CRMDex® in the treatment of nasolabial folds: a comparative study of same volume applied in one versus two sessions

Estudo comparativo da aplicação de CRMDex® em igual volume em uma versus duas sessões para correção dos sulcos nasogenianos

Original Article

Authors:
Meire Brasil Parada[1]
Samira Yarak[2]
Érica Monteiro[3]
Karime Marques Hassun[4]
Sérgio Talarico[5]
Ediléia Bagatin[6]

[1] Collaborating Dermatologist Physician, Dermatology Department, Cosmiatry, Surgery and Oncology Unit – Universidade Federal de São Paulo (Unifesp), Brazil.
[2] Coordinator, of the discipline of dermatology, Universidade Federal do Vale do São Francisco – Petrolina (PE), Brazil; PhD candidate, Pathology Department, Universidade Federal de São Paulo (Unifesp); and Voluntary Collaborating Dermatologist Physician, Dermatology Department, Universidade Federal de São Paulo (Unifesp).
[3] Collaborating Dermatologist Physician, Dermatology Department, Cosmiatry, Surgery and Oncology Unit – Universidade Federal de São Paulo (Unifesp).
[4] Physician, Dermatology Department, Cosmiatry, Surgery and Oncology Unit – Universidade Federal de São Paulo (Unifesp).
[5] Assistant Professor, Dermatology Department, Cosmiatry, Surgery and Oncology Unit – Universidade Federal de São Paulo (Unifesp).
[6] Assistant Professor, Dermatology Department, Cosmiatry, Surgery and Oncology Unit – Universidade Federal de São Paulo (Unifesp).

Correspondence:
Dra. Meire Brasil Parada
UNICCO Rua Estado de Israel 192
Vila Clementino
04022 000 – São Paulo – SP, Brazil

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ABSTRACT

Introduction: The interest in minimally invasive procedures for facial rejuvenation fostered the development of the cutaneous filling technique to treat wrinkles and folds. Hyaluronic acid is one of the most popular fillers, as it is considered the least immunogenic and safest in its category.

Objective: To evaluate and compare the efficacy, safety and duration of effect after the application of the filler CRMDex® in nasolabial folds, in one session versus two sessions.

Methods: Open clinical trial, with the randomization of nasolabial folds and comparison between two techniques. Women, aged 30 to 60 years old (n=30), presenting with accentuated symmetric nasolabial folds of minor to moderate degrees were subjected to intradermal injections of the same volume of CRMDex®. Three independent dermatologists evaluated the effectiveness of the treatment using the Wrinkle Severity Rating Scale.

Results: There was no difference in treatment effect for one versus two sessions. Both groups achieved a reduction of at least one degree according to the severity scale, and had a similar duration of the filling effect. The more frequent local adverse events (pain, erythema and edema) occurred during the injection and improved spontaneously.

Conclusions: There was no improvement in therapeutic response with the injection of smaller volumes per session. It seems that higher filler volumes may increase the risk of local adverse events.

Keywords: hyaluronic acid; biological reactions ; dermis; cicatrix.

RESUMO

Introdução: *O interesse por procedimentos minimamente invasivos para o rejuvenescimento facial proporcionou o desenvolvimento da técnica de preenchimento cutâneo para rugas e sulcos. O ácido hialurônico é um dos preenchedores mais populares, considerado menos imunogênico e mais seguro.*

Objetivos: *avaliar e comparar a eficácia, segurança e duração do efeito da aplicação do preenchedor CRMDex® nos sulcos nasogenianos, em sessão única e em duas sessões.*

Métodos: *ensaio clínico, aberto, com randomização dos sulcos nasogenianos e comparativo entre duas técnicas. Trinta mulheres, de 30 e 60 anos de idade, com acentuação simétrica dos sulcos nasogenianos de grau leve a moderado foram submetidas à aplicação intradérmica de CRMDex®. Três dermatologistas independentes avaliaram a eficácia utilizando a escala Wrinkles Severity Rating Scaling.*

Resultados: *o tratamento realizado em duas sessões não se diferenciou do realizado em uma sessão, pois ambos proporcionaram diminuição de pelo menos um grau na escala Wrinkles Severity Rating Scaling com similar duração do efeito preenchedor. Os efeitos adversos locais mais frequentes (dor, eritema e edema) ocorreram durante a injeção e melhoraram espontaneamente.*

Conclusões: *não houve otimização da resposta terapêutica com a injeção de volumes menores por sessão. Parece que volumes maiores podem aumentar o risco de efeitos adversos locais*

Palavras-chave: *ácido hialurônico; reações biológicas; derme; cicatriz.*

INTRODUÇÃO

The longevity of the human species allows an in-depth understanding of the facial alterations that occur with intrinsic (chronological) and extrinsic aging, which relates to external factors such as sun exposure, tobacco use, alcohol consumption, and stress [1-2].

