovine collagen. It is a permanent injectable soft tissue filler. All microspheres are in the range of 32-40 microns in size are completely round and have a smooth surface. Artecoll® also contains an average 0.3% lidocaine hydrochloride. Following its injection in the lower part of the dermis, the collagen vehicle is degraded within 1-3 months. The microspheres subsequently become encapsulated with a fine fibrous capsule, a process which will be completed within 2-4 months after injection. Since the PMMA microspheres are non biodegradable and too large to be phagocytosed or migrate, the resulting tissue augmentation will be long lasting.

Artecoll® may be used for glabellar frown lines, perioral lines (Figure 5), lip augmentation, acne scars, etc. It is *not* designed for fine wrinkle lines as it must be placed deep within the dermis. The volume to be injected depends on the depth and size of the wrinkle. It is strongly advised to inform the patient at least 2 injection sessions are required. Since the product is permanent, one does not want to overcorrect the defect. It is best to aim for a partial correction - wait until the product solidifies over the next few months and then re-inject to further augment the area of concern. This gradual correction of skin defects is safest and allows for a more natural, smoother, balanced result. Over aggressive injections may lead to irregularity or lumpiness while too superficial placement can result in permanent "beading" or "ridging". There have been recent reports of nodules or small lumps in the lips with this product which have been a source of discomfort and annoyance to the patient.<sup>11</sup> In some instances surgery was required to remove the Artecoll®<sup>11</sup>, an unwelcome thought when the patient is seeking cosmetic improvement and ends up with a potentially disfiguring surgery. Some investigators are therefore concerned about its use as a soft tissue filler for lip augmentation.<sup>11</sup>

As with other injectables, post-injection swelling and erythema is not unusual. Bruising occasionally occurs as well. Late side effects including persistent redness, visibility of Artecoll® through the skin, beading and contour unevenness are infrequent and seem to be technique related.<sup>12,13</sup> Careful injection in the deep dermis and avoidance of treating very thin skin will minimize the risk of beading and ridging. If significant beading or ridging occurs at the injection site an injection of Triamcinalone (2 mg/ml) may be of some help to soften and shrink the beading. Surgical excision with possible unacceptable scarring is occasionally the only answer to correct the problem. Acute allergic reaction to the collagen component are rare. The reported allergic rate with Artecoll® collagen is 0.78% compared to approximately 3% with Zyderm,

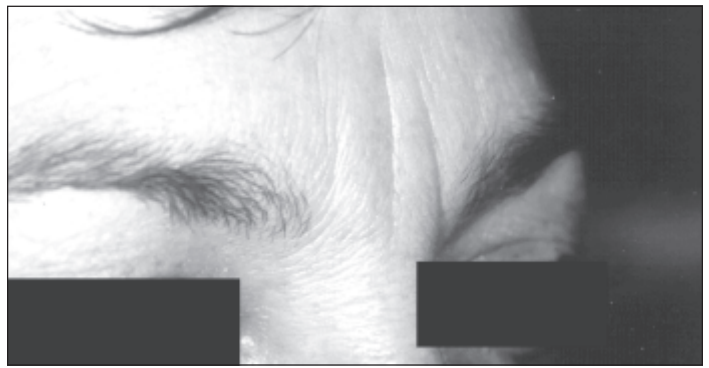


Figure 3a – Prominent vertical forehead lines.

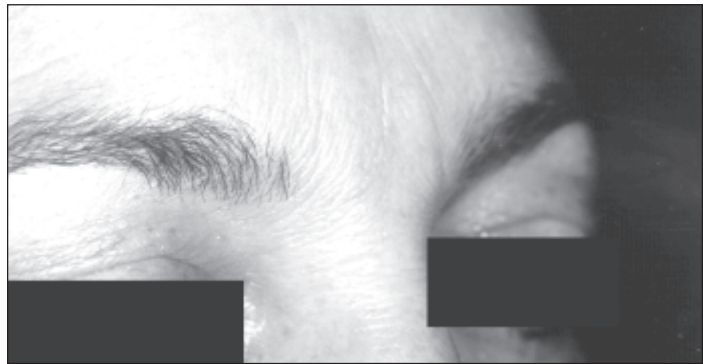


Figure 3b – Post Restylane™ injection.



Figure 4a – Lips pre injection.



Figure 4b – More definition to lips and philtrum post injection.



**Figure 5a** – Prominent Nasolabial folds (arrows) and marionette lines (arrows).



**Figure 5b** – Post Artecoll™ injection.

Zyplast.<sup>12</sup> Although Health Canada does not require skin testing prior to Artecoll® treatment, the distributors of Artecoll® in Canada (Canderm Pharma Inc.) recommend a single skin test to the collagen component of Artecoll®. If no reaction occurs by 1 month, Artecoll® treatment can be administered. A significant complication occasionally reported with PMMA micro spheres is granuloma formation, with a reported incidence of 1 in 1000.<sup>14,15</sup> In this situation rather than normal encapsulation of the PMMA beads occurring, a granulomatous response to the material ensues with areas of redness, inflammation and swelling. Intralesional triamcinolone or betamethasone are required to settle the reaction.

In summary, hyaluronic acid gels (Restylane™®, Hylaform®, Rofilan®), hyaluronic acid gels and dextran beads (Reviderm®) and polymethylmethacrylate micro beads in collagen (Artecoll®) are exciting new additions to currently available facial rejuvenation techniques. Each of these materials provide wrinkle reduction, contour improvement and volume augmentation when placed into various wrinkles lines, furrows or when used for lip augmentation. The duration of action varies from 6 months to permanency depending upon the product used. The temporary hyaluronic acid gel products are ideal for those patients just starting soft tissue augmentation. No skin

testing is required and the products can be injected on the same day of consultation. Artecoll®, a permanent filler, is best suited for those who have enjoyed temporary soft tissue fillers, like the effect, and are interested in more long lasting results.

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