Innovative wound care - New studies to increase evidence

Translation of an article originally published in:
Ergänzungsband Nr. II/2013 der MMW-Fortschritte der Medizin,
25. Juli 2013, Springer-Verlag

Innovative wound care – New studies to increase evidence

BY K. KRÖGER, M. STORCK, A. RISSE

In wound management, "evidence" is a term not without its problems: a wound is a symptom and not a circumscribed disease, it passes through various stages. Alternative forms of treatment are often possible in parallel, but differ in their convenience, effectiveness and cost.

Wound dressings are approved according to the German Medical Devices Act (MPG). This law specifies the indications for which they can be used, requires a biological safety test and checks that the "General requirements for undertaking the conformance assessment" are observed. The MPG thus guarantees that the device (in this case, the wound care product) causes no biological damage and is marketed in a defined quality. In addition, §19 (1) of the MPG requires that proof of the suitability of medical devices for the intended purpose be provided through an appropriate clinical evaluation. The clinical evaluation is based on clinical data, which include information about safety as well as performance and which have been obtained from the actual use of the medical device. Clinical data emanate from the following sources (see. §3 No. 25 MPG):

1. "A clinical trial of the respective medical device or
2. Clinical trials or other studies reported in the specialist scientific literature about a similar device, whose similarity with the clinical device in question can be demonstrated or
3. Published or unpublished reports of other clinical experiences, either with the medical device in question or a similar device whose similarity with the clinical device in question can be demonstrated."

Irrespective of this approval, properties of wound care products are being advertised, which the manufacturers highlight as advantageous in wound management on the basis of product development. The clinical user must weigh up these various advantages and justify the associated costs. This pressure to assess products is leading to the call for study-based evidence. Such evidence is based on randomized, controlled trials (RCTs). Against this background and under the di-

SUMMARY

Background: Today numerous products for wound care are available. A research-based evidence on which the clinician can base its selection, is still missing. In the guidelines randomized controlled trials (RCTs) have been left out.

Method: In the overview three current RCT with products for the treatment of chronically venous ulcers will be presented.

Results and Conclusions: The pre-mentioned studies show, that it is possible to provide a basis for evidence-based treatment in wound healing. The effective value of a wound treatment based on the costs and benefits must be defined by the health system. But products, for which data from randomized trials exist, should be evaluated in a different way to products, for which there are no such data.

Keywords: Wound care – Randomized controlled studies (RCT) – Evidence – Guidelines

Submitted on 02/04/2013 - Revision accepted on 14.05.2013

Prof. Dr. med. Knut Kröger, Klinik für Gefäßmedizin, HELIOS Klinikum Krefeld; Prof. Dr. med. Martin Storck, Klinik für Gefäß- und Thoraxchirurgie, Städt. Klinikum Karlsruhe; Dr. med. Alexander Risse, Diabeteszentrum, Klinikum Dortmund

The supplement this article is part of is not sponsored by the industry.

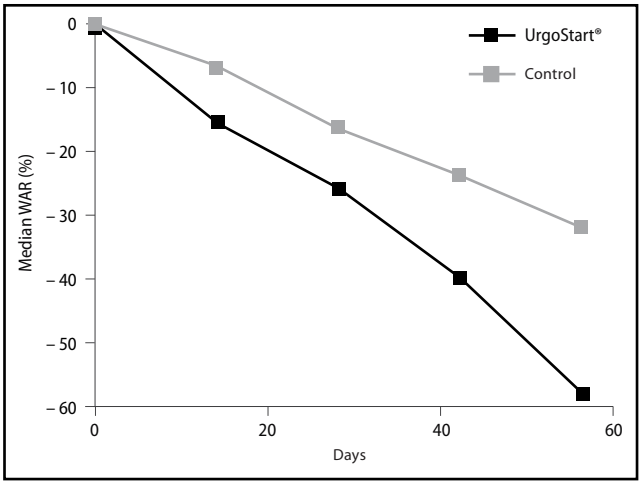

Fig. 1: **Relative Wound Area Reduction (WAR) calculated as the difference in the wound size on enrolment and after 8 weeks of treatment in patients with UrgoStart® (test, n = 93) compared with the control group (n = 94) (taken and adapted from [4]).**

