

Schiller Saal

10.30–12.00

V 11

Fibrotic Tissue Responses I

Fibröse Gewebereaktionen I

V 11-2

Fetal scarless healing***M. W. J. Ferguson***

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Wounds made on early mammalian embryos heal perfectly with no scar. In the mouse the transition from scar free to scar forming healing for an *in vivo* excisional wound is embryonic day 16. Analysis of the cellular and molecular differences between scar free and scar forming healing has highlighted the importance of the transforming growth factor beta family of molecules. TGF β 1 and TGF β 2 are present at low levels in embryonic wounds which heal without a scar. By contrast in adult wounds, which scar, they are at high levels following their release from degranulating platelets and inflammatory cells. By contrast, TGF β 3 is present at high levels in embryonic wounds that heal without a scar and low levels in adult wounds which scar: largely due to its morphogenetic role in skin development. Manipulation of adult wounds e.g. by elevating the levels of TGF β 3 or reducing the levels of TGF β 1 and TGF β 2 allow them to heal with markedly reduced or absent scarring.

V 11-3

Mechanisms and genes involved in the fibrotic tissue response***B. Eckes***

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Tissue fibrosis is thought to result from persistent activation of fibroblasts resulting in induced proliferation and production of connective tissue constituents. Among the best characterized stimuli are cytokines like TGF-beta, connective tissue growth factor (CTGF), some interleukins and others. Less well known is the perturbed response of fibroblasts to the altered matrix envi-

ronment, which differs from normal connective tissue not only in terms of biochemical composition, but also in terms of mechanical properties. We have begun to address the role of the matrix in determining the fibroblast phenotype and have found this cell type to be a very versatile cell.

V 11-4

Genetics of familial keloids***A. Marneros***

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Keloids are common proliferative fibrous growths that usually result from an excessive tissue response to skin trauma. Family studies suggested a genetic predisposition to keloid formation in affected families. These studies stimulated the search for gene mutations that may help understand the molecular mechanisms involved in keloid pathogenesis. The recent identification of gene loci associated with familial keloid predisposition is the first step towards the goal of finding such gene mutations.

Hegel Saal

10.30–12.00

V 12

Bridging the Gap: Tissue Engineering

Brücken bauen: Tissue engineering

V 12-1

Bridging the gap; tissue engineering – putting it to practise

J. Apelquist

J. Apelquist

A chronic ulcer is related to delayed healing, high probability for infection and co-morbidity.

Outcome of chronic ulcer is strongly related to type, site and cause of ulcer which has to be considered in multifactorial multidisciplinary treatment strategy. Control of infection, therapy of vascular disease, pressure relief, treatment of co-morbidity and wound management is essential parts of the treatment.

Topical wound management is an adjunctive to systemic and surgical treatment. However an increase in interest to improve the loss of heal as well as a rate of healing an absence of infection and ischemia in longstanding in nonhealing ulcer has been seen in recent years. A substantial number of agents and dressings with different suggested activities to improve wound healing has been tested and marketed. The rationale for these products has been the metabolic disturbances that has been described in many ulcers such as level, activity of growth factors, fibroblasts, changes in collagen metabolism, somatic activity and hemerological disturbances. A special interest has been focussed towards slow healing ulcers such as adiabatic neuropathic plantar ulceration, venous ulcer and pressure ulcers. Some promising data have been presented especially in neuropathic plantar ulceration in which tissue engineering products has been shown to improve healing rate as well as shorting the healing time in selective cases.

However choice of topical strategy in each case is still empiric since most studies are hampered by small sample size, lack of adequate description of type of ulcer, short follow up period, absence of strict criteria with regard to endpoints and follow up as well as total management strategy. A key problem seems to be that in many studies focus have been with regard to healing versus non-healing whereas changes of condition of an ulcer might be of great importance with regard to choice of local wound management in the different phases of healing. From clinical perspective the difficulty in the choice of tissue engineering products is to identify a typical responder to a specific treatment strategy. From health economic perspective a tissue engineering product has to improve healing rate or speed of healing of at least 30 % to achieve cost effectiveness according to present data.

The need for additional treatment options and impact of a new treatment strategy such as tissue engineering is huge since management of chronic ulcers is associated with prolonged suffering for the patient, high economic cost to the society due to prolonged hospitalization, rehabilitation and need for homecare and social services for disabled patients.

