

Combined Enzyme Therapy in Patients with Complications after Lip Contour Correction in Cosmetology

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ABSTRACT

The study was aimed to evaluate the effectiveness of a combined method of treatment that includes a course of laser phoresis of Longidaza and diadynamophoresis of collalysin 1000 collagenase units for the correction of complications after lips contour correction with hyaluronic fillers. Materials and Methods. The study included 31 women aged 25 to 32 years old with complications developed after the injection of stabilized hyaluronic acid-based filler in the lip area. The patients were divided into three groups that received a course of laser phoresis of Longidaza, diadynamophoresis of collalysin or their combination. Results. A combined course of laser phoresis of Longidaza and diadynamophoresis of collalysin exerts significant clinical effect, reduces edema and gel conturation, and stabilizes psychoemotional status. Besides, this therapeutic complex accelerates biodegradation of filler, promotes restructuring effect on lip tissue, and provides expressed effect of a decrease in the thickness of the dermis and increase in the coefficient of dermis density, which is likely to be associated with a reduction of intradermal edema that develops as a reaction to the superficially

injected filler. Conclusion. A combined course of laserphoresis of Longidaza and diadynamophoresis of collalysin in the lip area in patients with such complications as superficial filler injection or injection of an excessive amount of a drug based on stabilized hyaluronic acid is a highly effective method of treatment, which is confirmed by the resolution of clinical symptoms and the improvement of patients' quality of life.

Keywords: filler, stabilized hyaluronic acid, neuropathy, diadynamophoresis of collalysin, collagenase, hyaluronidase, complication after lip contour correction, laser phoresis of Longidaza

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INTRODUCTION

Currently, injection contour correction is the third most demanded cosmetological procedure [1]. Lip contour correction is one of the most popular manipulations that occupies the leading place in the rank of all the procedures that involve fillers injection. The number of drugs available as fillers for the correction of wrinkles and folds, lip contour, and volume is increasing annually. Usually, fillers contain stabilized hyaluronic acid, calcium hydroxylapatite, and polylactic acid. Still, preferable fillers for lip contour correction contain hyaluronic acid. Even though modern drugs for contour correction have a high safety profile, lately, there has been an increase in the pool of unfavorable events and complications in the early and remote post-injection rehabilitation periods [2]. There are several reasons for this tendency that vary from the failure to fulfill the procedure correctly and unawareness of anatomic peculiarities in the region to be corrected to the lack of standards and precise recommendations in cosmetology. The borderline between a safe amount of filler and the desired volume of the region to be corrected is very thin, which leads to the events of hypercorrection, superficial injection, often injections with short intervals in the same area as well as a mixture of numerous fillers with different compositions, which may not have proved the safety of biochemism in the case of their

interaction. Among the most often unfavorable events and complications in patients with lip contour correction, there are hypercorrection, superficial injection and skin induration that are visually manifested as a “pad”, migration of gel, change in the skin color in the site of filler injection (bluish color or Tyndall effect), periodic lip edema, skin dryness of the prolabium, discomfort (painfulness and change in the sensitivity) that sometimes limits the muscle movements in the area of the mouth. In patients that receive multiple injections of large volumes or too dense fillers, especially those that have thin skin, fibrous tissue alterations develop with time that not only slowly get reduced but also complicate biodegradation of previously injected fillers by forming a peculiar conglomerate “filler-fibrosis” of the skin that compresses the surrounding tissues. The above-mentioned symptoms can be observed in patients for months and even years.

There are numerous publications on the description of local sensory disturbances in the area of earlier injected fillers. This is manifested as hypesthesia, hyperesthesia, and paresthesia of different degrees of severity [3]. Often, neuropathy is associated with emotional disturbances manifested as increased anxiety, affectability, and depression.

The above-mentioned factors, that lead to the development of safe methods of treatment of unfavorable events and complications after lip contour correction and target not only

the acceleration of filler biodegradation but also pathological collagenogenesis, reduction of edema and painfulness as factors that significantly worsen the quality of life of patients, are acute issues in modern cosmetology, recreation therapy, and rehabilitation medicine.