Individuals over 30 years old currently seek procedures that do not require prolonged recovery or the interruption of their activities [3]. The interest for minimally invasive procedures has prompted the development of numerous rejuvenation techniques, among which is the cutaneous filling technique [1,2,4].

Many types of fillers are available on the market that correct folds and lines and/or restore facial volume caused by cutaneous aging, traumatic depressions, acne scars, and lipoatrophies (acquired or of genetic origin) [2,3]. In cutaneous aging, the most frequently corrected areas are the nasolabial folds, with the projection and/or increase in volume of the lips. This is an outpatient procedure that is minimally invasive, using only topical anaesthetics, and causes minimal discomfort. The degree of correction is predictable and the results are immediate [3].

Hyaluronic acid is a component of the extracellular substance of the human body; it is responsible for supporting extracellular structures and forming the fluid substance that anchors collagen and elastic fibers. Stabilized synthetic hyaluronic acid is produced by bacterial fermentation of non-animal, non-pathogenic streptococci (*Streptococcus equi*), which is extracted from the extracellular element and purified through alcohol precipitation.

The product is reabsorbable during isovolemic degradation and maintains its biocompatibility properties [5-7].

This study involved the use of CRMDex® (manufactured by BioPolymer GmbH & Co., Germany, and distributed in Brazil by Silimed - Comércio de Produtos Médico Hospitalares Ltda). CRMDex® is composed of dextranomer microspheres (polysaccharide - Deae Sephadex A 25) in a hydrogel of reticulated hyaluronic acid and hypromellose in neutral lactic acid solution. This blend of dextranomer microspheres in a sodium hyaluronan solution (DiHA) is biocompatible, non-immunogenic and capable of stimulating neocollagenesis.

Due to the demand for procedures that are minimally invasive, cause fewer side effects and more satisfactory results, this study evaluated and compared the efficacy, safety and duration of treatment effect of the application of the same total volume of CRMDex® in the nasolabial folds in one versus two sessions, with a 21-day interval.

METHODS

This randomized, open-label clinical study compared these two techniques at the Cosmiatric Outpatient Clinic of the Universidade Federal de São Paulo. Healthy women (n=30) aged 30-60 (average 50) with moderate symmetrical accentuation of the nasolabial folds and no previous history of permanent cutaneous filling were included in the study. All patients signed the term of free and informed consent. The study protocol was approved by the Research Ethics Committee of the Universidade Federal de São Paulo/Hospital São Paulo.

Patients were randomized to receive an intradermal application in the right and left nasolabial folds of either 1 ml or 0.5 ml of CRMDex® using a 27G needle. The second application of 0.5 ml was administered 21 days later, only on the side of the face that had received 0.5 ml in the first session. After the randomization and according to the design of the study, 2 groups of patients were constituted:

Group 1: 15 patients who received volumes of 0.5 and 1.0 of the filler in the right and left nasolabial folds respectively.

Group 2: 15 patients who received the same treatment, however in the reverse order.

The patients were followed up 60, 180, 270 and 360 days after the first application, with clinical and photographic evaluations conducted by 3 dermatologists using the Wrinkles Severity Rating Scale (WSRS) [8].

The software SSPS 16.0 was employed in the statistical calculations. Data relating to the efficacy, duration of effects and adverse events described by the patient and/or observed by the investigator were analyzed. The agreement coefficient Kappa was used to evaluate the homogeneity of the degrees of severity of the folds on the two sides of the face. Pearson's Chi-square was used to evaluate the efficacy, safety and duration of effect. A level of significance of 5% ($p < 0.05$) was adopted.

RESULTS

Only 26 patients concluded the study. According to the WSRS, the prevalent degree of severity of the folds was 3 (moderate) on the 2 sides of the face, with excellent concordance (Kappa = 93%, Table 1).