V 12-2

Bridging the gap: tissue engineering – clinical research, what's the evidence?

P. Vowden

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The successful enhancement, transfer and incorporation of bio-engineered skin, skin products or skin or matrix substitutes into a wound to enhance healing and, ideally, to improve scar formation and function remains the "Holy Grail" or cutaneous wound management. Autologous skin transfer techniques such as split or full thickness grafting and pinch grafting have been routinely used for decades in the management of acute and some chronic wounds. Despite the obvious advantage of immediate skin coverage of a large cutaneous defect these techniques have never, however, been regarded as the mainstay of management of chronic ulcers.

Increasing understanding of the orchestrated and choreographed mechanism of healing that occurs in an acute wound and the defects that exist within a chronic wound environment have allowed a range of products to be developed aimed at manipulating or substituting elements within a chronic wound to favour healing. This process is in effect in vitro tissue engineering and may, for example, take the form of extracellular matrix substitution, protease control or the introduction of specific growth factors into the wound. All these interactions have the advantage of not requiring the addition of viable cells to the wound which makes these techniques more universally applicable as the majority of wound care occurs outside of specialist centres where the skills and facilities that allow living tissue transfer to occur exist.

Progress is however being made in both the provision of dermal, keratinocyte and bi-layer tissue engineered skin substitutes. Products like Integra (Integra Life Sciences) are now widely used

in burns management and may have a role in the management of some chronic wounds (Jeschke et al., 2004). Dermagraft (Smith & Nephew), a dried dermal substitute with an acceptable shelf life, has also established a role in chronic wound management (Allenet et al., 2000, Marston et al., 2003, Omar et al., 2004). Viable skin products are however more difficult to manage and place significant demands on the organisation of wound care if they are to be effective. Encouraging results have been reported with Apligraf (Novartis), a bioengineered bi-layer skin substitute, derived from cultured neonatal foreskin both in the management of diabetic foot ulceration (Brem et al., 2000) and venous ulcers (Brem et al., 2004). Cost-effectiveness studies indicate that these results were at a lower overall treatment cost (Fivenson and Scherschun, 2003, Sibbald et al., 2001, Redekop et al., 2003) but as yet no universal reimbursement strategy exists that would allow the more widespread introduction of this or similar technologies.

Each patient has a finite amount of skin available for donation. To overcome this and to reduce donor site discomfort and allow repeated application of viable cells to the wound techniques have been developed to allow keratinocyte enhancement in laboratory culture and the development of a cell carrying dressing. Using this technique Moustafa et al (2004) have reported on the use of Myskin (CellTran) in the successful treatment of neuropathic diabetic foot ulceration. Similar work by Intercytex has concentrated on allogenic human dermal fibroblast transfer. Results from a Phase IIb are soon to be reported and further clinical trials are underway. This group are also developing a product based on the dermal fibroblasts but overlaid with human keratinocytes.

The development of these live dressing demonstrates the advances that have already been made in engineering functional dermal and skin replacements. These products will always seem expensive, especially when compared with conventional dressings. We as clinicians therefore need to ensure that we understand how and when to use such products so that we can maximise any advantage for the patient and demonstrate that they represent a cost-effective and efficient alternative to «standard» care. To do that we must be able to recognise the state of the wound bed and potentially manipulate the wound environment before we apply these products. The final answer may not lay in engineering skin products in the laboratory but in bringing the laboratory to the patient. That is, in vivo tissue engineering not in vitro engineering techniques. This talk will enlarge on the concepts presented here and look in more detail at how we can generate a wider and cost-effective introduction of these and similar therapies to the wider patient group with acute and chronic wounds.

