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"Arbat Beauty Institute Active Longevity Clinic"

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CLINICAL INVESTIGATION REPORT

"Effectiveness of application of Fermencol using electrode pharmaphoresis with Farmateb apparatus in patients with hypertrophic and keloid scars"

1.Topicality of research

The problem of treating hypertrophic and keloid scars in cosmetology has not ceased to be a topical one, due to a number of factors. Firstly, keloid scars are characterised by being located on open areas of the body, especially the face and neck, and patients therefore often come for help specifically from cosmetic clinics. Secondly, the number of plastic surgery procedures to rectify cosmetic defects, remove wrinkles, scars and skin growths is currently increasing. Account is not always taken of the possibility that post-operative skin may produce a keloid scar, meaning that keloid formation is sometimes unforeseen. As a result, hypertrophic or keloid scars, more or less pronounced, can sometimes form after an operation because of a cosmetic defect. Thirdly, there is currently no single strategy for treating keloid scars, and most applicable methods (surgical excision, hormone therapy, X-ray treatment) do not always prevent a recurrence or produce a good cosmetic result, and can sometimes be accompanied by complications (M. Khitilova, V. Kulganek, V. Gorn, 1960; R. D. P. Craig, 1971). An analysis of treatment results shown in literature indicates that recurrences occurred with a single method or with complex treatment in 40-50% of cases (E. A. Kharitonova, 1997).
The choice of treatment method must be based on knowledge of principal chains of keloid pathogenesis, which have been quite well studied (E. G. Kolokolchikova, 1980; Z. K. Mackevicius, 1987; A. G. Melikyants, O. N. Kutkova, 1992; N. P. Omelyanenko, L. D. Zherebtsov, I. N. Mikhailov, 1977). Many authors indicate that the effectiveness of keloid treatment depends to a significant extent on early application of curative and preventive measures (K. F. Sibileva, 1964; L. A. Bolkhovitinova, M. N. Pavlova, 1977; S. B. Konovalskaya, 2003; A. P. Kelly, 1988; J. Nuovo and A. Sweha, 1994; H. L. Nielsen, C. Von Buchwald, J. Rosborg, 1994; S. S. Urisote, K. A. Arndt, J. S. Dover, 1999 &c). Of the importance of modern treatment of this range of pathological scars there is no doubt. Alongside the various methods of treating pathological scars, much importance is attached to the physiotherapeutic method of treatment, the basis of which is the reaction of the body to physiotherapeutic action through neuroreflector and neurohumoral channels, as well as local effects on scar formation (A. E. Guller, 2006; V. E. Illarionov, 2003; D. D. Goldberg, 2010; J. L. Clayton, R. Edkins, B. A. Cairns, C. S. Hultman, 2013). During treatment and prevention of scar formations, ultraphonophoresis and electrophoresis are most commonly applied, with medicines that exert a fibrolytic action (L. S. Kruglova, 2007). Pharmaphoresis is an innovative new type of medicinal electrophoresis. This is a method of combined action on the body by complex low-voltage impulse current and medication introduced with its assistance (M. Miesfari, A. D'Africa, F. Morabito, 2001). In the mechanism of action of electrode pharmaphoresis, equal importance is attached to the electric current as an active biological irritant and to the medication, which penetrates tissue to a depth of 10-12 cm without residue because of the electrogenic movement [(89%), 3% because of electroosmosis and 8% because of diffusion]. In this case, the medication penetrates the body through the skin, mucous membranes or wound surface (V. S. Martin, J. A. Albanesi, 2002; M. R. Prausnitz, R. Langer, 2008).
One of the new pharmaceutical preparations is fermencol. The preparation "Fermencol" is a unique natural complex of isoenzymes of collagen with molecular mass of 23-36 kDa, capable of splitting a triple-helix collagen molecule. This complex shows not only a collagenolytic, but also a general proteolytic, action, This means that the action of the enzyme complex is not limited just to hydrolysis of the triple helix of native collagen, but that the collagen breaks fright down to separate amino acids. The scar shrinks because of hydrolysis of collagen, caused by destruction of hyaluronic acid.
Electrode pharmaphoresis, in contrast to other pharmacotherapeutic methods, has distinctive features: the medication is introduced in the minimum required quantity, in terms of milligrams or fractions thereof, sufficient to produce a good curative effect. The increased pharmacological activity of the medicine is explained by the action of the special current, which creates a favourable background for the medicine to act, and also the introduction of the most active part of the medicinal compounds with the presence therein of an electrical charge (ion, mole-ion) that allows it to interact not just chemically, but also electrically, with cells. 2. There are no side-effects particular to other methods of introducing the medication, as it enters the body in small amounts and avoids the bloodstream. 3. The pharmacological preparation goes straight to the seat of the problem. 4. In contrast to normal medicinal electrophoresis, where of a huge number of pharmaceutical preparations only about 200 names can act in any way