No systemic side effects were reported or observed. The more frequent local adverse effects expected in cutaneous fillings, such as erythema, edema, hematoma and pain, occurred during and soon after the injection and improved spontaneously. There was a significant difference between the two techniques only in regards to erythema and edema, with a smaller occurrence in the two applications ($p < 0.05$). Late adverse effects, such as the appearance of nodules, were rare and observed in both techniques without significant difference. For the other events there was no significant difference between the two forms of treatment (Table 2).

The majority of patients presented at least one WSRS grade of improvement in the nasolabial folds (Tables 3 and 4). The results from the two applications did not differ significantly from the single application, since the number of folds that presented improvement (defined as a decrease of at least one WSRS grade) was the same (Figures 1, 2 and 3). No differences were observed regarding the duration of the treatment effect up to 360 days after the procedure (Figures 1 and 2).

DISCUSSION

The interest in less invasive procedures that do not entail prolonged recovery or the withdrawal from usual activities 3 led

Table 1 - Distribution and Kappa coefficient of the degree of severity of right and left nasolabial folds before treatment (Image 1)

	Left fold			
Right fold	Grade 2	Grade 3	Grade 4	**Total**
Grade 2	1 (3,3%)	0 (0,0%)	0 (0,0%)	1 (3,3%)
Grade 3	0 (0,0%)	19 (63,4%)	0 (0,0%)	19 (63,4%)
Grade 4	0 (0,0%)	1 (3,3%)	9 (30,0%)	10 (33,3%)
Total	1 (3,3%)	20 (66,7%)	9 (30,0%)	30 (100,0%)

WSRS (Wrinkle Severity Rating Scale)

to the development of numerous rejuvenation techniques, including cutaneous filling [1,2,4].

Hyaluronic acid, considered the least immunogenic of the fillers, is the most popular. [9]

Currently, there are several dermal fillers containing hyaluronic acid available. However, whether results can be better, last longer and cause fewer adverse effects with a greater number of sessions of smaller volume injections, remains in doubt.

The use of cutaneous fillers requires mastery of the technique, which must be conducted with care, with a minimum of trauma and bleeding to reduce complications [10].

This study compared the safety, efficacy and duration of the filling effect of the application of the same volume of CRMDex®, in a single session versus two sessions, in the nasolabial folds.

Data on optimizing the filling effect by injecting smaller volumes of the substance in a greater number of applications is

Table 2 - Distribution of adverse events reported by patients after the first session, according to treatment type (Image 1)

	Two applications	One application	p-value
Erythema			0,009
Yes	12 (40,0%)	22 (73,3%)	
No	18 (60,0%)	8 (26,7%)	
Edema			0,001
Yes	15 (50,0%)	27 (90,0%)	
No	15 (50,0%)	3 (10,0%)	
Hematoma			0,166
Yes	3 (10,0%)	7 (23,3%)	
No	27 (90,0%)	23 (76,7%)	
Nodule			0,256
Yes	7 (24,1%)	11 (37,9%)	
No	22 (75,9%)	18 (62,1%)	
Pain			0,815
Yes	8 (40,0%)	13 (43,3%)	
No	12 (60,0%)	17 (56,7%)	
Others			0,612
Yes	1 (3,3%)	3 (10,0%)	
No	29 (96,7%)	27 (90,0%)	

Significance level of 5% ($p < 0.05$)

Table 3 - Distribution of the degrees of WSRS severity of the nasolabial folds, before and 180 days after the procedure, for the folds treated in two sessions (Image 1)

	Final WSRS				
Initial WSRS	Grade 1	Grade 2	Grade 3	Grade 4	**Total**
Grade 1	0	0	0	0	0
Grade 2	0	1 (3,8%)	0	0	1 (3,8%)
Grade 3	1 (3,8%)	11 (42,3%)	4 (14,8%)	0	16 (61,5%)
Grade 4	0	2 (7,7%)	7 (26,9%)	0	9 (34,6%)
Total	1 (3,8%)	14 (53,8%)	11 (42,3%)	0	26 (100,0%)