References

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V 12-3

Microengineered hydrogel dressings as vehicles for grafting human skin cells

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There should be clinical benefit in technology that is capable of delivering autologous or allograft cells to the site of traumatic injuries such as burn, or to chronic lesions such as skin ulcers. Few of the currently available strategies for delivering cells to wounds appear to afford any protection to vulnerable grafted cells against mechanical and metabolic stress either during the procedure or immediately afterwards. We report the use of a prototype fibronectin-derivatised polyvinylalcohol/polyvinylacetate co-polymer hydrogel 'dressing' as a vehicle for amplification and grafting of human dermal fibroblasts and keratinocytes onto human dermis. The rationale for taking this route is to simplify the development process since hydrogels are already deployed in the treatment of skin lesions to relieve distressing symptoms such as pain. The amorphous and cohesive microstructure of some hydrogels allows them to closely contour surfaces, yet without the tendency to adhere, suggesting that donor cells would be brought into close opposition with the wound bed. Fibronectin was identified experimentally as an optimal attachment factor for the hydrogel in terms of both amplification of fibroblastic and epithelial cell numbers, and for inducing maximum motility in adherent cells. It was considered that during the grafting process cells would transfer between the hydrogel surface and the wound bed partly by differential adhesion but that this would be reinforced by population pressure and migration. Taking these factors into account, protective niches were microengineered into the surface of hydrogel sheets to serve as reservoirs for donor cells. The design of these niches also provided a conduit for migrating cells to better establish physical contact with the recipient substratum and therefore enhance the efficiency of cell transfer when compared to planar surfaces.

Hall Maritim

10.30–12.30

V 34

Introduction to wound care

Einführung in die Wundbehandlung

V 34-1

Behandlung chronischer Wunden in der stationären und ambulanten Pflege – die Verantwortung der Pflege bei den gegebenen gesellschaftlichen und gesetzlichen Rahmenbedingungen

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Als Pflegekraft in einer Gesundheitseinrichtung tätig zu sein bedeutet, dass die Leistungen nach dem jeweiligen Stand der wissenschaftlichen Erkenntnisse und in der gebotenen Qualität erbracht werden. Unterstützung erhält die Pflege in ihrer Arbeit durch z. B. Medizinprodukte. Die rasante Entwicklung der technischen Möglichkeiten eröffnet ständig neue Methoden oder Verbesserungen der bestehenden Verfahren. Die Erleichterungen, die diese mit sich bringen, werden gerne angenommen. Die Regelungen jedoch, die notwendig sind, um die Gefahren durch die Anwendung zu minimieren, werden nicht immer durchgängig von allen Verantwortlichen getroffen und eingehalten. Dass der unkritische Einsatz auch Gefahren mit sich bringt, wird in der Regel dann nicht reflektiert, wenn die tägliche Erleichterung groß und die Gefahren nicht augenfällig bzw. „nur“ bei einer Verkettung von unglücklichen Umständen auftreten oder erkennbar werden. Die Entwicklungen der Industrie sind positiv zu bewerten, da in jeder Innovation Chancen stecken. Der gewünschte besondere Schutz von alten und/oder kranken Menschen in gewerblichen Versorgungseinrichtungen hat besondere/strengere Gesetze, Verordnungen, Richtlinien und Rechtsprechung hervorgebracht. In dem Moment, in dem ein pflegerischer Mitarbeiter einer Einrichtung tätig wird, haftet er für die Qualität ebenso wie seine Fachvorgesetzten und der Betreiber einer Einrichtung. Eine Vielzahl von Gesetzen sind zu beachten. Professionalität beinhaltet im Unterschied zur Laienpflege, dass Chancen und Risiken von Verfahren, Medizinprodukten und Medikamenten bekannt sind, dass diese richtig eingesetzt werden und Vorsorge zur Vermeidung von Gefährdungen getroffen werden. Die Prozesssteuerung ist komplex und sollte zu einer den Anforderungen entsprechenden individuellen Betriebsorganisation führen. Im Unterlassen solcher Regelungen ergeben sich dann auch die einklagbaren Ansprüche der Bewohner und ihrer Angehörigen.

V 34-2

Wound rinsing solutions for cleansing of chronic wounds – drugs or medical devices?

Wundspüllösungen zur Reinigung chronischer Wunden – Arzneimittel oder Medizinprodukte?

K. Kaehn

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Wound incrustations and chronic wounds are always colonized by bacteria of the normal skin flora. These bacteria may be affected during wound rinsing by preservative agents (i. e. polyhexanide) intended to stabilize rinsing solutions after opening the bottle. However, this fact do not justify classification of rinsing solutions as drugs. Colonization is clearly different from infection (an illness) and rinsing is not intended to kill harmless bacteria but to gently remove incrustations - a source of pro-inflammatory mediators. Therefore, wound rinsing solutions containing bactericide agents for preservation should always be classified as medical products. Chronic wounds which are infected must be treated on a doctors prescription. Either infected tissue areas are extirpated by surgery or infection is treated by antiseptics or antibiotics. During infection periods cleaning by use of wound rinsing solutions is usually continued.

