

Polyethylene Glycol (PEG) as a Crosslinking Agent in Hyaluronic Acid Dermal Fillers: Scientific Rationale and Clinical Relevance

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Introduction

Non-surgical techniques using hyaluronic acid (HA) fillers for facial rejuvenation provide safe, effective, and reproducible aesthetic outcomes. HA injections have become the second most popular non-surgical cosmetic procedure after botulinum toxin treatments. In 2023, over 5.5 million procedures were performed with HA fillers (ISAPS International Survey on Aesthetic/Cosmetic Procedures).

Role of HA Fillers in Aesthetic Medicine

HA, in gel form, varies in density, viscosity, rheological properties, and concentration. This diversity allows for optimal product selection based on treatment indication, anatomical area, injection depth, the physician's technique, and the patient's individual needs. To extend the duration of HA's effects, it undergoes a cross-linking process, which involves creating covalent bonds between HA molecules and a cross-linking agent, forming a three-dimensional structure. This cross-linking enhances the physicochemical properties of HA without changing biocompatibility and biological activity [1].

Common Cross-Linking Agents in HA Fillers

The most common cross-linking agents in soft tissue fillers include Butanediol Diglycidyl Ether (BDDE), 1,8-Diepoxyoctane (DEO), Divinyl Sulfone (DVS), and Polyethylene Glycol Diglycidyl Ether (PEGDE). Cross-linking technologies vary in terms of the degree of cross-linking, the amount of cross-linking agent used, and the concentration of HA. These modifications significantly affect the rheological properties of the gels, which in turn influence the aesthetic outcome [1,2].

PEG as a Cross-Linking Agent: Innovation in Fillers

A recent innovation in the production and cross-linking of HA is the use of Polyethylene Glycol (PEG). Research suggests that PEG may offer substantial benefits in the safety and performance of HA-based fillers. Both PEG and HA are polymers, and their cross-linking forms scaffold-like matrices that resemble a three-dimensional network, ensuring better filler integration into the tissue [3–5]. The resulting fillers exhibit excellent rheological properties, enabling optimal adaptation and integration with anatomical structures [6–8].

Mechanical Strength and Stability of PEG Fillers

PEG provides a higher degree of structural uniformity and flexibility in network formation, enhancing the mechanical strength and thermodynamic stability of the resulting hydrogels [9–13]. Moreover, PEG's biocompatibility is associated with a reduced inflammatory response and lower immunogenic potential, crucial in minimizing adverse events. These properties improve the safety profile of PEGylated HA fillers and expand their clinical utility, enabling the safe use of combination therapies with energy-based devices; without compromising tissue integrity or increasing the risk of complications [9–13]. Advantages of PEGylated fillers are thermodynamic stability, reduced local inflammatory response, along with the immunomodulatory effect.

Thermodynamic Stability in Combination Therapies

One of the critical aspects when combining HA fillers with heat-emitting devices is the filler's resistance to heat. The thermal resistance of HA fillers is influenced by the cross-linking agent. HA-PEG gel fillers demonstrate greater thermal resistance than BDDE gel fillers [13]. This makes the selection of dermal fillers crucial when using IR, RF, HIFU, or other heat-emitting devices during the treatment. Thermal degradation caused by sudden high temperatures can have similar effects to intense mechanical stress on the product, increasing susceptibility to endogenous hyaluronidase activity. Furthermore, thermal damage to the tissue surrounding the filler can lead to inflammation, activating cellular processes such as the enhanced release of endogenous hyaluronidase [14]. Thus, when combining multiple technologies in a single session, it is essential to choose the right filler that ensures an optimal aesthetic outcome while maintaining the highest possible safety profile, something guaranteed by PEGylation.

Safety Aspects of PEGylated Fillers

Another advantage of PEGylated fillers is their safety profile. Injectable soft tissue fillers stimulate an influx of phagocytic neutrophils and mononuclear cells, which promotes macrophage recruitment and fibroblast activation. Although the composition of HA fillers appears straightforward, the associated inflammatory response is multifactorial. The three main components – HA, water, and a cross-linking agent – can each influence the initiation and progression of inflammation.

HA is a naturally occurring substance in the human body, short-chain fragments of this molecule may have proinflammatory effects. Similarly, high local concentrations of water can contribute to inflammation by altering osmotic pressure. The cross-linking agent plays a significant role in influencing the immunogenicity of the entire filler formulation. PEG, as a cross-linking agent, appears to provide an immunomodulatory effect, mitigating the proinflammatory potential of the other filler components. It may also provide local anti-inflammatory properties [12,15,16].

PEG-HA fillers demonstrate high biosafety in vitro by reducing immune cell recruitment, reactive oxygen species (ROS) production, and mRNA expression of proinflammatory cytokines, under both resting and stimulated conditions [12,15,17]. These findings suggest that PEG-HA fillers carry a low risk of immunologically mediated adverse effects, particularly granulomatous reactions and cellulitic processes. Additionally, they may promote an anti-inflammatory phenotype in immune cells, contributing to the overall therapeutic benefit [15,17]. In vivo studies confirm these findings, demonstrating a reduction in antigen recognition and presentation – evidenced by a statistically significant decrease in CD4+ and CD8+ T lymphocytes, as well as B cells, monocytes, and macrophages near the injected material. These results have been corroborated by retrospective and prospective long-term studies [11,12]. Clinical studies further support the safety of PEG-crosslinked HA, showing no granuloma formation, foreign body reaction, or other complications over a three-year period [17].

Conclusions

The use of PEG as a cross-linking agent in fillers offers numerous benefits, including non-toxicity, and non-immunogenicity, which are conferred onto the filler through PEGylation. These properties ensure safety and provide protection against the risk of immunological adverse reactions [11,12,15]. The injected filler integrates well with structures in the connective tissue, such as collagen fibres, blood and lymphatic vessels, glands, and nerves. PEGylation endows the fillers with excellent rheological properties that allow for optimal adaptation to anatomical areas while maintaining the desired shape over extended periods. The high content of polar groups in the molecular structure enables the fillers to bind large amounts of water [6], which positively influences the extracellular matrix. This enhances hydration, improves permeability, and facilitates the diffusion of nutrients from blood vessels to the skin, including the epidermis, thus restoring a youthful homeostatic balance. PEG-based fillers are an excellent option for specialists seeking modern, safer solutions that provide effective results when used independently, and above all in combination with energy-based devices, offering the advantages of a holistic approach [11,16].

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