Gray – no change
Pink – decrease of one grade
Green – decrease of two grades

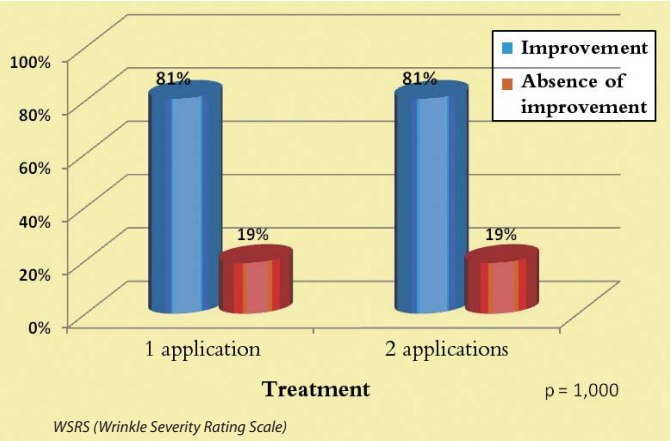
scarce in the scientific literature. It is known that immediately after the injection of the filler there is an inflammatory reaction that can vary in intensity and duration, depending on the site of application, type of dermal filler, injection technique, needle type, speed of injection, injected volume and patient's response [11,12].

Healing is a complex process, which can be influenced by internal and external factors. Healing is characterized by three phases, regardless of wound type: initial phase – inflammatory, with chemotaxis, liberation of cytokines and growth factors; proliferative phase – with the synthesis of conjunctive tissue; and remodelling phase – when the maturation of the healed wound takes place through the cross-linking process, among the collagen molecules [13]. The trauma caused by the 27G needle is minimal; however, it is capable of generating a cicatricial reaction through cellular and extracellular interactions similar to what occurs in other types of wounds and, therefore, may induce neocollagenesis [14]. Based on the knowledge of the healing process, this study assessed whether it is possible to optimize the therapeutic response by injecting the same volume of filler in two sessions. The results of this study demonstrated that treatment using two applications did not differ from a single application, since both produced an improvement of at least one WSRS (Figure 1) . In addition, no between-group differences were observed regarding the duration of the effect of the filler,

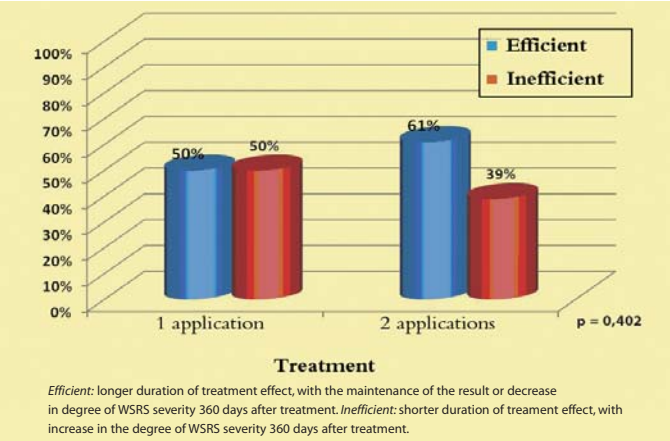
Table 4 - Distribution of the degrees of WSRS severity of the nasolabial folds, before and 180 days after the procedure, for the folds treated with a single session (Image 1)

	Final WSRS				
Initial WSRS	Grade 1	Grade 2	Grade 3	Grade 4	**Total**
Grade 1	0	0	0	0	0
Grade 2	0	1 (3,8%)	0	0	1 (3,8%)
Grade 3	0	13 (50,0%)	3 (11,5%)	0	16 (61,5%)
Grade 4	0	1 (3,8%)	7 (26,9%)	1 (3,8%)	9 (34,6%)
Total	0	15 (57,7%)	10 (38,5%)	1 (3,8%)	26 (100,0%)

Gray – no change
Pink – decrease of one grade
Green – decrease of two grades



Graph 1: Distribution of the improvement of nasolabial folds by type of treatment, according to the WSRS (Image 1)