Chronische Wunden sind Problemwunden und ihre Behandlung stellt hohe Anforderungen an die Qualifikation des Pflegepersonals. Ziel der Pflege muss es immer sein, einen möglichst frühzeitigen Heilerfolg herbeizuführen. Dies ist geboten, um die Lebensqualität der Patienten zu verbessern und um unter dem augenblicklichen Kostendruck in der Pflege wirtschaftlich zu arbeiten. Zur Wundversorgung gehört bei jedem Verbandwechsel die Wundreinigung mit sterilem Verbandmaterial. Die Reinigung ist auf den Verschluss der Wunde ausgerichtet und wird bei chronischen Wunden, sowohl bei infizierten als auch bei nicht infizierten, routinemäßig mittels Spülung durchgeführt. Als Spüllösungen werden in der Praxis häufig sterile Medizinprodukte wie Ringer- oder Kochsalzlösung eingesetzt, z. T. sogar auch

ungefiltertes Leitungswasser, dessen Verwendung rechtlich als problematisch einzustufen ist. Physikochemisch können Salzlösungen und Wasser die am Wundgrund anhaftenden denaturierten Eiweiße (Wundbelag) nicht lösen. Daher werden spezielle Wundspüllösungen mit oberflächenaktiven Substanzen, z.B. einem Betain-Tensid, angeboten. Dieses ist auf Grund seiner Struktur und Ladungsverteilung in der Lage, den Wundbelag anzulösen und Eiweißaggregate in Tensid-Mizellen einzuschließen und so in „Lösung“ zu bringen. Um Anbruchflächen der speziellen Wundspüllösungen haltbar zu machen, enthalten die Produkte als Konservierungsstoff das mikrobiozide Polyhexanid. Abgesehen vom intendierten Verwendungszweck (Reinigung) ist die Tatsache, dass Polyhexanid grundsätzlich in der Lage ist, auch Keime in der Wunde abzutöten, nicht ausreichend, um polyhexanidhaltige Wundspüllösungen als Arzneimittel einzustufen. Einmal ist die mikrobiozide Wirkung von Polyhexanid nicht metabolischer, sondern elektrostatischer Natur. Das passt nicht auf die Definition eines Arzneimittels, aber gut auf die eines Medizinproduktes. Zum anderen ginge in der Pflege viel Zeit verloren, wenn wiederholt beim Hausarzt „Arzneimittel“ rezeptiert werden müssten, die lediglich der Wundreinigung dienen. Das ist, zugegeben, ein praktisches Argument, aber es dient letztendlich dem Wohl der Patienten. Die Wundversorgung (Verbandwechsel, Reinigung) ist eine Aufgabe im Verantwortungsbereich der Pflege. Diese Verantwortung kann nur wahrgenommen werden, wenn auch die entsprechenden Kompetenzen in der Pflege gebündelt sind. Nur wenn die Wunde im nekrotisierenden und/oder infektiösen Zustand ist, muss sie durch einen Arzt chirurgisch und/oder medikamentös (Antiseptika bzw. eventuell Antibiotika) behandelt werden.

V 34-3

Feuchte Wundbehandlung: Eine Übersicht über derzeitige Produktgruppen

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In den vergangenen 20 Jahren ist eine verwirrende Anzahl von Produkten zur Wundbehandlung auf den Markt gekommen. Schlagworte wie „Feuchte Wundbehandlung“ oder „Wundmanagement“ haben teilweise eher zur Verwirrung als zur Klärung beigetragen. Auf den ersten Blick scheinen viele neue Produkte teurer als „altbewährte“ Vorgehensweisen. Jedoch bieten sie neben einer oft schnelleren Befundbesserung bzw. Abheilung auch therapeutische Möglichkeiten bei bisher „infausten Wundzuständen“. Die Fülle der Produkte erfordert aber ein sehr differenziertes Wissen, um ihren adäquaten und kostengünstigen Einsatz zu ermöglichen. Anhand der Einteilung in verschiedene Produktgruppen ist es möglich, zwischen grundsätzlichen Materialeigenschaften und lediglich Modifikationen unterschiedlicher Wirkstoffsysteme zu unterscheiden. Der Vortrag dient dazu, einerseits eine Gliederung der wesentlichen auf dem Markt vorhandenen Produkte in Produktgruppen zu erleichtern, andererseits die unterschiedlichen Produktgruppeneigenschaften näher zu differenzieren. Ziel einer solchen Schulung ist, dass jeder Anwender für den Standardgebrauch über ein adäquates Repertoire von Produkten mit den Kenntnissen über ihre Eigenschaften verfügt. Darüber hinaus ist das Wissen über weitere Produktmodifikationen und Wundproduktspezialitäten notwendig, um in „Sonderfällen“ die angewandte Therapie entsprechend anpassen zu können. Kriterien für den täglichen Einsatz sind aber nicht nur Produkteigenschaften bezüglich der Anwendung auf Wunden, sondern auch solche der Handhabung sowie der Personal- und Sachkosten. Hilfreich sind hierzu auch der Gebrauch verschiedener auf dem Markt erhältlicher „Wundfibel“ bzw. Taschenbücher für den täglichen Gebrauch. Eine Übersicht wird hierzu gegeben.