For the correction of such unfavorable events and complications, specialists use a specific enzyme hyaluronidase that accelerates biodegradation of earlier injected hyaluronic acid-based filler. Complete elimination of the injected material contributes to the quick resolution of unfavorable reactions. Hyaluronidase is introduced in a form of injection and by means of physiotherapeutic methods [4], [5]. Primarily, cosmetologists use hyaluronidase injections, especially, in urgent situations and acute complications (thrombosis or vascular embolism after the injection of hyaluronic acid-based fillers) [6]. However, in patients with delayed or late unfavorable events, the physiotherapeutic method of hyaluronidase application has certain benefits in comparison with its form for injection, in particular, non-invasiveness of the method, more comfortable administration of higher doses of the enzyme to patients with expressed overcorrection in especially sensitive areas (for example, lips), soft and gradual impact and the possibility of administration on large areas of the pathological process, as well as avoidance of uneven texture in cases with more aggressive effect of injected hyaluronidase. Besides, it is possible to spread hyaluronidase more evenly within the area of previously injected hyaluronic filler in patients with fibrous tissue alterations in this area because of its cellular structure, wherein fragments of hyaluronic filler are packed into fibrous cells. There are a lot of data on the methods of skin administration of hyaluronidase, in particular, electrophoresis, phonophoresis, diadynamophoresis, etc. Laser phoresis is more often used in patients with associated skin edema. Still, in severe cases, when the earlier injected hyaluronic acid gel is bound with numerous intracutaneous fibrous alterations that compress the surrounding tissues, this method is not sufficient.

In such cases, for the correction of the above-mentioned unfavorable events, specialists usually use different physiotherapeutic methods that target the enhancement of intra-tissue metabolism and the reduction of intra-tissue edema, intra-cutaneous fibrosis, and pain syndrome. Usually, electrophoresis and phonophoresis of non-steroid or hormonal drugs, low-level laser therapy, darsonvalization, and magnetotherapy are used.

Among specific enzymatic drugs that provide the lysis of collagen (the main component of cicatrix), collagenase is one of the most studied drugs for the treatment of cicatricial and fibrous processes [7]. The Russian State Drug Register contains data on the drug "Collalysin" (INN "Collagenase"), LSR-005615/09 is a proteolytic enzymatic drug obtained from *C. histolyticum*. Collalysin is produced as a lyophilisate powder at the dose of 100 to 1000 collagenase units (CU) for solution for injections and electrophoresis. It is recommended for the treatment of burns, correction of cicatrices, etc. [8]. The mechanism of the therapeutic effect of "Collalysin" is based on the capacity to transform peptide bonds of native insoluble collagen into a soluble form by means of hydrolysis. The positive effect of external treatment

of collagenase cicatricial tissue is similar to the effect observed after the injection of hormonal anti-inflammatory drug triamcinolone into the cicatrix [9]. Collagenase can be introduced into the skin by non-invasive methods, for example, electrophoresis [10].

Dynamic currents are used for deeper administration of active substances for a long time. The benefit of this type of administration in comparison with other types of phoresis is not only in the comfortable administration of large volumes of enzymes (for example, collagenases) into vast areas of the pathological process in patients with expressed cicatricial processes on especially sensitive areas but also in a more diverse effect on the organism, i.e. biodegradable, vasodilating, trophic, and expressed analgesics that reduce the manifestations of neuropathy.

The development of local neuropathy, which is observed in many patients, is based on neural tissue ischemia caused by the edema. There are numerous pharmaceutical and physiotherapeutic methods of correction of local edema and neuropathy. The etiopathogenesis of this complication after lip contour correction is based on the compression of the surrounding tissues by a conglomerate of the stabilized hyaluronic acid filler and fibrous tissues. The application of hyaluronidase for the acceleration of the biodegradation of the residues of hyaluronic acid and diadynamophoresis of collagenase collalysin for the degradation of pathologically produced collagen and anti-edema and the pain-relieving effect is a scientifically grounded combined method of treatment of unfavorable events in cosmetology that significantly improves the esthetic profile and the quality of life of patients.

THE STUDY WAS AIMED

To evaluate the effectiveness of combined enzyme therapy that included a combined course of laser phoresis of Longidaza and diadynamophoresis of collalysin for the correction of such complications that develop after lip contour correction as hypercorrection of filler against the background of fibrosis with signs of neuropathy study included 31 patients aged 25 to 32 years old that applied to "Clinics of Esthetic Medicine", LLC in 2018-2020 because of complications after lip contour correction that were performed in third-party organizations. The majority of patients had signed forms of informed consent or documentation on earlier injected fillers. The anamneses showed that all patients had multiple injections of hyaluronic fillers for the past 5-6 years for the form correction and volume expansion of lips. On average, during this period, each patient received 5 ml of stabilized hyaluronic acid-based drugs of different brands. The desired volume of the injected filler was often determined by the patients themselves. After the procedure, patients developed edema of different degrees of severity, moderate pain syndrome, and single hematomas. Within the first days after the contour correction, the majority of patients topically applied "Traumel" cream, antihistamine, and diuretic drugs. All patients had the last filler injection more than 6 months ago. During the past 4-5 months, patients developed moderate edema, insignificant painfulness during palpation, dryness, color change, paresthesia, or lip numbness. To relieve these manifestations,

patients applied topical homeopathic (Traumel) or moisturizing creams that did not bring positive results.

