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New galenic antiseptic substance containing iodine (K 3 complex) and hyaluronic acid for treatment of chronic, hardly healing wounds

Abstract

The treatment of chronic non-healing wounds poses a challenge in daily practice. Regardless of the wound causing disease, which also has to be diagnosed and treated, a multitude of other reasons play an important role in the nature of the chronic wound. In this connection the local wound milieu is fundamental, especially the antagonistic effects of local constructive and destructive processes, and the microbial load of the wound. The special challenge is thereby the difficulty to identify the concrete complex of problems both clinically and paraclinically. In this regard active milieu- and broad-acting antimicrobial preparations play a significant role. Such substances are, for example hyaluronic acid and PVP-iodine, which have been already applied successfully in the management of problematic wounds, but never before in a combination of administration and effect. This paper describes the results of an Observer Study, in which the woundhealing of 49 patients with chronic non-healing wounds with signs of chronic infection, was stimulated. In particular, Pseudomonas infection was treated successfully without inhibition of wound healing. The wound cleansing effect was higher in combination with foam (Ligasano) based on depot effect.

Keywords: wound infection, iodine, hyaloron acid, chronic wound healing disorders

Introduction

Wounds do not occur randomly, but always have a causality. In this context, chronic wounds play a special role because they are characterized in terms of the absence of clear reparative processes over a "certain period" (where a generally accepted definition is still lacking). Under the guidelines of the German Society of Phlebology, an ulcer cruris is considered to be chronic if showing no tendency to heal within 3 months or has not healed within 12 months.[1]

In addition to the underlying disease many cofactors are now known, that can affect the impaired wound healing cascade.[2]

The optimization of the typical milieu factors surrounding the wound creates the conditions, necessary for the reparative processes and to launch the completion of the healing process.

These are basic influencing factors for the local wound healing, which are not currently fully understood in their complexity and mutual influence, possibly because the factors identified in this regard are so fundamentally different.

The microbial situation at a local level has a special significance for the chronic wound.[3] Hereby the clarification of the actual situation with the typical methods of investigation ("swab") is only imperfectly possible.

Instead, the compliance of appropriate clinical signs of the wound, which indicate a change in the microbiological situation, is especially significant.[3]

In this context it is clear that the diagnosis of a wound infection is based on the classic signs of infection described below.[4]

- Redness
- Swelling
- Overheating
- Pain
- Functional limitation

Additionally, other parameters have to be considered:

- Exudate: strong increase in the exudate, eventually raised the viscosity, color change, odour (offensive smell)
- Stagnation of wound healing and
- Serological evidence of systemic infection such as leukocytosis

Defining and identifying features of critical colonization are not yet universally established.[4] It is considered that increased proliferation of germs can lead to a critical load of germs, which in some cases rapidly becomes a local infection.

Often, the colonization is a permanent condition. The germload could lead to an inflammatory stimulus that contributes to the chronic nature of a wound.[3] The critical colonization describes probably more a conceptual model than a specific microbiological situation, which might be suitable, however, to describe the dynamics of the microbial situation in (chronic) wounds.

Therefore, therapeutically, the mastery of the microbial situation is undoubtedly, a significant challenge to the local treatment regime. Hereby, the application of substances should be carried out in such a way that maximum tolerance is combined with good antimicrobial efficacy.

Basics

PVP-IODINE IN USE ON WOUNDS

From a clinical perspective Polyvinylpyrrolidone (PVP-iodine) is still a standard antiseptic. It has good skin, mucous membrane and tissue compatibility.

So far, no development of resistance to iodine has been demonstrated.[3] Iodine, antibacterial preparations, such as povidone-iodine and iodine Cadexomer are among the most frequently used products and have both a broad antibacterial and antifungal spectrum. There are also reports that PVP-iodine inhibits bacterial biofilms. However, in the evaluation of the cytotoxicity of the commonly used antimicrobial agents iodine solutions *in vitro* showed a significant toxic effect both on human keratinocytes as well as on fibroblasts.[5]

Thomas *et al.* were able to show that povidone-iodine used in a dose-dependent manner reduces the migration and the proliferation of cultured fibroblasts.[6]

This follows the presumption that remedies containing iodine can lead to a significant delay in wound healing, although clearly a strong influence of concentration and administration must be admitted.[3] However, some data suggest that PVP-iodine preparations promote tissue repair in non-healing wounds. But so far the mechanisms are not entirely clear.[7] On the other hand the use of a combination of substances improves wound healing and the (apparently) adverse effects of iodine are positively affected.[5]

For longer-term application in extensive wounds, mucous membranes or sinuses, it can lead to clinically significant Iodine resorption.[3]

HYALURONIC ACID USED ON WOUNDS

"Haluronan" is a collective term for hyaluronic acid under physiological pH conditions occurring in its polyanionic form. In 1934, Karl Meyer and John Palmer found and characterized in the aqueous humor of the bovine eye, a polysaccharide found with mucoid characteristics.[8] They gave it the name of hyaluronic acid, derived from the Greek word for the property glassy - "hyaloid" - which refers to the presence in the vitreous of the eye and part of the glucuronic.

Hyaluronic acid is one of the essential components of natural extracellular matrix of the skin, joints, eye and many other tissues and organs, where the growth, migration, differentiation and proliferation of cells takes place.[9]

Hyaluronic acid is a non-sulfated glycosaminoglycan (GAG), which is produced in very large amounts by dermal fibroblasts and epidermal keratinocytes from glucose.

The glycosaminoglycan hyaluronic acid has a polymeric structure and is produced by the enzyme hyaluronsynthase (HAS). This enzyme synthesizes a long, linear polymer chain, composed from repetitive disaccharidubits of a size of 400 dalton.