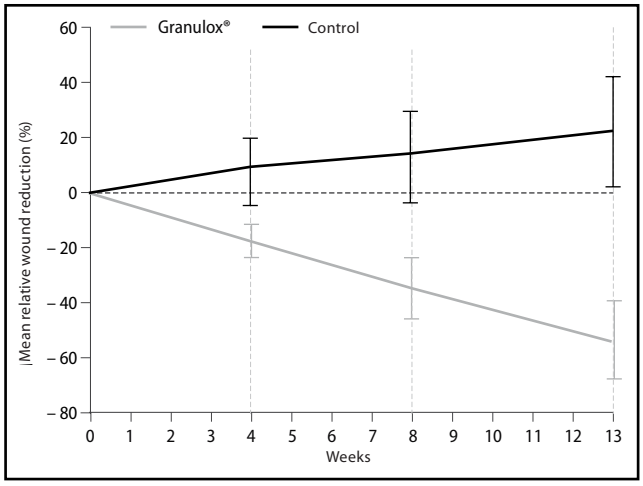

Fig. 2: **Relative wound area reduction calculated as the difference between wound size on enrolment and after 13 weeks of treatment in patients in the group treated with the haemoglobin spray Granulox® (Group 1, n = 36), and the control group (Group 2, n = 36) who received no haemoglobin spray (taken and adapted from [1])**

rection of the German Association for Wound Healing and Wound Treatment e.V., the guideline on the "Local treatment of chronic wounds in patients with the risk factors of peripheral arterial occlusive disease, diabetes mellitus, chronic venous insufficiency" was published in June 2012 [6]. This guideline admittedly meets the formal criteria of the S3 level of evidence, in that a series of specialist societies have taken part in its development and a critical assessment of the literature was undertaken. However, as no corresponding RCTs are available, the key conclusions are based on a consensus, which more closely approximates the character of an S1 level guideline. In addition, there are no clear decision criteria that actually provide on the spot assistance to the wound experts engaged in patient care. Therefore, users – as well as those who actually fund the cost of the products – are now calling for RCTs in the area of wound healing.

Randomised controlled trials in wound healing

Although the call for such studies is loud, the question of their feasibility in relation to the healing of chronic wounds has to be raised: aspects of blinding, standardisation and also outcomes must be addressed.

- Blinding in pharmacological studies is readily possible through the use of a placebo of identical appearance. Blinding in relation to wound dressings requires that these are visually indistinguishable. In reality, this is only rarely possible.
- Although wound healing is talked about in general terms, the genesis of wounds differs. For example, venous ulcers cannot be compared with arterial wounds or pressure sores. The nature of the wound and the extent of the underlying disease have a major influence on the chance of healing. RCTs should therefore only cover a well-defined entity of chronic wounds.
- Wound healing is a dynamic process that passes through several different phases. Hence, it must be precisely defined at which wound stage a wound must be, in order for it to be included.
- The age of a wound has decisive significance for the course of healing. The longer a wound has existed, the longer it takes to heal.
- Comorbidity is a major influence in terms of wound healing. Although the genesis of a venous leg ulcer is primarily venous, it heals less well in a patient with diabetes or an underlying rheumatic disease; conversely, a primarily arterial wound is also affected by a concomitant chronic venous insufficiency.
- Wound healing is regarded as the optimum outcome or endpoint of a study on the benefits of a wound dressing. In a similar way to pharmacological studies, in which mortality or myocardial infarction, for example, are defined as outcomes, wound healing would also be a hard outcome. Wound healing takes time and not all wounds can ultimately be completely healed.
- Unlike in pharmacological studies, wound treatment is not simply a matter of the patient taking the study medication. In reality, wound management requires a wound expert with standardised care and needs a close regional integration.

All the above considerations render the undertaking of randomised trials on wound dressings not impossible, but require a "rethinking", in order to create the necessary conditions. Innovative manufacturers

of products for wound healing are not afraid of these restrictions. For instance, results of new RCTs on various wound management products that deserve particular attention have recently appeared. Because of the long development time of the S3-Guideline, these studies were not included in it.