through electrophoresis, any active substance can be introduced by means of pharmaphoresis without using special buffers and solvents, which are replaced by a special current-conducting gel.
Pharmaphoresis combines all these methods of action and is of particular importance amongst modern transdermal methods of introducing medicines. The source of current is the Farmateb electronic unit complex, which consists of an electronic rectifier, pulse-reducing filters, an outgoing regulation potentiometer and a "self-diagnosing" measuring unit, which every 20 milliseconds measures the specific conductivity and dielectric permeability of tissue. The processor unit manages all the functions of the electrical field, consisting of three high-speed processors. On the basis of the treatment programme parameters (17 programmes in the complex), the values of the electrical signal emitted are calculated by the processor unit to form an impulse, which allows the active ingredient of the medication to penetrate to a depth of 12 cm with all dielectric permeability dispersion areas (alpha 10/2 Hz, beta 10/4-10/8 Hz and gamma 10/9-10/10 Hz (M. Misefari, A. D'Africa, F. Morabito, 2001). Because in this kind of electrical field the tension of the internal cellular membranes is a thousandth or less, and the biological membrane acts as a screen for the intracellular environment against continuous and very low-frequency external electrical fields, the cells are not damaged (T. Marling, U. F. Pliquett, 2002; A. Matarasso, S. L. Matarasso, 2001; M. Misefari, A. D'Africa, F. Morabito, 2001).
Indications for electrode pharmaphoresis are very wide indeed and are determined by the pharmacological properties of the medicine introduced and of the electrical current. Contraindications may include systemic blood disorders, chronic cardiovascular conditions in the decompensation stage, generalised skin damage and loss of skin sensitivity, pregnancy, cachexia and toxic conditions.

2. Aims of research

Aim: To assess the efficacy and safety of the method of introducing Fermencol (collagenolytic enzyme complex), from the transdermal medicine introduction apparatus known as Farmateb or Trans Epidermal Barrier Physio (Farmateb Medical, Russia, registration certificate no. FS32012/12945 dated 25.09.2012), into patients who have had post-operative or post-traumatic keloid and hypertrophic scars for up to 3 years. To assess the efficacy of the Fermencol on clinical indicators in patients with scar-related skin changes.
Task of research:
1. To develop indicators for applying Fermencol by means of electrode pharmaphoresis in post-operative and post-traumatic hypertrophic and keloid scars lasting up to 3 years.
2. To study the efficacy and safety of applying Fermencol by means of electrode pharmaphoresis in patients with scar-related skin changes.
3. Dates of clinical examinations Start of investigation: December 2013 – End of investigation: April 2014
4. Type of research : Open investigation was conducted with participation by 10 patients with post-operative and post-traumatic hypertrophic and keloid scars. To carry out the electrode pharmaphoresis, Fermencol (OAO NPK Vysokiye Tekhnologii, Russia) was used.
5. Criteria for including and excluding subjects - Criteria for inclusion in research
• Patients aged 10-54 years with verified diagnosis of hypertrophic or keloid scars in formation stage.
• Absence of contraindications to physiotherapy (electrotherapy).
• Signed and informed consent.
• High patient compliance levels.
Criteria for non-inclusion in research
• Contraindications to physiotherapy (electrotherapy).
• Hypertrophic or keloid scars lasting less than 1 year.
• Medical history of allergic reaction to enzyme preparations.
• Accompanying or unstable somatic conditions (any disease or condition that in the opinion of the investigator complicates interpretation of the results of the treatment or makes application of procedures within the context of the present research impossible).
• HIV infection.
• Pregnancy and lactation.
• Suspected malignant formations.
• Acute psychiatric manifestations (psychosis, delirium, hallucinations).
• Low patient compliance.
• Patients with indications of drug dependency or continuous use of alcohol in their medical history, likely to adversely affect patient compliance in relation to undergoing the investigation procedures.
• Participation in other clinical research during the last 30 days before commencement of this research.
Criteria for exclusion from research
• Mistaken inclusion.
• Serious deviation from the research protocol.
• Manifestation in the patient of criteria for exclusion during the research.
• Wish to withdraw from the research.
• Serious unwanted effects or significant deviations in laboratory analyses, requiring a change in therapy applied.
• Missing more than two sessions.