The individual proteoglycans as the basic structure of the hyaluronic acid molecules contain D-glucuronic acid and N-acetylglucosamine.

In this aminodisaccharide the two blocks are linked using ß1-3 glycosidic bond , but the various disaccharides are held together by ß1-4 glycosidic bonds. The number of disaccharides can be up to 10 000 or even higher, which makes up the mass of each molecule, up to 4 million daltons.

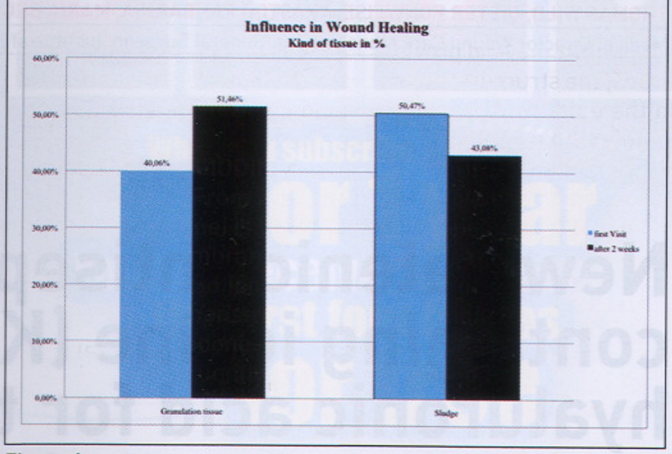

Figure 1.

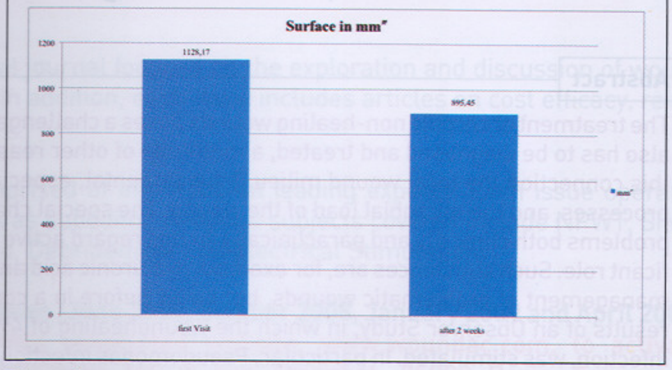

Figure 2.

HYALURONIC ACID IS SYNTHESIZED WITH THE PARTICIPATION OF THE ENZYME

Hyaluron synthase (HAS) on the inside of the plasma membrane. Three human isoforms of HAS have been characterized: HAS1, HAS2, HAS3. Using the basic substrates such as UDPN-acetylglucosamine and UDP-glucuronic acid, the molecule is composed of hyaluronic acid and with increasing numbers of synthesized molecules, the translocation of the molecular chain of hyaluronic acid is promoted to the outside.

The synthesis of hyaluronic acid in human skin is subjected to special regulation. While the cell density is low, synthesis is increased and the mobility and the proliferation rate is promoted. If the cell density is high, then the performance of hyaluronic acid synthesis and cell growth are maintained at low levels. Several growth factors such as for example EGF, PDGF, TGF-beta2, IGF-I, FSH, and cytokines such as Interleukin1 and interferon gamma may influence the synthesis of hyaluronic acid.

The distribution of hyaluronic acid in different parts of the skin seems to be different and there is an unusually high percentage of hyaluronic acid in both the extracellular matrix of the basal layer of the epidermis, as well as in the papillary dermis, which lies next to the epidermis. From here a drop in the concentration of hyaluronic acid in the direction to the reticular dermis is noted.

Taking the absolute levels of hyaluronic acid into account, the following observation emerges: in the epidermal cellular interstices 10 times more hyaluronic acid is present than in the dermis.

Hyluronacid is not just a passive structure builder governed by active metabolism hyaluronic acid can be involved in cellular growth processes.[10]

Hyaluronic acid provides because of its hydrophilic properties, the structure and viscosity of the extracellular matrix. In the epidermis, hyaluronic acid binds large quantities of water, which contributes to the hydration of the tissue.[5]

It plays an important role in every phase of wound healing, both as a structure-forming molecule as well as a signal molecule in intercellular signal transduction. In hemostasis, hyaluronic acid promotes the recruitment of inflammatory cells such as neutrophils, macrophages, lymphocytes and fibroblasts.

In the proliferative phase hyaluronic acid stimulates the migration and proliferation of keratinocytes and the low hyaluronic acid fragments promote angiogenesis. In the granulation phase, the hyaluronic acid plays an important role in the activation of macrophages, neutrophils and in the production of various extracellular matrix proteins. Through the involvement of hyaluronic acid in the various healing processes, hyaluronic acid promotes the formation of early granulation tissue and smooth surface of the wound which forms a wound bed suitable for autografting.[5]

In the biomedical literature, the great advantage of hyaluronic acid in wound healing and the additional exogenous supply of hyaluronic acid for the acceleration of wound healing has been confirmed.[5,9]

Hyaluronic acid owes its broad application in the medical field to its amazing biocompatibility.[10]

The administration of a high molecular weight hyaluronic acid with potassium iodide complex (Hyiodine ®) is a new application form of a viscous solution that contains 1.5% sodium hyaluronate sodium and 0.1%, potassium concentration.[11]

Hyalurpnic acid, which is contained in Hyiodine, is biotechnologically processed and corresponds to the natural form of human hyaluronic acid.

Iodine and potassium iodide prevent the decomposition of sodium hyaluronate through or around the wound's existing microorganisms.[5]

Results of an observer trial are shown in *Figure 1* and *Figure 2.* ■

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