Challenge study [4]

The Urgo company, Sulzbach, carried out a multicentre, controlled, randomized, double-blind Phase III trial in France of its product UrgoStart®, in which 187 adult patients with a venous leg ulcer were enrolled in 45 study centres. 93 patients were allocated to the UrgoStart® group and 94 to the control group.
The wound dressing contains the nano-oligosaccharide factor (NOSF). NOSF inhibits matrix-metalloproteases, which are found to excess in chronic wounds and which break down important growth factors as well as healthy tissue. The NOSF-induced inactivation of the matrix-metalloproteases should counteract these mechanisms that inhibit wound healing and thus accelerate the wound healing process.
At the time of enrolment in the study, the mean wound size was 16.8 cm^2. In 68% of cases, wound healing appeared to be stagnating or had even worsened. The wounds had existed for a mean of 15.3 months and in 55% of the study participants for more than 12 months. In 53.5% of cases, the wounds were recurrent.
The study outcome was healing after 8 weeks of in-patient and/or outpatient treatment. After 8 weeks, 58.3% of the wounds treated with UrgoStart® and 31.7% of those in the control group showed a reduction in the wound area (Fig. 1). This difference of 26.7% (95% confidence interval of the median difference: 38.3 to 15.1%) was significant (p= 0.0021).

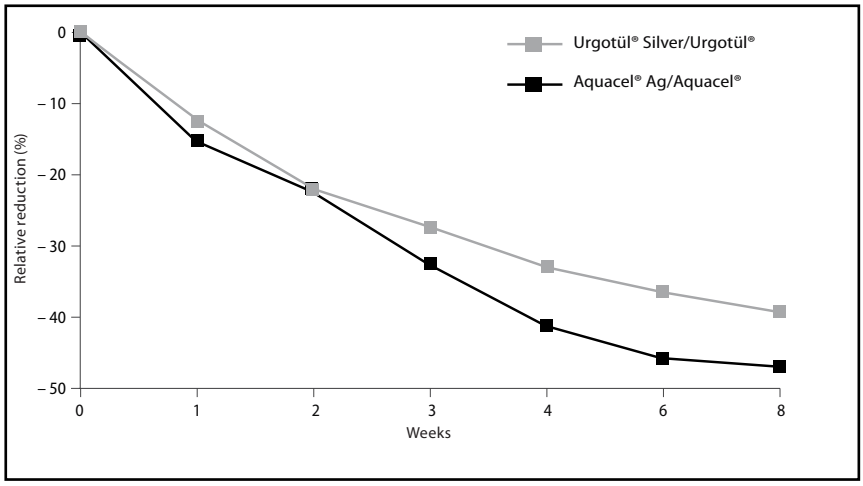

Fig. 3: **Relative reduction in mean wound size compared to wound size on enrolment in the study (the differences are significant) (taken and adapted from [3]).**

Haemoglobin spray study [1]

The SastoMed company, Georgsmarienhütte, undertook a single centre, prospective, controlled, randomized, single-blind trial with its haemoglobin spray Granulox® at the Institute of Dermatology of the Karls University Prague, in which 36 patients were each assigned to treatment with the haemoglobin spray or to the control group.
The haemoglobin spray Granulox® contains water-soluble haemoglobin, which is uniformly distributed in the exudate. Haemoglobin can bind oxygen and then release it again. After spraying, atmospheric oxygen is bound and transported along the concentration gradient to the wound base. In this way, Granulox® breaks through the diffusion barrier of the exudate and leads oxygen from the surrounding air to the wound base.
Enrolled were only those patients who showed no wound-healing tendency after two weeks of standardised best-practice treatment for a venous leg ulcer on an in-patient basis at the Institute of Dermatology of the Karls University Prague.
At the time of enrolment in the study, the wound size was between 2.5 cm2 and 50 cm2. In all cases, wound healing was stagnating or had even worsened, as this was an inclusion criterion. The wounds had existed on average for 2 years (3 months to 6 years).
The study outcome was the change in wound area over the treatment period of 13 weeks. After 13 weeks, 91.6% of the wounds treated with Granulox® showed a reduction in wound area. The average wound size in the treatment group decreased by 53.4%, whereas the average wound size in the control group increased by 21.3% (Fig. 2). This difference of 53% was significant (p= 0.0001).

