

Efficacy of Hyaluronic Acid in Treatment of Diabetic Foot Syndrome

The results of systematic review and meta-analysis of RCS

Please find below the review of the article written by C. P. Chen, W. Hung and S. H. Lin from National Taiwan University and Harvard School of Public Health (Boston, Massachusetts, USA), in which the results of a systematic review and meta-analysis of randomized controlled studies (RCSs) are presented in Medline, Cochrane, Embase, Google Scholar databases, confirming the efficacy of drugs based on hyaluronic acid (HA) in improving complete wound healing in patients with diabetic foot syndrome. The authors concluded that the use of HA applications is a necessary therapeutic option for this category of patients.

Diabetic foot syndrome is one of the major complications of diabetes mellitus (DM). Foot ulcers are diagnosed in approximately 5% of DM patients. In 50% of cases non-traumatic lower limb amputation is performed due to diabetic foot syndrome. Peripheral neuropathy and vascular pathology are considered to be the main factors causing the occurrence of chronic foot ulcers (Rathur H. M., Boulton A. J., 2005). Currently, the standard treatment of foot ulcers involves restoration of adequate blood supply to tissues, debridement, treatment of infections, as well as removal of external pressure on a foot skin (Saap L. J., Falanga V., 2002).

In recent years, a better understanding of wound development pathophysiology led to implementation in practice of physiological approach in the treatment of diabetic foot syndrome. One emerging technology is the use of biomaterials in the form of gels, membranes, meshes containing HA benzyl ester (HYAFF-11), on which grafts cultivated from autologous fibroblasts and keratinocytes are placed (Harris P. A. et al., 1999; Galassi G. et al., 2000). Also drugs based on

recombinant human platelet growth factor IV (becaplermin gel) (Wieman T. J. et al., 1998), two-layer living human skin equivalent (Veves A. et al., 2001), allogenic skin substitutes (Grey J. E. et al., 1998).

HA is a polysaccharide, which is included in the connective, epithelial and neural tissues of the body. HA contributes to cell proliferation and migration - two key processes required for wound healing. In addition, it is a pronounced hydrating tissues agent, as water mass absorbed by HA molecule may exceed its own in 3 thousand times.

According to the results of recent meta-analysis (Voigt J., Driver V. R., 2012), in eight out of ten studies included in it better healing of burns, surgical wounds, and chronic ulcer defects in case of HA-based drugs use in comparison with traditional treatment methods or placebo has been demonstrated. However, it should be kept in mind that even with the correct choice of therapy method the diabetic foot syndrome in a half of all cases is still a cause of non-traumatic limb amputation. Therefore, the proven effect of HA on wound healing should be considered in treatment prescription to patients of this category. In a number of RCSs the authors estimated wound healing efficacy of various technologies with the use of HA in patients with this diagnosis in comparison with control group (Tankova T. et al., 2001; Caravaggi C. et al., 2003; Abbruzzese L. et al., 2009; Uccioli L. et al., 2011; Prosdocimi M. et al., 2012). In general, these RCSs have shown HA benefit in diabetic ulcers scarring, while most of them included a relatively small sample - from 35 to 180 participants.

The aim of this meta-analysis was to compare the outcomes of diabetic foot ulcers treatment in groups with HA-based drugs use and control ones.

Methods of the research

Search of prospective RCSs, in which HA efficacy in treatment of foot ulcers due to diabetes was carried out in Medline, Cochrane, Embase, Google Scholar databases (until January 31, 2014). Therewith, search keywords were: hyaluronic acid, hyaluronate, diabetic foot syndrome, diabetic ulcer, wound, hyaluronate. Criteria for inclusion in the study: determined diagnosis of DM type 1 or type 2, presence of diabetic foot ulcers in the majority of patients, the use of HA derivatives or compounds such as zinc hyaluronate, hydrogels, or tampons with HA. Retrospective and non-randomized trials, comments, descriptions of clinical cases were not analysed.

The primary outcome, by means of which the treatment efficacy by groups was estimated, was complete healing of ulcer defects after 12 weeks of therapy.

Study results and their discussion

Five studies, four of which have subsequently entered quantitative meta-analysis, underwent qualitative analysis.

378 and 328 participants were included in a systematic review and quantitative meta-analysis, respectively. The total number of patients in these trials ranged from 30 to 160 (Table 1). Ulcer defects in all of the examined were diagnosed on the feet, except for the study by L. Abbruzzese et al. (2009), in which in some patients wounds had