During the examination, the lip skin was pale pink. Some patients had single areas with bluish skin color, occasionally, the skin was edematous and tense. The palpation revealed multiple dense areas. Patients complained about unpleasant sensations in the lip area (pin and expanding sensation, “uncomfortable”, numb feeling).

In all patients, ultrasonic scanning of the lip area revealed numerous diffuse hypoechogenic foci 0.01-0.05 ml in diameter at different levels that were surrounded by diffuse hyperechogenic areas. The epidermis was thinned, the dermis was deformed and its thickness was significantly increased. There was no borderline with the hypodermis and the echogenicity of the surrounding tissues was reduced.

All patients received collagenase (“Collalysin” 1000 CU) by means of diadynamophoresis using a “Mustang-Physio-MELT-2K” apparatus (RU No. FSR 2008/03578 dated October 31, 2010) as a 10-procedure course and (or) Longidase 3000 U by means of laser phoresis using a “Mustang-2000” apparatus (RU No. FSR 2008/03578 dated December 31, 2010) as a 10-procedure course on the daily basis.

The combined therapy started with diadynamophoresis of collalysin and continued with laser phoresis of Longidase.

Patients were divided into 3 groups.

The group of comparison 1 (n=11) included patients that received only a 10-procedure course of laser phoresis of Longidase, 3000 U.

The group of comparison 2 (n=10) included only a 10-procedure course of diadynamophoresis of collalysin (daily). The main group (n=10) included patients that received a course of diadynamophoresis of collalysin combined with laser phoresis of Longidase 3000U (10 procedures, daily).

The duration of therapy in each group was 10 days.

For the objective evaluation of the condition of patients and their dynamics, the authors performed the following studies:

1. The evaluation of the general status of patients and psychometric diagnostics (Beck Anxiety Inventory and State-Trait Anxiety Inventory) for the analysis of state and trait anxiety.

2. The evaluation of the degree of pain syndrome was performed by the visual analogue scale (VAS).

3. Ultrasonic scanning for the identification of echo structural peculiarities of the epidermis, dermis, and hypodermis Dub Cutis 22-75, TRM, Germany, sensor 22 MHz (registration No/ RZN 2016/5165 dated April 26, 2017). The authors evaluated the thickness of the epidermis, dermis, the coefficient of dermis density, which indirectly reflected the severity of dermis edema, and the dynamics of the filler degradation.

The patients were examined before the treatment and 1 and 3 months.

The method of administration of collalysin by means of diadynamophoresis: dry substance “Collalysin” 1000 CU was diluted in 10 ml of distilled water. The obtained solution was used for moistening 2 pads (bifurcated electrode), the rest 2 pads were moistened with distilled water. The size of the electrodes was 35×45 mm. The electrodes were placed in a transverse position; the type of modulation was a short

period. The drug was administered from positive electrodes. One electrode was placed on the upper lip, the other – on the lower lip. Negative electrodes were placed in the projection of the second branch of the trigeminal nerve. The time of exposure was 5 minutes, the current power – until moderate vibration sensations. The course included 10 procedures on a daily basis. The total dose for the course was 10,000 CU.

The method of administration of Logidaza using laser phoresis: dry substance Longidaza 3000 Units was diluted in 4 ml of gel for ultrasonic therapy (gel “Repak-T”). The obtained solution was applied topically on the upper and lower lip. The authors used an infrared laser in the pulse mode. The mode was contact and labile. The power was 50 W, pulse-repetition frequency was 80 Hz, the time of exposure was 10 minutes (5 minutes on upper and 5 minutes on lower lip). There were 10 procedures on a daily basis.

The procedures were tolerated well, additional anesthesia was not required.

All statistical calculations were performed using Statistica for Windows 10 (Statsoft).

RESULTS AND DISCUSSION

The authors obtained the following results. Visually, 1 month after the beginning of the therapy, the signs of hypercorrection and compaction significantly reduced in all three groups. However, in the main group, the effect was more visible. In three months, in the main group, edema, contouring, and skin compaction were not visually observed, but there were dense areas palpated. During the period of observation, no temporary edemas were registered in both groups.