Aquacel® Ag and Urgotül® Silver study [3]

In a prospective, international, multicentre, randomized, open comparative study, the company Convatec (Germany) compared the effectiveness of two silver dressings on the healing of venous ulcers at risk of infection. One group of 145 patients were treated with Aquacel® Ag for 4 weeks followed by a further 4 weeks with Aquacel®. The other group consisted of 136 patients, whose ulcers were treated with Urgotül® Silver for 4 weeks followed by a further 4 weeks with Urgotül®. Risk of infection was defined by the presence of

at least 3 of the following 5 clinical signs: pain between 2 dressing changes, perilesional erythema, oedema, foul odour and marked exudate.
At the time of enrolment in the study, ulcer size had to be between 5 and 40 cm2 and the ulcer duration not more than 2 years. On average, the ulcers had existed for 8 months and 40% of them showed no tendency to heal and another 40% had even worsened prior to inclusion in the study. The study outcome was the change in wound area over the treatment period of 8 weeks. After 8 weeks of treatment, the relative wound size reduction in the Aquacel® Ag group was 49.6% ± 52.5% compared to 42.8% ± 60.0% in the Urgotül® Silver group (Fig. 3)
The difference of 6.8% ± 56.3% (95% confidence interval of the mean -6.5 to 20.2) was above the pre-defined non-inferiority limit (-15%). Treatment with Aquacel® Ag was thus shown to be comparably effective to that with Urgotül® Silver.

Conclusions

The studies described are proof of a change in wound care and show that it is possible to create a foundation for an evidence-based treatment in wound management. Naturally, even these studies have their own limitations and the discussion about a universally accepted clinical and/or health economics outcome has not yet ended. The effective added value of a wound treatment relative to its costs and benefits must be defined by the healthcare system. When is one wound dressing superior to another? When it achieves healing of 10% more wounds, but the treatment lasts longer? When it achieves healing of the same number of wounds, but in a shorter time? When it achieves healing in double the number of wounds, but costs four times as much?
Adequate compression is the fundamental basis of venous ulcer treatment and an RCT from England shows that this compression can lead to a healing of the ulcer within six months in about two-thirds of patients [2]. Therefore, an improvement in wound healing is generally likely to occur under compression even in the control arm. For instance, in the Challenge study, the wound area in the control group reduced by 31.7% after eight weeks. The study participants had also not been previously defined as refractory to treatment. The same applies to the study on the two silver-containing wound dressings, which showed reductions in wound sizes of 42% and 49% respectively.
This was different in the study with the haemoglobin spray. Here standardised treatment was first given under in-patient conditions and only those patients who showed no healing tendency were subsequently enrolled in the study. Hence, a negative selection took place and accordingly an improvement in wound healing in the control arm during the course of the study was not to be expected. The effect of the haemoglobin spray on wound healing is therefore even more convincing (Tab.1).
The care of people with chronic wounds presents a complex challenge that cannot be reduced to a single wound dressing. There is rarely a single cause for the persistence of a chronic wound. On the other hand, those wound care products that have shown a significant advantage in randomized studies, ought to be assessed differently to the many wound products for which no data are available to date. Double standards must not be applied here. If reimbursement of the cost of wound care products is refused due to lack of evidence, then reimbursement must only be granted to those products where evidence is available. Thus the funders (health insurance schemes) could influence the wound products market in the

Tab. 1: **Comparison of the three described RCTs concerning the healing of venous ulcers.**