Mozart Saal

10.30–12.00

V 35

Skin & exudate**Haut & Exsudat**

V 35-2

The effect of incontinence on the skin barrier function in the perianal region

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Introduction: Bedridden elderly patients often have urinary and/or fecal incontinence which leads to a reduced skin barrier function, and increases the risk of a skin breakdown. However, there is no clinical evidence of a reduced skin barrier function in the perianal region. The purpose of this study is to compare the perianal skin barrier function between elderly patients with or without incontinence.

Methods: This study used a cross sectional observational design. The participants were 32 elderly patients with incontinence (= incontinence group, mean age 85.5 ± 6.5) and 29 elderly patients without incontinence (= independent group, mean age 83.0 ± 7.6). We evaluated the skin barrier function in the region from the anal to coccyx by focusing on the following factors; skin inspection, skin hydration, skin pH, and the amount of ceramide per stratum corneum (SC) weight. Informed consent was obtained from all participants.

Results: The incontinence group showed significantly greater skin hydration, skin pH, and total amounts of ceramide than the independent group ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$, respectively). The 20 patients with incontinence showed a flattened SC and none of the patient in the independent group did so. In the incontinence group, those who had a flattened SC showed a significantly greater skin pH and total amount of ceramide than those with a normal SC ($p = 0.0317$, $p = 0.0152$, respectively).

Conclusions: The main finding of this study was flattened SC in the incontinence group which may be caused by protein degeneration due to the presence of urea which has a possibility to cause a degeneration of the skin texture. High levels of skin pH

in the flattened SC group may indicate that urea plays a significant role in protein degeneration. In general, high levels of ceramide indicate a good skin condition. In contrast, the flattened SC group showed high levels of ceramide. The higher levels of ceramide could be explained by reduced activity of ceramidase or the detachment of the SC due to the repeated mechanical irritation related to frequent cleansing. In conclusion, these results demonstrated the possibility that flattened SC may be a useful indicator of a reduced skin barrier function in the perianal region.

V 35-3

An economic evaluation of skin damage prevention regimens among nursing home residents with incontinence: product and laboratory costs

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Introduction: Reports of high rates of incontinence in nursing home (NH) residents suggest prevention of ID is a major nursing concern. Little is known about the cost of ID prevention. The purpose of this study was to examine cost and efficacy of four ID prevention regimens in NH residents.

Methods: Residents ($n = 1,918$) in 16 U.S. NHs, randomly selected, were screened for eligibility; 981 residents qualified and were enrolled. All were incontinent and started free of perineal skin damage. Age and sex did not differ among the groups ($p > .05$). The regimens included use of a barrier film applied 3 times weekly (A) and three ointment barriers of different composition applied after each incontinence episode (B, C, D). Skin product costs (cleanser and moisture barrier) using time/motion measures were used for an economic analysis. Measures of caregiver labor (number and time) for ID prevention on 888 qualified residents (712 F, 176 M; age < 90 yrs = 72 %, 90 yrs. = 28 %) were used in the economic analysis and are reported. Staff assessed resident skin damage for 6 weeks to determine efficacy of the regimens.

