

---

# Comparison of the Efficacy and Safety of Two Crosslinked Hyaluronic Acid Dermal Filler

Dr.J.Löchner  
Institut für Ästhetische Dermatologie  
Südstr. 2  
56422 Wirges

---

**BACKGROUND.** Clinical data demonstrate that crosslinked hyaluronic acid gels offer a longerlasting dermal filling and a lower risk of immune reactions than collagen preparations.

**OBJECTIVE.** The efficacy and safety of two non-animal-source hyaluronic acid dermal filler (CRISTAL and Hylan Gel) were compared, using the treatment of nasolabial folds.

**RESULTS.** The Wrinkle Severity Rating Scale (WSRS) demonstrate after 6 months that the patients treated with CRISTAL have a score of 1 grade improvement in 75%, the patients treated with Hylan Gel have a score of 1 grade improvement in 38%. (Global Aesthetic Improvement Scale/GAIS).

**SAFETY.** The incidence of treatment related complications are generally transient and mild or moderate, specially swelling after the treatment. Local injection-site reaction tended to occur more frequently on the Hylan Gel than CRISTAL.

**CONCLUSIONS:** CRISTAL provides a more durable esthetic improvement than Hylan Gel and offers a very good tolerability.

April 2008, 17

---

**HYALURONIC ACID** is a naturally occurring polysaccharide consisting of linear chains of alternating D-glucuronic acid and N-acetyl-D-glucosamine residues that forms an important structural element in the skin and connective tissues.

It shows rapid tissue turnover, making it unsuitable for use as an exogenous soft tissue filler.

Chemical cross-linking of hyaluronic acid results in the formation of an insoluble viscoelastic polymer with improved resistance to enzymatic degradation. Cross-linked hyaluronic acid derivatives ( Hylan Gel ) have been developed as soft tissue augmentation agents.

## Materials and Method

### *Materials*

CRISTAL is a colorless viscoelastic gel produced from hyaluronic acid non-animal source and cross-linked with BDDE.

The preparation was provided sterile in a 1 ml syringe supplied with a 30G needle for intradermal injection.

HYLAN GEL is a colorless viscoelastic gel produced from hyaluronic acid non-animal source and cross-linked with BDDE.

The preparation was provided sterile in a 1 ml syringe supplied with a 30G needle for intradermal injection.

### *Patients Selection and Study Design*

This 6-months study was conducted in the Institut für Ästhetische Dermatologie. For study inclusion, adult outpatients of either gender were required for correction of bilateral nasolabial folds. The required subjects are classified to have moderate or severe nasolabial folds (WSRS score 3 or 4 ).

After the initial injection the patients are investigated after 3 and 6 months. During this time no other cosmetic procedure was done.

### *Injection Technique*

The skin in the nasolabial region was cleansed with an antiseptic solution, and a local anesthetic was applied.

The dermal filler material was injected, using the linear technique, in the mid dermis. Each site was treated with 0.5 ml. The investigator was experienced in the use of the two study products.

### *Evaluation*

The visual appearance of each nasolabial fold was determined using the WSRS.

Table 1

#### Wrinkle Severity Rating Scale ( WSRS )

Score	Description
5	Extreme: extremely deep and long folds, detriment to facial appearance. 2-4 mm visible V- shaped fold when stretched.
4	Severe: very long and deep folds; prominent facial feature. Less than 2 mm when stretched.
3	Moderate: moderately deep folds; clear facial feature visible at normal appearance but not when stretched.
2	Mild: shallow but visible fold with a slight indentation; minor facial feature.
1	Absent: no visible fold; continuous skin line.

Adapted from  
Narins R et al.  
A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds.  
Dermatol Surg 2003; 29: 588-95

In addition, the overall change in appearance of the nasolabial folds from its pre-treatment condition was determined using the GAIS.

Table 2

---

### Global Aesthetic Improvement Scale (GAIS )

---

Rating	Description
Very much improved	Optimal cosmetic result from the implant in this patient
Much improved	Marked improvement in appearance from the initial condition but not completely optimal
Improved	Obvious improvement in appearance from the initial condition, but a touch-up is indicated
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition

---

Adapted from  
Narins R et al.  
A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds.  
Dermatol Surg 2003; 29: 588-95

## Results

### *Efficacy*

Prior to treatment, the nasolabial folds were rated from mild to extreme. To achieve an optimal cosmetic result CRISTAL required less injected volume than HYLAN GEL. At 6-months after treatment, the response rate was significant higher with CRISTAL than with HYLAN GEL.