Graph 2: Before and after treatment. Image 1

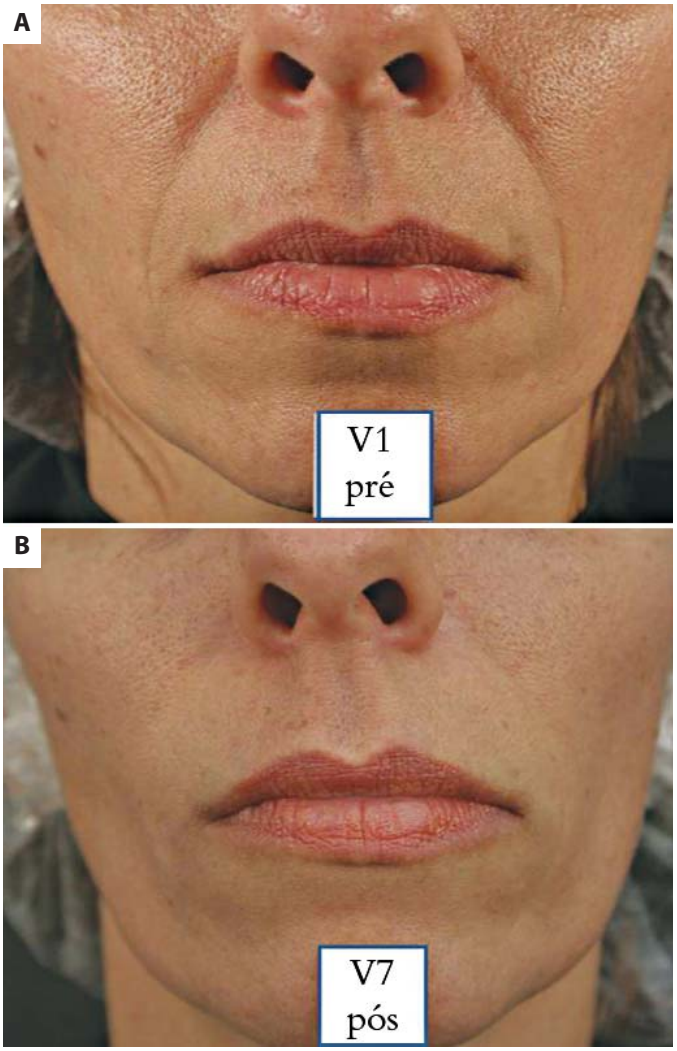


Figure 1: Before and after treatment

according to the WSRS (Graf 2) (Figures 1 and 2).

Regarding adverse events, patients reported a significantly higher frequency of erythema and edema in the treatment with a greater volume in a single session ($p<0.05$). [14] Early adverse effects occurred during the injection and improved spontaneously. Late adverse effects, as such as prolonged edema and nodules, were rare. There was no optimization of the effect of the filling with the injection of smaller volumes in a greater number of sessions.

We believe that the outlook regarding cutaneous fillers that are already approved is the search for better results through techniques with fewer risks of adverse events.

CONCLUSION

This study seems to indicate that the greater the volume of filler injected, the greater the risks of early adverse events, and that smaller doses with the same final volume can produce the same results, with fewer adverse effects. ●

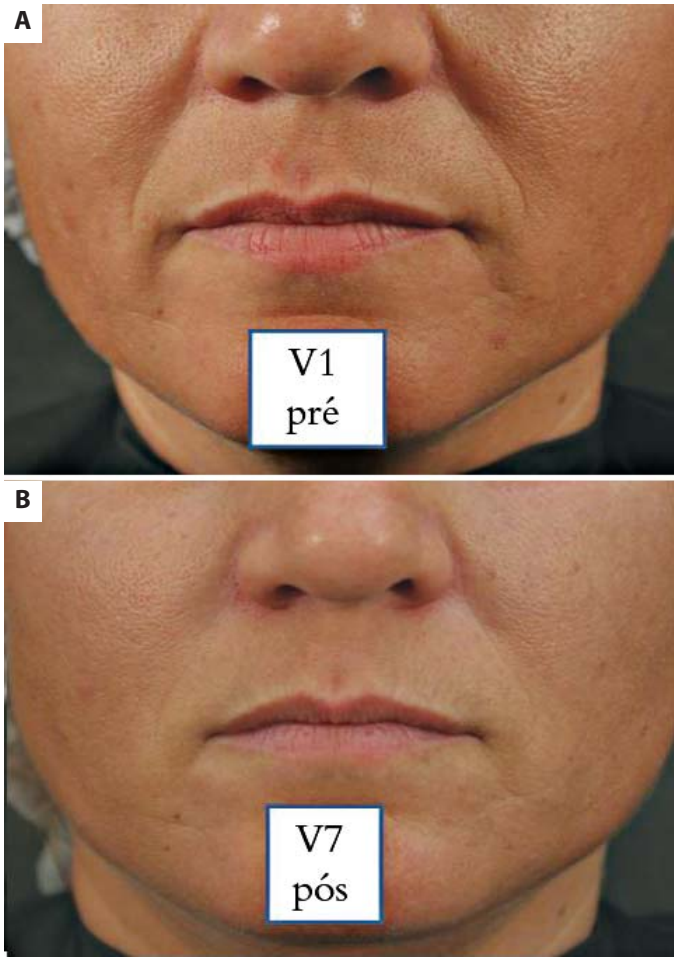


Figure 2: Before and after treatment

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