

HYALURONIDASE OINTMENT IN TREATMENT OF HYPERTROPHIC SCARS

¹Alibegashvili M., ¹Loladze M., ¹Gabisonia T., ³Gabisonia G., ²Tsitsishvili D.

¹G. Eliava Institute of Bacteriophages, Microbiology and Virology, Tbilisi;

²Clinic Of Aesthetic Medicine "Woman and Health", Tbilisi; ³Georgian American University (GAU), Tbilisi, Georgia

One of the problems of medicine is the prevention and treatment of postoperative and posttraumatic scars. The significant complications in the form of cicatricial degenerations, mainly hypertrophic scars, are often arising on site of second- and third-degree burns, traumas. Scar tissue is a natural result of any type of plastic surgery, or any other surgical procedure.

Hypertrophic scars are unique dermal fibroproliferative disorders that occur following trauma, burns, surgery or inflammation. They are raised, erythematous, pruritic, fibrous lesions that typically remain within the confines of the wound and are often associated with contractures of the healing tissues. Such scars are usually permanent and resistant to known methods of therapy. Post-surgical scar formation is common complication of plastic surgery. Many treatment regimens have been used in the past, including excisional surgery, pressure therapy, laser therapy, pharmacological therapy and so, and none has been universally successful [8].

The Hyaluronidases belong to the enzyme group that breaks down hyaluronic acid. Hyaluronic acid is becoming increasingly important, recognized now as a major participant in such basic processes as cell motility, wound healing, embryogenesis. It fills up the intercellular spaces of connective tissue and the walls of blood vessels and lymphatics. Hyaluronic acid fulfills barrier and tropic functions in the organism and plays an important role in permeability regulation in tissues and ducts. As a rule, hyaluronic acid undergoes a number of qualitative and quantitative alterations in some pathological processes of the organism [12].

The enzyme hyaluronidase is used in medicine in cases of different pathology of conjunctive tissue, which are caused by accumulation of hyaluronic acid. At the same time, hyaluronidase, splitting hyaluronic acid - the important component of tissue barriers, accelerates the vascular and tissue permeability and thereby increases the rate of absorption and access of various drugs, facilitates diffusion of injected substances. By this basis hyaluronidase preparation are used in combination with antibiotics, protein preparations and other drugs. The enzyme improves their effectiveness while is reducing many of complications. Increasing the cellular and tissue penetration of drugs, hyaluronidase minimizes painfulness and risk of formation of coetaneous necrosis. All these properties determine the wide use of the enzyme hyaluronidase in medicine [2,3,7,11].

The method of isolation and purification of microbial hyaluronidase has been developed in G.Eliava Institute of Bacteriophages, Microbiology and Virology (IMBV) On the basis of highly purified and highly active microbial hyaluronidase the medicinal preparation for injection - "Bilidase" has been created. Hyaluronidase ointment used in this study was prepared on the base this preparation.

The objective of present study is to investigate the efficacy of hyaluronidase ointment in treatment of postoperative cicatricial degeneration.

Material and methods. A total number of 14 patients with postoperative hypertrophic scars on different part of face were enrolled in the study. All patients had at least 6 months or a longer history of the lesion. All patients were treated with hy-

aluroidase ointment by help of physiotherapeutic procedures - iontophoresis 1 procedure per day for 10 days twice at 4-week intervals.

All patients were examined 4 times: before treatment, after each cycle of treatment as well as 4 weeks after the last treatment. Scar conditions were assessed in terms of pigmentation, vascularity, pliability and height in accordance with the Vancouver Scar Scale (VSS) conducted by two therapists. Assessments by the patients on pain and pruritis caused by the scars were also recorded (Table).

Results were expressed as means \pm standard error. Statistical analysis was done by the Student's t test with significant defined as a p value less then 0.05.

Results and discussion. All patients had a significant improvement in the clinical appearance of the scars after treatment with hyaluronidase ointment. Each of the four parameters (pigmentation, vascularity, pliability, and height) was improved significantly after treatment with hyaluronidase ointment (Fig. 1). Total score after 2 cycles of treatment was 0.85 ± 0.9 vs 10 ± 1.5 ($p < 0.001$) (treated scars vs untreated ones). Even after 1 cycle of treatment all rated parameters were improved remarkably -5.14 ± 0.9 vs 10 ± 1.5 ($p < 0.001$). There was not significant differences between scores rated after 2 cycle of treatment and 4 weeks after the last treatment.