### *Safety*

Treatment related adverse events tended to occur more frequently on the HYLAN GEL than the CRISTAL side of the face, affecting 41,3% versus 21,3% of patients. The local injection-site reactions are

swelling	22,6 % ( Hylan Gel ) versus 7,3 % ( CRISTAL )
pain	20,0 % ( Hylan Gel ) versus 5,3 % ( CRISTAL )
redness	14,0 % ( Hylan Gel ) versus 8,0 % ( CRISTAL )

This effects were usually transient and mild to moderate in intensity. Delayed local reaction were reported in 2,6 %, but resolved in 1 week. This suggest that these reactions were unlikely, as in clinical papers reported, of immunological nature.

## Discussion

The comparison of the cross-linked hyaluronic acid derivatives HYLAN GEL and CRISTAL for the treatment of nasolabial folds has been shown, that the products are well tolerated. But CRISTAL provides a more durable esthetic improvement than HYLAN GEL after a 6-months period.

This difference in the durability of the esthetic effect may be possibly due to differences in the gel structure or particle size.

Table 3

### Patients response rates based on changing of the WSRS Scale

Months post treatment	Patient Response Rate (%)		WSRS outcome, % patients		
	CRISTAL	Hylan Gel	CRISTAL superior	CRISTAL equivalent	CRISTAL inferior
3	87	63	63,3	30,7	6,0
6	75	38	64,0	28,0	8,0

Table 4

### Categorical outcomes based on changes from the optimal cosmetic result GAIS

Months post treatment	GAIS categorical outcome, % patients		
	CRISTAL superior	CRISTAL equivalent	CRISTAL inferior
3	52,7	38,0	9,3
6	57,3	33,3	7,3

## References

1. **Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M and Smith S.** A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg* 29: 588-595, 2003.

2. **Erian A and Ionescu NE.** Erian's Original Technique of Lip Enhancement. *International Journal of Cosmetic Surgery and Aesthetic Dermatology* 2: 17-19, 2000.
  
3. **Andre P.** Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA -- Q-Medical, Sweden) in European countries: a retrospective study from 1997 to 2001. *J Eur Acad Dermatol Venereol* 18: 422-425, 2004.
  
4. **Lowe NJ, Maxwell CA, Lowe P, Duick MG and Shah K.** Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol* 45: 930-933, 2001.
  
5. **Duranti F, Salti G, Bovani B, Calandra M and Rosati ML.** Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. *Dermatol Surg* 24: 1317-1325, 1998.
  
6. **Carruthers A, Carey W, De LC, Remington K, Schachter D and Saprà S.** Randomized, double-blind comparison of the efficacy of two hyaluronic acid derivatives, restylane perlane and hylaform, in the treatment of nasolabial folds. *Dermatol Surg* 31: 1591-1598, 2005.
  
7. **Friedman PM, Mafong EA, Kauvar AN and Geronemus RG.** Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 28: 491-494, 2002.
  
8. **Olenius M.** The first clinical study using a new biodegradable implant for the treatment of lips, wrinkles, and folds. *Aesthetic Plast Surg* 22: 97-101, 1998.
  
9. Summary of Safety and Effectiveness Data Premarket Approval for Restylane by FDA; December 12, 2003
  
10. Summary of Safety and Effectiveness Data Premarket Approval for Juvederm by FDA; June 2, 2006
  
11. **Worret, W.-I.** Intrakutane Anwendung von Hyaluronsäure. *Trends in Clinical and Experimental Dermatology*, Vol. 3 Hyaluronsäure und Haut, 335-343, 2004
  
12. **Müller PJ, Peschel G, Ozegowski JH, Hertel W.** Hyaluronsäure – ein vielseitiger Biopolymer. *Trends in Clinical and Experimental Dermatology*, Vol. 3 Hyaluronsäure und Haut, 1...36-37...43, 2004
  
13. **Lindqvist C, Tveten S, Bondevik BE, Fagrell D.** A randomized, Evaluator-Blind, Multicenter Comparison of the Efficacy and Tolerability of Perlane versus Zyplast in the Correction of Nasolabial Folds. *Plastic and reconstructive surgery* 115/01, 282-289