Results: Overall occurrence of skin damage was 4.6 % of which 74 % was attributed to ID; neither incidence differed significantly among the groups ($p = 0.07$ for both). The median number of incontinence episodes/day differed among the groups (A = 6.2, B = 6.3, C = 7.0, D = 6.7; $p = 0.005$). Different numbers of staff provided ID prevention care (range = 1 to 4; $p < 0.001$). Due to these differences, the analysis standardized the cost of product and staff labor per 100 episodes of incontinence/week provided by one caregiver. The median total product cost of regimen A (\$ 14.36) was less than B(\$ 29.21), C (\$ 44.67), and D (\$ 27.04) $p < 0.0001$. Median barrier cost of A (\$ 3.98) was less than B (\$ 22.17), C (\$ 24.57), and D (\$ 20.67) $p < 0.0001$. The median labor cost of regimen A (\$ 27.15) was significantly less than B(\$ 93.02), C (\$ 46.95), and D(\$ 51.43; $p < 0.001$). Median labor cost of applying barrier A(\$1.80) was less than B (\$ 16.94), C (\$ 13.79), and D (\$ 15.96; $p < 0.001$).

Conclusions: Use of a skin barrier film applied 3 times weekly is effective in preventing ID and saves significant staff labor costs.

V 35-4

Combining high pressure water jet debridement with a biosynthetic dressing for the treatment of deep partial thickness and indeterminate thickness burns

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Over the past two years the two departments have successfully treated deeper partial thickness burns and indeterminate thickness burns with a combination therapy employing a new high pressure waterjet technology (VERSAJET, Smith and Nephew) with a biosynthetic dressing containing neonatally derived fibroblasts (TRANSCYTE, Smith and Nephew). Waterjet technologies have been employed in the commercial arena for the precision cutting of stone and metal alloys. In altering the orientation and pressure settings of the tangentially directed high pressure waterjet, this modality can be used as both a cutting and debriding tool, effectively vacuuming debris from the field with minimal splash or spray. It affords significant control, eliminates the risks posed by sharps and appears to promote tissue preservation effectively. TRANSCYTE, is a commercially available biosynthetic dressing consisting of a silicone layer overlying collagen and derived fibroblasts. This dressing has been shown to facilitate epithelialization in partial thickness wounds and has been also been utilized as an excisional wound dressing. We feel that by combining the attributes of these two modalities we have been able to successfully treat particularly deep thermal injuries in functionally critical and aesthetically sensitive areas like the face. To date, in over 20 patients we have witnessed no complications. All wound sites epithelialized within 6–14 days post treatment. One partial region in one patient did ultimately require treatment with an enzymatic debriding agent and successfully skin grafted.

V 35-5

Quantifying wound exudate

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The objective assessment of chronic wound therapies for exudate management (WRAP Study) tested methods that could be used to improve understanding of dressing performance in the presence of wound exudate. One facet of the project was the development of a single in vitro test method that is able to measure the fluid handling properties of a range of dressing types within the design stage of dressing production. To support the development and validation of this test method, information was required about the levels of exudate production. Having found a paucity of information in the literature, the aim of this study was to identify a valid and reliable method for measuring wound exudate. Two different methods were tested. Method A measured the weight of exudate collected in dressings by 'before and after' weighing of all dressing materials that would come into contact with wound exudate. The weight of the dressing materials prior to dressing the wound was then subtracted from their soiled weight after removal, to obtain a measure of exudate volume. The wound was measured and photographed on day 0 and again when the dressings were removed. Method B measured wound exudate collected as part of topical negative pressure therapy (TNP). Wound exudate output was measured on days 1, 3 and 5 and specimens of wound fluid were also sent for microbiological analysis. The wound was photographed on day 0 and day 5 and the wound areas calculated using a digitising pad. Method A: Complete data were collected on 3 patients and it was possible to measure an approximate level of exudate volume. It was time consuming and required a special scale. Method B: Complete data were collected for 10 patients, giving a total of 30 measurements. Using the wound surface area and the exudate levels it was possible to calculate the level of exudate production in wounds without great depth or undermining. There are problems with both these methods of exudate measurement, but the measurement of wound fluid collected in TNP canisters seems to be simpler to use than that of weighing dressings and deserves further investigation.