6. Clinical characteristics of patients

With the method of introducing Fermencol using electrode pharmaphoresis, patients were divided as follows:
10 patients with post-operative and post-traumatic hypertrophic or keloid scars present for up to 3 years.

7. Treatment provision plan

The patients underwent pharmaphoresis with a range of collagenolytic enzymes from apparatus for transdermal introduction of medicinal substances, namely Farmateb Trans Epidermal Barrier Physio (Farmateb Medical, Russia,

registration certificate no. FS32012/12945 dated 25.09.2012). The apparatus uses an alternating electrical field modulated according to frequency and amplitude and/or combination thereof; this field increases permeability of skin

layers, facilitates opening of ion channels in tissue cells, and allows medicines, even those with high molecular mass, to penetrate deep into the tissue. To provide the pharmaphoresis, the preparation Fermencol was used, this being a unique natural complex of collagenase isoenzymes with molecular mass of 23-36 kDa capable of splitting a triple-helix collagen molecule. This complex is not only collagenolytic, but also generally proteolytic. This means that the action of the enzyme complex is not limited to hydrolysis of the triple helix of native collagen, but also destroys the collagen fragments and turns them into separate amino acids. Hydrolysis of the collagen has the effect of reducing the scar.
The method of applying the procedures was as follows: after cleaning of the scar surface with antiseptic solution, the skin area was treated with the Fermencol containing the collagenase complex, and the action was commenced without waiting time. The electrode-pen was placed at an angle of 45 degrees, and the action was exerted through stable contact. Individually for each patient, a treatment programme was chosen in accordance with the scar parameters.
The recommended concentration was 0.5-1.0 mg/ml for correction of keloid scars, and 0.1-0.2 mg/ml for hypertrophic scars. An individual course of treatment was chosen for each patient, taking account of depth and length of action (5-15 minutes). The course consisted of 10 sessions carried out across one day.

9. Description of criteria for assessing clinical efficacy, tolerance, safety

The therapeutic efficacy of Fermencol was determined in accordance with positive dynamic of principal diagnostic criteria and indicators of effect on the quality of the patient's life, or the "dermatological life quality index" (DLQI). The clinical parameters were assessed at each visit by the patient (overall condition, local status). The DLQI index was assessed before and after the treatment.
The principal indicators of results of treatment were:
- Assessment of clinical parameters of scar.
- Local subjective feelings (itching, burning, pain).
- Dimensions (volume, height).
- Unevenness of surface contours.
- Intensity of colouring.
- Thickness and tightness of movement.

Criteria for assessing effectiveness of methods of treatment of pathological scars

Table 1
Clinical parameters Nature of change, result achieved
R E D U C T I O N Local subjective feelings (itching, burning) Overall condition (psycho-emotional state) of patient improved
Dimensions (volume, height) Reduction, smoothing
Improvement in outward appearance of scar formation
Unevenness of surface relief Smoothing of contour against background of settling
Intensity of colouring Noticeable difference in colour between scar and surrounding area
Density, tightness of movement Softening & reduced tightness of scar-affected tissue with minimal activity
The results of the treatment in patients with scar changes were assessed according to the following clinical criteria:
Significant improvement: Cessation in growth of scar, disappearance of subjective sensations, smoothing, softening, smoothing of contour against background of settling down to level of surrounding tissues, reduction in colour difference between scar and surrounding tissue.
Improvement: Cessation or interruption in growth of scar, disappearance or significant reduction of subjective sensations, smoothing, softening, settling and reduction in intensity of colour of scar.
Stabilisation of process: Cessation or interruption in growth of scar, reduction of subjective sensations, smoothing, softening, settling, reduction in intensity of colour of scar.
Deterioration: Maintenance of negative dynamic or further progression of scar.
Improvement and significant improvement were noted as the overall effect of the method of treatment.
The laboratory methods for assessing efficacy used a high-frequency 22-MHz scanning and deep penetration to 10 mm. The scanning was carried out before treatment and after the end of the physio procedures. Efficacy was analysed using mathematical methods and computer technology, and on the basis of clinical examinations and patient surveys.
Safety of application of the preparation was assessed according to evaluation of side effects (allergic reactions, increased intoxication, inflammatory and infiltration reactions at place of introduction of preparation) and patient surveys.