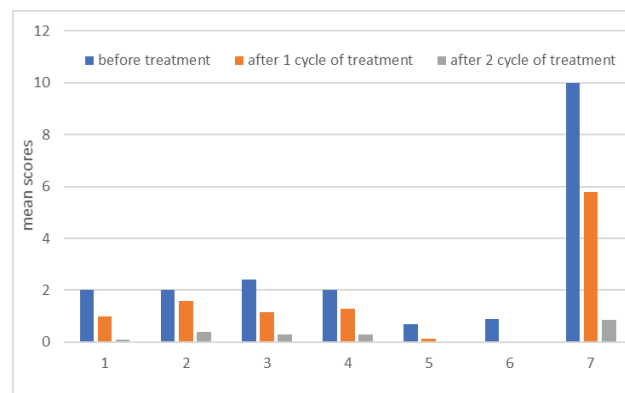


Fig. 1. 1- Pigmentation rating; 2-Vascularity rating; 3-Pliability rating; 4-Scar height rating; 5- Pain; 6- Pruritis; 7-summary of rating scores

It was observed significant recovery of vascularity of skins - mean score $0,36 \pm 0,4$ vs $1.9 \pm 0,4$ before treatment ($p < 0.001$), as well as vascularity of scar - mean score $0,31 \pm 0,5$ vs $2,0 \pm 0,6$ before treatment ($p < 0.001$).

After 2 cycle of treatment it was observed normal flat scars in all studying cases - mean score $0.18 \pm 0,3$ vs $2,25 \pm 0,4$ before treatment ($p < 0.001$). Pigmentation of scar tissues was also normalized, but not completely in some cases - mean score $0.31 \pm 0,05$ vs $2.25 \pm 0,4$ before treatment ($p < 0.001$). Only 4 patients complain of occasional pain and pruritis of their scars before treatment. None of them require medication to alleviate pain. Pre- and post-treatment photographs of three of the patients are shown in Figs. 2-4.

Table 1. Vancouver Scar Scale for assessment of scar conditions

Pigmentation	
0	normal skin
1	hypopigmented skin
2	hyperpigmented
3	pigmentation combined with pyoderma
Vascularity	
0	normal color and capillary refill
1	pink skin with slight increase in local blood supply
2	red scar with a significant increase in the local blood supply
3	purple scar with excessive local blood supply
Pliability	
0	normal skin
1	supple skin that yields with minimal resistance
2	yielding scars that give way to pressure while offering a moderate resistance
3	a firm scar that moves as a solid, inflexible unit
4	any type of contracture
Scar height (maximal vertical elevation of the scar above the normal skin)	
0	flat scar, flush with normal skin
1	<2 mm
2	2 to 5 mm
3	>5 mm
Pain	
0	none
1	occasional
2	requiring medication
Pruritis	
0	none
1	occasional
2	requiring medication



Fig. 2. Patient A: before treatment (left) and after 2 cycle of treatment (right). Total VSS scores before treatment 10.5, after treatment 0.5



Fig. 3. Patient B. before treatment (left) and after 2 cycle of treatment (right). Mean VSS scores before treatment 9.75 and after treatment 0.75

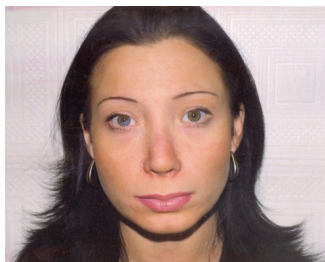


Fig. 4. Patient C. before treatment (left) and after 2 cycle of treatment (right). Mean VSS scores before treatment- 8.5 and after treatment - 1

Most skin wounds heal with little scarring, even when they involve the dermis. However, abnormal scarring, mainly a hypertrophic scar can often develop. It is suggested that in the case of hypertrophic scars hyaluronidase preparations promote diffusion of endogenous enzymes in cicatricial tissues and in such a way facilitate degradation of excessive collagen and proteoglycan's aggregates [3].