	Challenge		**Haemoglobin spray**		**Silver-containing wound-dressings**	
	UrgoStart®	Control	Granulox®	Control	Aquacel® Ag	Urgotül® Silver
Number	n = 93	n = 94	n = 36	n = 36	n = 145	n = 136
Age (years)	72,6 ± 13,0	74,4 ± 12,1	65	59	68,7 ± 13,1	71,2 ± 12,1
Women (%)	66,7	63,8	69	58	64,8	66,2
Ulcers present (months)	15,6 ± 9,1	15,1 ± 8,7	24	24	0,80 ± 0,6	0,72 ± 0,5
Wound size (cm^2)	17,0 ± 15,6	16,6 ± 15,8	18,7 ± 9,9	17,5 ± 9,3	17,9 ± 15,2	17,4 ± 14,0
Absolute reduction (cm^2)	6,9 ± 11,4	2,5 ± 11,9	8,5 ± 5,1	–2,7 ± 4,5	8,76 ± 12,8	7,21 ± 9,5
Relative reduction (%)	45,2 ± 47,9	21,4 ± 81,0	53,4 ± 27,4	–21,3 ± 40,2	49,6 ± 52,5	42,8 ± 60,0

medium term, to the effect that the industry has to address the question of evidence. At present, the few products with RCTs such as Urgo-Start® or Granulox® stand out from the rest. This is particularly clear if one turns to the current guidelines on the "Local treatment of chronic wounds: in patients with peripheral arterial occlusive disease, chronic venous insufficiency and diabetes mellitus" [5]. An extensive search of the literature found 4998 references, of which only 38 related to controlled, randomized studies that had been used for the qualitative analysis. That means less than 1% of the publications correspond to today's criteria of modern scientific research of the evidence. An accepted body of evidence with respect to the benefits of individual products for wound management would be desirable for all those concerned and particularly for the affected patients.

Innovative wound care – New studies to increase evidence

Background: Today numerous products for wound care are available. A research-based evidence on which the clinician can base its selection, is still missing. In the guidelines randomized controlled trials (RCTs) have been left out.
Method: In the overview three current RCT with products for the treatment of chronically venous ulcers will be presented.

Results and Conclusions: The pre-mentioned studies show, that it is possible to provide a basis for evidence-based treatment in wound healing. The effective value of a wound treatment based on the costs and benefits must be defined by the health system. But products, for which data from randomized trials exist, should be evaluated in a different way to products, for which there are no such data.

Keywords: Wound care – Randomized controlled studies (RCT) – Evidence – Guidelines

Conflict of interests
Knut Kröger has given paid lectures on behalf of URGO GmbH, SastoMed GmbH, medi GmbH, Sanofi and Bayer, Alexander Risse has given paid lectures for Lilly Germany, NovoNordisk, Berlin-Chemie, Sanofi, URGO, GVW and ZFD. Martin Stork declares that there is no conflict of interest.

LITERATUR

1. Arenbergerova M, Engels P, Gkalpakiotis S, Dubská Z, Arenberger P. Einfluss von topischem Hämoglobin auf die Ulcus cruris venosum Wundheilung. Hautarzt 64 (2013), 180–186.
2. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 363 (2004), 1854–1859.
3. Harding K, Gottrup F, Jawień A, et al. A prospective, multi-centre, randomised, open label, parallel, comparative study to evaluate effects of AQUACEL® Ag and Urgotul® Silver dressing on healing of chronic venous leg ulcers. Int Wound J 9 (2012), 285–294.
4. Meaume S, Truchetet F, Cambazard F, et al. on behalf of the CHALLENGE Study Group. A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-Oligo-Saccharide Factor wound dressing in the local management of venous leg ulcers. Wound Rep Reg 20 (2012), 500–511.
5. Rüttermann M, Maier-Hasselmann A, Nink-Grebe B, Burckhardt M. Lokaltherapie chronischer Wunden: Bei Patienten mit peripherer arterieller Verschlusskrankheit, chronisch-venöser Insuffizienz und Diabetes mellitus. Dtsch Arztebl Int 110 (2013), 25–31.
6. www.dgfw-ev.de (Zugriff am 25.06.2013).
7. www.gesetze-im-internet.de/bundesrecht/mpg/gesamt.pdf (Zugriff am 11.06.2013).

Address for correspondence:
Prof. Dr. med. Knut Kröger
Klinik für Gefäßmedizin
(Department of Vascular Medicine)
HELIOS Klinikum Krefeld GmbH
Lutherplatz 40
47805 Krefeld
Germany
Tel.: +49 2151 32 - 1669
Fax: +49 2151 32 - 1906
Email: knut.kroeger@helios-kliniken.de