10. Description of methods of statistical processing of results

Generally accepted standard methods for statistical processing were applied, with results determined by the mean arithmetical value (M), error of mean arithmetical value (m), and reliability of difference in average values in patient groups according to Student's criteria (t, p). The procedures were carried out at the cosmetology base of OAO Arbat Beauty Institute Active Longevity Clinic.

11. Results

Clinical assessment of efficacy of treatment
1. Efficacy of correction of pathological scars according to outward appearance of scar area, compared with initial (first) data from patients with hypertrophic or keloid scares was assessed on the Vancouver scale. A reduction in severity of the clinical parameters that characterised the outward appearance of the area was noted: protrusion (settling, smoothing) and/or width (narrowing), density (softening), intensity of colour (paling), pronouncement of contours, unevenness of surface relief (smoothing) and increase in mobility of scar and suppleness of surrounding tissues. On each control examination the parameters in which the therapeutic effect had been achieved, the severity of localised unpleasant sensations (pain, itching, burning, disruption of sensitivity &c), and overall patient satisfaction

with the treatment, were all assessed. The main indicator of a positive result of treatment of an unrestrained or hypertrophic scar was the interruption of its growth outside the borders of the initial traumatised area and the absence of recurrence in the immediate and later stages of surveillance.

As a result of the treatment given (n=10 with post-operative and post-traumatic scars present for up to 3 years), 7 patients presented a significant improvement (70%), and 3 patients showed an improvement in condition (30%). No deterioration in dynamic was noted. The overall efficacy of the complex treatment of patients with hypertrophic and keloid scars was therefore 70%. All patients included in the research were interviewed using the standard life quality survey form in which they answered the questions given in the presence of a doctor before and after the treatment. The patients assessed their condition on a three-level rating for each question given, and the data obtained were then analysed statistically. Interpretation of index: the higher the value, the more adversely the condition was affecting the life of the patient. Before restorative treatment was administered, all DLQI indicators were significantly raised, both in patients with hypertrophic scars and in those with keloid scars. This particularly affected self-evaluations, communicative powers and mood. The most significant reduction in quality of life was noted in keloid scar patients. Also, when the scarring was on visible sections of the body and widespread, this had a pronounced negative effect on the psychological and emotional state of the patients. As a rule, these patients concealed their outward appearance because of the cosmetic unattractiveness of the scar, limited themselves in choice and purchase of clothes, and avoided intimate relationships. Before the treatment, patients with hypertrophic scars had average values on separate DLQI indicators, which varied within quite broad limits from 1.22 ± 0.11 (interaction) to 2.01 ± 1.04 (sporting activities). The overall DLQI value at the beginning was 16.46 ± 1.20. After treatment, including application of fermencol pharmaphoresis, indicators in all parameters reduced quite significantly and varied within limits from 0.31 ± 0.06 (sporting activity) to 0.68 ± 0.05 (intimate relations) ($p < 0.05$). The summary index thus improved by 71.34% and totalled 4.79 ± 0.05 ($p < 0.05$) (table). In the initial condition, average values patients with keloid scars in separate DLQI parameters varied within limits from 1.36 + 0.11 (work, study) to 2.38 + 0.20 (subjective sensations indicator). Summary DLQI index value before treatment was 18.26 ± 1.47. After application of electrode pharmaphoresis, indicators for separate parameters were reliably and significantly reduced, within limits from 0.45 + 0.04 (business activity) to 1.34 + 0.22 (sporting activity). The summary index improved by 48.22% and totalled 9.24 ± 0.22 ($p < 0.05$) (table). Dynamic of DLQI (rating) in patients with hypertrophic (HS) and keloid (KS) scars before and after application of electrode pharmaphoresis