Hyaluronidase has been demonstrated in vivo experiments to increased granulation tissue, diminish edema formation and accelerate wound healing processes [4]. In previous work we have studied efficacy of hyaluronidase preparation "Bilidase" for treatment of post-traumatic cicatricial degenerations in the model of the post-burn cicatrices in guinea-pigs. The data of experimental investigation indicate that enzyme hyaluronidase has a significant therapeutic effect. It promotes normalization of structure and histochemical state of cicatricial degenerative tissue, maturation of connective tissue [1].

Clinical studies of efficacy of hyaluronidase injection for treatment of hypertrophic scar are promising. Wollina U. reported that use of small volumes of bovine hyaluronidase caused improvement of scars considering texture, tautness and secondary wound healing. It was demonstrated by improvement of the Vancouver Scar Scale from 6.3 ± 1.9 before to 2.1 ± 1.6 [14]. In the clinical study Tabola R used hyaluronidase injections for treatment of hypertrophic scars and reported that hyaluronidase injections resulted in significant reduction in the size of the lesion and complete relief of pain and pruritus [13]. Han JH colleagues reported that hematoma and fibrosis after facial trauma improved after hyaluronidase injection for early treatment [6]. Hyaluronidase treatment was also affective in combination with corticosteroids [5].

The data of this investigation indicate that treatment of post-operative scars with hyaluronidase ointment significantly improves the function as well as a cosmetic appearance of scar tissues. Hyaluronidase ointment could also be recommended for preventing the scar formation in plastic surgery.

REFERENCES

1. Loladze M., Alibegashvili M., Turmanidze Ts., Iashvili B., Kutivadze D. and Chanishvili T. Use of bilidase for the treatment of experimental hypertrophic postburn cicatrices. // Bulletin of Experimental Biology and Medicine. 2005 139(1):98-100
2. Bühren B., Schrupf H., Hoff N., Bölke E., Hilton S. and Gerber P.A. Hyaluronidase: from clinical applications to molecular and cellular mechanisms. // European Journal of Medical Research (2016) 21:5. 1-7
3. Cavallini M., Gazzola R., Metalla M. and Vaienti L. The Role of Hyaluronidase in the Treatment of Complications From Hyaluronic Acid Dermal Fillers. // *Aesthetic Surgery Journal*, V 33, N 8, 2013, 1167–1174
4. Fronza M. et al. Hyaluronidase modulates inflammatory response and accelerates the cutaneous wound healing. // *PLoS ONE* 2014, 9(11): e112297. <https://doi.org/10.1371/journal.pone.0112297>
5. Goyal N.N., Gold M.H. A novel triple medicine combination injection for the resolution of keloids and hypertrophic scars. // *The Journal of Clinical and Aesthetic Dermatology*. 2014. 7(11):31-34
6. Han J.H., Junekyu Kim J., Yoon K.C and Shin H. W. Treatment of post-traumatic hematoma and fibrosis using hyaluronidase injection. // *Archives of Craniofacial Surger* 2017. Vol.19 No.3, 218-221

7. LeBlanc C. and Stern R. Hyaluronidase: A Potential New Treatment for Acute Respiratory Distress Syndrome. // *Journal of Pulmonary & Respiratory Medicine*. 2017, 7:3 p. 1-4. doi: 10.4172/2161-105X.1000407
8. Lee K.C., Dretzke J, Liam Grover L., Logan N and Moiemmen N. A systematic review of objective burn scar measurements. // *Burns & Trauma* (2016) 4:14, 2-33.
9. Martín-Cartes J. et al. Use of hyaluronidase to prevent peritoneal adhesions in laparoscopic ventral hernia repair by means of intraperitoneal mesh fixation using spiral tacks. // *Surgical Endoscopy* 2008. - V 22 (3) 631–634.
10. Nekoroski T, Paladini RD, Sauder DN, Frost GI, Keller GA. A recombinant human hyaluronidase sustained release gel for the treatment of post-surgical edema. // *International Journal of Dermatology* 2014. - 53: 777-85.
11. Silverstein S.M., Greenbaum S., Stern R. Hyaluronidase in ophthalmology. // *The Journal of Applied Research* 2012; 12(1):1-13.
12. Stern R, Jedrzejewski MJ. Hyaluronidases: Their genomics, structures, and mechanisms of action. // *Chemical Reviews*. - 2006. - V 106 (3): 818-839.
13. Tabola R, Augoff K, Grabowski K, Cirocchi R. Role of Hyaluronidase in the Treatment of Hypertrophic Scars. // *Dermatologic Surgery* 2018 - 44(8). - 1155-1157.
14. Wollina U, Nonsurgical facial scar revision by Hyaluronidase - A case series. // *Journal of Applied Aesthetics* 2015, 36(4):164-166