According to the Beck Anxiety Inventory (BAI), the evaluation of psychovegetative alterations and depression, performed before the treatment, revealed high scores. Positive dynamics during the treatment was observed in all three groups. However, more expressed results were registered in the main group, wherein the BAI score was 34% lower than in the group of comparison 1 already one month after the beginning of the therapy and 40% lower than in the group of comparison 2. In 3 months, in the main group, this parameter was within the norm, while in the groups of comparison 1 and 2, this parameter was in the range of “subdepression”. The interpretation of the BAI score was made by the following scale: 0-9 points – no symptoms of depression; 10-15 points – light depression (subdepression); 16-19 points – moderate depression; 20-29 points – expressed depression; 30-63 points – severe depression.

Similar data were obtained after the evaluation of the State-Trait Anxiety Inventory (STAI) that is an informative method of self-evaluation of state and trait anxiety. Before the therapy, the score was high in all groups. One month after the beginning of the therapy, patients from all groups had positive dynamics. However, in the main group, patients were in the range of “low anxiety”, while in the groups of comparison, the score was in the range of “moderate anxiety”. Three months after the beginning of the therapy, the STAI score in all the studied groups was within the norm. The interpretation of the STAI score was made by the following scale: up to 30 points – low level of anxiety, 31-45

points – moderate anxiety, 46 and more points – high level of anxiety (Table 1).

Table 1: The results of the evaluation of psychovegetative changes (Beck Anxiety Inventory and State-Trait Anxiety Inventory) in the studied groups before the treatment and 1 and 3 months

Parameters	Group of comparison 1 (n=11)			Group of comparison 2 (n=10)			Main group (n=10)		
	Before treatment	1 month	3 months	Before treatment	1 month	3 months	Before treatment	1 month	3 months
Beck Anxiety Inventory (BAI), points	21.61 ±1.82	16.93 ±1.12*	11.17 ±1.03*	21.98 ±1.75	18.61 ±1.17*	12.18 ±1.04*	21.79 ±1.63	11.20 ±0.98*#	6.49 ±0.49*#
State-Trait Anxiety Inventory (STAI), points	35.97 ±2.46	30.85 ±2.18*	15.11 ±1.26*	36.02 ±2.45	31.94 ±2.79*	15.21 ±1.37*	35.87 ±2.68	21.59 ±1.94*#	13.97 ±1.16*

Notes: * – $p < 0.01$ – the level of significance before and after the treatment; # – $p < 0.05$ – significance of differences between analog parameters in the main group and the groups of comparison

Pain syndrome was characterized by unpleasant sensations in the lips (pin sensations, periodic numbness, expansion, discomfort) and was evaluated by the VAS. Positive dynamics of VAS was observed in all studied groups one and three

months after the beginning of the therapy. However, in the main group, the VAS score decreased more significantly. In one month, in the main group, the score was lower by 1.8 times than in the group of comparison 1 and by 1.5 times than in the group of comparison 2. In three months, in the main group, the VAS score was lower by 3 times than in the group of comparison 1 and by 2.6 times than in the group of comparison 2 (Table 2).

Table 2: VAS score in patients during the period of observation

Group	VAS parameter		
	Before treatment	In 1 month	In 3 months
Group of comparison 1 (n=11)	7.11 ±0.54	3.87±0.41*	2.83 ±0. 23*
Group of comparison 2 (n=10)	7.08 ±0. 59	3.29±0.17*	2.47 ±0.31*
Main group (n=10)	7.19 ±0.51	2.14 ±0.29*#	0.94 ±0.18*#

Notes: * – $p < 0.05$ – significance of the differences in the group in comparison with the parameter values before the treatment; # – $p < 0.05$ – the significance of the differences between analog parameters in both groups of comparison

Besides, the authors evaluated the pathological process, in particular, the thickness of the epidermis, the thickness of the dermis, and the coefficient of dermis thickness. The data were calculated as mean parameters for the upper and lower lip.

It was impossible to evaluate the dynamics of biodegradation of the injected filler before and after the treatment numerically because there were multiple small diffusely located hypoechogenic foci with alternating hyperechogenic areas, primarily, in the hypodermis. However, during the treatment, patients from all groups had a significant decrease in the number of hypoechogenic foci, and the density of hyperechogenic areas significantly reduced. The dermis-hypodermis borderline became more precise.