Table 2

HS KS DLQI form questions HS before treatment HS after treatment KS before treatment KS after treatment
Subjective sensations, pain 1,56
±0,12 0,56
±0,04* 2,38
±0,20 0,88
±0,05*
Feeling of assurance 1,68
±0,15 0,64
±0,07* 1,85
±0,15 1,12
±0,18
Business activity 1,53
±0,12 0,38
±0,03* 1,56
±0,11 0,45
±0,04*
Choice of clothes 1,84
±0,15 0,56
±0,08* 1,94
±0,12 1,11
±0,22
Active recreation 1,88
±0,11 0,49
±0,05* 1,82
±0,11 0,85
±0,35
Sporting activity 2,01
±0,14 0,31
±0,06* 2,04
±0,18 1,34
±0,22
Work and study 1,75
±0,09 0,38
±0,02* 1,36
±0,11 0,55
±0,10*
Communication 1,22
±0,11 0,47
±0,06* 1,81
±0,18 1,25
±0,14*
Intimate relations 1,68
±0,12 0,68

±0,05* 1,94
±0,13 1,08
±0,25
Daily routine 1,32
±0,12 0,45
±0,03* 1,58
±0,11 0,67
±0,11*
Ultrasound scan indicators for epidermis

Table 3
No. Surname, forename, patronymic Epidermis Thickness, mcm Acoustic density before after before After
1 Isakova, A. N. 78 78 29 23
2 Abramova, A. A. 86 86 202 50
3 Popova, M. A. 102 102 224 41
4 Eremenko, T. S. 70 70 186 178
5 Klebeko, A. I. 78 78 139 125
6 Garaniadze, M. A. 86 86 123 81
7 Finogenova. N. N. 86 86 74 70
8 Katchev, B. V. 141 125 164 112
9 Pinchuk, E. A. 94 86 179 152
10 Pashkova, N. S. 70 70 155 133
80.10±
20.79 86.70±
16.37 147.50±
59.39 96.50±
51.31
After treatment, thickness of epidermis reduced by 2.76%; acoustic density was reduced by 52.84%.
Ultrasound scan indicators for dermis

Table 4
No. Surname, forename, patronymic Dermis Thickness, mcm Acoustic density before after before After
1 Isakova, A. N. 4586 4164 14 5
2 Abramova, A. A. 3836 3836 22 12
3 Popova, M. A. 4531 4531 11 11
4 Eremenko, T. S. 3922 3648 12 12
5 Klebeko, A. I. 3492 3039 21 21
6 Garaniadze, M. A. 5945 5875 12 10
7 Finogenova. N. N. 3281 3281 16 10
8 Katchev, B. V. 3461 3461 7 4
9 Pinchuk, E. A. 5789 5563 5 4
10 Pashkova, N. S. 4516 3227 19 15
4336.00±
933.70 4062.00±
983.60 13.90±
5.66 10.40±
5.27 After treatment, thickness of epidermis reduced by 6.74%; acoustic density was reduced by 33.65%.
Assessment by patients of comfort and efficacy of treatment given

Table 5
Parameters Subjective sensations during procedure
(max. 3) Convenience of application (max. 3) Efficacy
(max. 3) Overall assessment (max. 9)
Patients with hypertrophic & keloid scars (n+10) 2.4 2.6 2.8 7.8
Assessment of safety of treatment .In no cases in which the Fermencol treatment was applied by means of electrode pharmaphoresis were side effects noted in any of the 10 procedures. The subjective assessment using photographs (before and after electrode pharmaphoresis with Fermencol), and the doctor's clinical assessment, revealed a good immediate therapeutic and cosmetic effect.

12. Conclusions

Clinical observations have revealed that the preparation Fermencol is an effective pharmacological preparation, capable of interrupting growth of connective tissue and causing reverse development of fibrosis. Clinical research conducted has shown that:
- It does not have an irritating or sensitizing effect, and has a good correcting effect on scar tissue, especially in the formation stage.
- Application of Fermencol using electrode pharmaphoresis can be added to the instructions for application of this product.
- The preparation is topical for application in dermatocosmetic practice in treatment establishments for the treatment of scar tissue on skin.
- Transdermal introduction of medicines using the Frame TEB apparatus, which allows the active substance to penetrate to a depth of 12 cm, is topical for application in dermatocosmetic practice in treatment establishments for the treatment of scar tissue on skin.