SUMMARY

HYALURONIDASE OINTMENT IN TREATMENT OF HYPERTROPHIC SCARS

¹Alibegashvili M., ¹Loladze M., ¹Gabisonia T., ³Gabisonia G., ²Tsitsishvili D.

¹G. Eliava Institute of Bacteriophages, Microbiology and Virology; ²Clinic Of Aesthetic Medicine "Woman and Health"; ³Georgian American University (GAU), Tbilisi, Georgia

We have studied efficiency of hyaluronidase ointment created on the base of microbial hyaluronidase preparation "Bilidase" in treatment of postoperative hypertrophic scars. A total number of 14 patients with postoperative hypertrophic scars on different part of face were enrolled in the study.

All patients were treated with hyaluronidase ointment by help of iontophoresis for 10 days -1 procedure per day and than retreated 1 time with the same regimen at 4-week interval. Scar conditions were assessed in terms of pigmentation, vascularity, pliability, height, pain and pruritis in accordance with the Vancouver Scar Scale (VSS). The data of this investigation indicate that treatment of postoperative scars with hyaluronidase ointment significantly improves the function as well as a cosmetic appearance of scar tissues. Each of the investigated parameters was improved significantly after hyaluronidase treatment. Total score after 1 cycle of treatment was 5.14 ± 0.9 vs 10 ± 1.5 before treatment and after 2 cycles of treatment. total score was 0.85 ± 0.9 vs 10 ± 1.5 before treatment ($p < 0.001$). Hyaluronidase ointment could also be recommended for preventing the scar formation in plastic surgery.

Keywords: Hyaluronidase ointment, microbial hyaluronidase, postoperative hypertrophic scars

РЕЗЮМЕ

МАЗЬ ГИАЛУРОНИДАЗЫ ДЛЯ ЛЕЧЕНИЯ ГИПЕРТРОФИЧЕСКИХ РУБЦОВ

¹Алибегашвили М.Г., ¹Лоладзе М.Ж., ¹Габисония Т.Г., ³Габисония Г.Т., ²Цицишвили Д.И.

¹Институт бактериофагии, микробиологии и вирусологии им. Г. Элиава;

²Клиника эстетической медицины “Женщина и здоровье”; ³Грузино-американский университет, Грузия

Изучена эффективность гиалуронидазной мази, созданной на основе препарата микробной гиалуронидазы “Билидаза”, в лечении постоперационных гипертрофических рубцов. В исследовании включены 14 пациентов с постоперационными гипертрофическими рубцами в разных частях лица. Лечение проводили путем введения гиалуронидазной мази ионофорезом в течение 10 дней, каждодневными процедурами. Повторный курс лечения проводился с четырехнедельным интервалом. Оценка состояния рубца осуществляли по “шкале оценки Ванкуве-

ра”, которая учитывает васкуляризацию, пигментацию и подвижность рубца, боль и зуд.

Результаты исследования показали, что при лечении гиалуронидазной мазью значительно улучшаются функциональные и косметологические показатели рубцовой ткани. До лечения общий средний балл составлял $8,1 \pm 0,35$, после первого курса лечения - $5,14 \pm 0,9$, а после второго курса - $0,85 \pm 0,9$ ($p < 0,001$). Использование гиалуронидазной мази может быть рекомендовано также при операциях пластической хирургии для предупреждения формирования постоперационных рубцов.