The thickness of the epidermis in the studied groups after the therapy increased in the first and third months of the observation and was not statistically different. However, the results of the ultrasonic study of the skin showed that a combined course of diadynamophoresis of collalysin combined with laser phoresis of Longidaza provides an expressed decrease in the thickness of the dermis and increase

in the coefficient of the density of the dermis, which was associated with a reduction of the intradermal edema that developed as a reaction to the compression of subdermally located dense areas that are presented by conglomerates consisting of numerous fragments of stabilized hyaluronic acid and pathologically produced collagen. It should be noted that there was an improvement of the ultrasonic picture and a significant reduction of the signs of intradermal edema in the main group, especially, in the early period of observation (1 month after the beginning of the treatment). The thickness of the dermis decreased by 15.6% in comparison with the groups of comparison 1 and 2, wherein a decrease in this parameter was by 6.8% and 8.7%, respectively, and the coefficient of the ultrasonic density of the dermis increased by 14.2%, while in the groups of comparison 1 and 2, it increased by 4.1% and 4.9%, respectively. These data indirectly indicate a faster reduction of the intradermal edema in the early period of observation (by more than 2 times) in the main group in comparison with both groups of comparison. In three months of the observation, the studied parameters were more illustrative. In the main group, the thickness of the dermis decreased by 19.3% in comparison with groups of comparison 1 and 2, wherein it decreased by 9.7% and 11.7%, respectively. The coefficient of the ultrasonic

density of the dermis increased in the main group by 15.1% while in the groups of comparison 1 and 2, it increased by 7.4% and 8.8%, respectively (Table 3).

Table 3: The results of ultrasonic scanning of the skin before the treatment and 1 and 3 months

Parameter	Before treatment			In 1 month			In 3 months		
	Groups			Groups			Groups		
	1	2	3	1	2	3	1	2	3
The thickness of the epidermis, μm	70.214 ± 0.631	70.208 ± 0.863	70.197 ± 0.763	71.091 $\pm 0.705^*$	71.094 $\pm 0.661^*$	71.101 $\pm 0.499^*$	71.099 $\pm 0.387^*$	71.102 $\pm 0.549^*$	71.109 $\pm 0.591^*$
The thickness of the dermis, μm	1927.45 ± 0.542	1938.82 ± 0.444	1931.36 ± 0.475	1796.38 $\pm 0.425^*$	1770.14 $\pm 0.483^*$	1630.07 $\pm 0.514^*\#$	1740.49 $\pm 0.502^*$	1711.98 $\pm 0.498^*$	1558.61 $\pm 0.538^*\#$
Coefficient of ultrasonic thickness of the dermis, %	1.294 ± 0.276	1.289 ± 0.285	1.291 ± 0.219	1.347 $\pm 0.253^*$	1.352 $\pm 0.313^*$	1.474 $\pm 0.341^*\#$	1.390 $\pm 0.224^*$	1.402 $\pm 0.277^*$	1.489 $\pm 0.301^*\#$

Notes: * – $p < 0.05$ – the significance of the difference in the group in the dynamics before the treatment and 1 and 3 months; # – $p < 0.05$ – the significance of the differences between analog parameters in groups of comparison 1 and 2. The obtained results provide grounds for the recommendation of diadynamophoresis of collalysin combined with laser phoresis of Longidaza as a complex measure that has a significant effect in patients with remote complications developed after lip contour correction. This combined method significantly reduced the signs of compaction, hypercorrection, visualization of filler in the site of injection, and signs of neuropathy. It also accelerates the period of recreation that synergistically affects the esthetic profile of the patient and significantly improves the quality of life and psychoemotional status of patients with similar complications and unfavorable events.

Despite a seeming simplicity of the performance of one of the most demanded procedures in cosmetology (lip contour correction), specialists have to remember about possible unfavorable events and complications that can develop in the early and remote recovery period. The administration of excessive volume of filler or superficial injection can lead not only to continuous edema but also to the conturation of the filler, change in the lip color, appearance of compacted areas, and development of local neuropathic manifestations associated with the disturbance of microcirculation and edema. Multiple injections can lead to the formation of fibrous alterations in the lip tissue. To avoid such complications, specialists need to evaluate the depth of injection of the drug, its density according to the thickness of the skin, and to choose the volume of the injected filler reasonably. For the evaluation of the lips status, specialists need to perform ultrasonic scanning for the identification of fibrosis foci and encapsulation of the drug. For the correction of the identified areas of hypercorrection or compaction, enzyme-containing drugs should be included in the treatment plan.

CONCLUSION

Combined administration of diadynamophoresis of collalysin and laser phoresis of Longidaza in patients with

such complications after lip contour correction as compaction foci, conturation, temporary edema, Tyndall effect, and signs of neuropathy exerts positive effect that leads to the improvement of the psychoemotional condition, reduction of painful and neuropathic events, and normalization of morphological skin picture. According to the ultrasonic scanning, a combined method of treatment is more effective than an individual indication of one of the methods only. Complex application of enzymes for the treatment of complications after lip contour correction is a highly effective method that quickly resolves clinical symptoms and improves the quality of life of patients.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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