Table 1. Characteristics of RTSs included in meta-analysis

RCS author	Wound localization	Curative measures	Initial wound condition					Number of patients	Age, years*
			Severity by Wagner	ABI, mm Hg *	Infection, %	Neuropathy, %	Area of the ulcer defect, cm ² *		
L. Uccioli et al., 2011	Foot	In the studied group autologous tissue-grafts were placed on the membrane HYAFF-11 and transferred to the wound	1-2	0.9 ± 0.2	0	NA	8.8 ± 9.4	80	61 ± 10
		Standard therapy was prescribed to a control group	1-2	0.9 ± 0.7	0	NA	6.7 ± 7.7	80	62 ± 11
L. Abbruzzese et al., 2009	Leg or foot	Studied group: HA applications (vulnamin gel)	NA	1.1 ± 0.2	0	100	25.9 ± 8.8	15	61.8
		Control group: inert gel + standard therapy	NA	1.0 ± 0.1	0	100	27.3 ± 10.4	15	62.4
F. R. Cuevas et al., 2009	Foot	Studied group: application of zinc hyaluronate	1 (n = 2) 2 (n = 18) 3 (n = 5) 4 (n = 0)	1.1 ± 0.2	NA	100	13.3 ± 11.8	25	56.8 ± 8.8
		Control group: standard therapy	1 (n = 0) 2 (n = 20) 3 (n = 5) 4 (n = 0)	1.0 ± 0.2	NA	96	7.0 ± 5.3	25	60.1 ± 8.4
C Caravaggi et al., 2003	Foot	In the studied group autologous tissue-grafts were placed on the membrane HYAFF-11 and transferred to the wound	1-2	Median 0.7 (interquartile range 0,3)	0	NA	5.3 ± 6.8	43	NA
		Standard therapy was prescribed to a control group	1-2	Median 0.7 (interquartile range 0.2)	0	NA	6.2 ± 7.6	36	NA
T. Tankova et al., 2001	Foot	Studied group: application of zinc hyaluronate	1 (n = 20) 2 (n = 16) 3 (n = 5) 4 (n = 2)	ABI: NA Neuroischemic ulcers (n = 16)	67.4 (29/43 ulcers)	62.8 (27/43 ulcers)	10.32 ± 4.6	35 (43 ulcers)	55.7+12.4 in both groups
		Control group: standard therapy	1 (n = 13) 2 (n = 10) 3 (n = 3) 4 (n = 2)	ABI: NA Neuroischemic ulcers (n = 11)	71.4 (20/28 ulcers)	60.7 (17/28 ulcers)	11.46 ± 5.4	24 (28 ulcers)	

* Data are presented as a mean value ± standard deviation; NA - data not available.

ABI – ankle-brachial index.

Table 2. Treatment outcomes and incidence of adverse effects development in RCS participants included in meta-analysis

RCS author	Groups	Complete wound healing in 12 weeks, %	Complete wound healing in 20 weeks, %	Time before complete healing, days*	Adverse effects, %		
					Serious adverse effects	Any adverse effects	infection
L. Uccioli et al., 2011	Studied Control	24	50	50	8.3	21.4	15.4
		21	43	58	2.2	16.1	11.4
L. Abbruzzese et al., 2009	Studied Control	93	NA	60.4 ± 24.8	0	53.3	26.7
		60	NA	79.9±18.6	0	66.7	33.3
F. R. Cuevas et al., 2009	Studied Control	96	100	7.8 ± 3.5 weeks	NA	NA	NA
		8	NA	NA	NA	NA	NA
C Caravaggi et al., 2003	Studied Control	65.3	NA	57	16.3	25.6	NA
		49.6	NA	77	27.8	30.6	NA
T. Tankova et al., 2001	Studied Control	93	NA	74 ± 31	2.3	2.3	67.4
		82	NA	92 ± 25	7.1	7.1	71.4

*Data are presented as a mean value ± standard deviation; NA - data not available.

higher localization. According to data of various studies, the severity of ulcers by Wagner classification varied from the 1st to the 4th, the level of ankle-brachial index ranged from 0.7 to 1.1 mm Hg. Wounds in the majority of patients were not infected, except for the study by T. Tankova et al. (2001), in which infections were found in approximately 70% of individuals of both core and control groups (Table 1). The area of ulcer defect ranged from 6.7 to 27.3 cm². On the background of HA applications use, the indicator of complete wound healing after 12 weeks of treatment ranged from 24.0 to 96.0%, the median time of complete healing - from 50 to 74 days; for patients not treated with drugs based on HA (control group) - from 8.0 to 82.0%, and from 58 to 92 days, respectively (Table 2). L. Uccioli et al. (2011) and F. R. Cuevas et al. (2009) reported complete ulcer scarring in 20 weeks in 50-100 % of cases in the studied group, and in 43 % – in the control group (Uccioli L. et al.).

Thus, in accordance with a combined odds ratio it was found that the rate of complete diabetic ulcers healing after 12 weeks of treatment was significantly higher in patients who used HA applications, compared with those treated with standard therapy.

In different studies, a small (0 to 27.8%) incidence of adverse reactions associated with HA therapy was recorded. The most common of these was wound infection (Table 2). In general, the authors came to the conclusion about good tolerability.

In recent years, researchers evaluated the efficacy of HA drugs in different forms for treatment of patients with diabetic foot syndrome. L. Uccioli et al. and C. Caravaggi et al. studied the outcomes of using HYAFF membranes and nonadherent paraffin gauze wipes in relieving diabetic ulcers. These studies

revealed that although the complete wound healing indicators were comparable in both treatment approaches, reducing the ulcer defect area by 50% was achieved much faster in HA applications group (on average in 40 vs. 50 days, $p = 0.018$). At the same time, ulcers on the dorsal surface of the foot healed significantly faster in patients of this subgroup. In the study by L. Abbruzzese et al. vulnamin gel containing HA was used. As a control, patients were prescribed inert gel application. As a result, it was found that the rate of diabetic ulcers healing after 3 months was significantly higher in patients applying the HA-based gel, as compared with the control group ($p < 0.05$). According to study data by T. Tankova et al., the use of zinc hyaluronate for diabetic foot syndrome treatment was accompanied by a significant increase in rate of wound healing compared with the control group (74 and 92 days, respectively; $p = 0.008$).

For further research it is of interest to determine the dependence of HA application efficacy on the localization of diabetic ulcers, advisability of concomitant therapy, and so forth.

The authors of this meta-analysis concluded that HA is effective and safe mean of treatment of diabetic ulcers by increasing their rate of healing, regardless of pharmaceutical form. The obtained results support HA drugs prescription in this category of patients.

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