რეზიუმე

ჰიალურონიდაზის მაღამო ჰიპერტროფიული ნაწიბურების მკურნალობისათვის

¹მ. ალიბეგაშვილი, ¹მ.ლოლაძე, ¹ტ.გაბისონია, ³გ.გაბისონია, ²დ.ციციშვილი

¹გ.ელიაშვილი სახ. ბაქტერიოფაგიის, მიკრობიოლოგიისა და ვირუსოლოგიის ინსტიტუტი; ²ესთეტიკური მედიცინის კლინიკა „ქალი და ჯანმრთელობა“, თბილისი; ³ქართულ-ამერიკული უნივერსიტეტი, თბილისი, საქართველო

შესწავლილია მიკრობული ჰიალურონიდაზის სამკურნალო პრეპარატის “ბილიდაზა” საფუძველზე შექმნილი ჰიალურონიდაზის მაღამოს ეფექტურობა პოსტოპერაციული ჰიპერტროფიული ნაწიბურების მკურნალობაში. ჰიალურონიდაზის შემცველი პრეპარატები ფართოდ გამოიყენება სამედიცინო პრაქტიკაში. კვლევაში ჩართული იყო სახის სხვადასხვა ნაწილში ოპერაციის შემდგომი ჰიპერტროფიული ნაწიბურის მქონე 14 პაციენტი. ჰიალურონიდაზის მაღამოს შეყვანა ხდებოდა იონოფორეზის საშუალებით. პაციენტებს მკურნალობა უტარდებოდა ყოველდღიური პროცედურებით 10 დღის განმავლობაში. მკურნალობის განმეორებითი კურსი ტარდებოდა 4-კვირიანი შუალედით. ნაწიბურის შეფასება ხდებ-

ოდა პიგმენტაციის, ვასკულარიზაციის, ძვრადობის, სიმბლლის, ასევე ტკივილისა და ქავილის მიხედვით „ვანკუვერის შეფასების სკალის“ შესაბამისად. გამოკვლევის შედეგებმა აჩვენა, რომ ჰიპერტროფიული ნაწიბურების ჰიალურონიდაზის მაღამოთი მკურნალობა მნიშვნელოვნად აუმჯობესებს ნაწიბურის ქსოვილის როგორც ფუნქციურ, ასევე კოსმეტიკურ მახასიათებლებს. მკურნალობამდე შეფასების საშუალო ჯამური ქულეები შეადგენდა $8,1 \pm 0,35$ -ს, მკურნალობის ერთი კურსის შემდეგ - $5,14 \pm 0,9$ -ს, ხოლო მკურნალობის ორი კურსის შემდეგ - $0,85 \pm 0,9$ -ს ($p < 0,001$). ჰიალურონიდაზის მაღამოს გამოყენება ასევე შეიძლება პლასტიკური ოპერაციის შემდგომი ნაწიბურების წარმოქმნის საწინააღმდეგოდ.

PREVALENCE OF PAH MUTATIONS IN GEORGIAN PKU PATIENTS COMPARED TO MOST FREQUENT PAH MUTATIONS IN EUROPEAN POPULATIONS

^{1,2,4} Agladze D., ³ Iordanishvili S., ⁴ Margvelashvili L., ³ Kldiashvili E., ^{2,5} Kvlividze O.

¹Research Institute of Clinical Medicine, Tbilisi; ²School of Medicine, New Vision University;

³Petre Shotadze Tbilisi Medical Academy; ⁴Pediatric Surgery Center (KidCo), Tbilisi;

⁵Georgian Foundation for Genetic and Rare Diseases (GeRaD), Tbilisi, Georgia

Metabolic disorders (MD) are often life-threatening health conditions, which are caused by deficiency or absence of various metabolic enzymes. Majority of MD are from the group of inherited metabolic diseases (IEM). Metabolic disorders differ in types of inheritance pattern. The incidence of MD can vary in different populations. Because of diversity of MD, it is necessary to provide personalized treatment plans for patients. Phenylketonuria (PKU) is

one of the most frequent metabolic disorders in the world. In Georgian population its frequency is 1:6060 newborns (Table 1). For European countries the frequency is 1:10000 [1,8,10].

The biggest step in diagnostics of PKU was the discovery of PAH gene and PAH mutations. Population studies described different mutations and their frequencies for various populations. Studies have revealed more than 900 different mutations in PAH gene [5].