V 36

Growth Factors

Wachstumsfaktoren

V 36-1

Preliminary analysis of IGF/IGFBP/ Vitronectin complexes (VitroGro®) as a topical agent in the treatment of deep dermal partial thickness burns in a porcine wound healing model

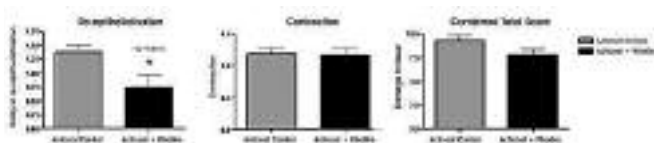
Z. Upton¹, R. Kimble², D. Harkin¹, L. Cuttle²,
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Introduction: We have previously demonstrated that complexes comprised of IGFs (insulin-like growth factor), IGFBPs (insulin-like growth factor binding-proteins) and vitronectin (Vn) [VitroGro®] significantly enhance the proliferation and migration of human keratinocytes. Here, a porcine wound healing model was developed as porcine skin most closely resembles that of humans. The model involved creating two 16 cm diameter scalds on the flanks of anaesthetised pigs. These dermal partial thickness wounds are treated and heal with scarring within 6 weeks. b>

Methods: 2 treatments, with 4 pigs/treatment, were assessed in a double-blind study. Wounds were dressed with Acticoat-7 (Smith & Nephew) with dressing change once per week with co-application of VitroGro®-Kc (containing 132 ng/cm² Vn, 44 ng/cm² EGF, 44 ng/cm² IGF-1 and 132 ng/cm² IGFBP-3) or sterile water, followed by catheter application 3 times/week of VitroGro® or sterile water, as well as application of sterile water 3 times/day. Once the wounds re-epithelialised, they were dressed in Jelonet (Smith & Nephew). At the initial scalding, and every weekly dressing change, measurements were taken. After 6 weeks, the pigs were euthanised and tissue sections were taken for histological analysis.



[Figure 1 - V 36-1: Clinical measures.

Results: There was a significant increase in re-epithelialisation in the VitroGro® treated group, compared with Acticoat alone. Histologically, there was a statistically significant improvement in organised granulation tissue in the VitroGro-Kc treated group.

Our working hypothesis is that a reduction in this granulation tissue layer would equate to decreased scarring, however this would need to be proven by further longitudinal studies. Cosmetically, the VitroGro-Kc treated group did appear slightly improved compared to the Acticoat control.

Conclusions: In future work, we wish to:

1. Directly compare other best-practice dressings used for burns, with and without VitroGro-Kc treatment; and
2. Analyse healing when exposed to different doses of VitroGro-Kc. The enhanced wound healing response obtained here was with much lower doses of IGF-I and EGF (44ng/cm² wound) than previous studies examining growth factors in wound healing.

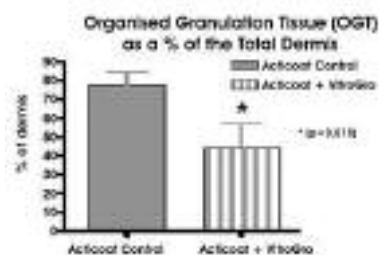


Figure 2 - V 36-1: Histological measures.

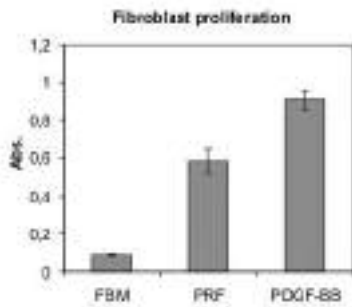


Figure 1 - V 36-2.

V 36-2

Effects of platelet-rich fibrin on fibroblast activities in vitro and in vivo

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Introduction: Platelets contain potent growth factors and are used topically in various carrier systems in the treatment of acute and chronic wounds. Including platelets in autologous fibrin prepared at the bedside is a novel formulation (VIVOSTAT[®], Vivolution, Denmark). The aim of these studies are to assess the effect of the topical autologous platelet-rich fibrin (PRF) on fibroblasts cultured in vitro and on the collagen production by fibroblasts in expanded polytetrafluoroethylene (ePTFE) tubes implanted subcutaneously in patients subjected to elective laparoscopic cholecystectomy.

Methods: In vitro, the effect of PRF on fibroblast proliferation was assessed in confluent and growth-arrested adult human dermal fibroblasts (Cambrex). The fibroblasts were treated with fibroblast basal medium containing 2 % fetal calf serum (FBM) in the absence (n = 12) or presence of preformed PRF clots (n = 12) or of 10 ng/ml platelet-derived growth factor-BB (n = 12, PDGF-BB) for 20 hours in 96-well culture plates. BrdU incorporation was measured during the final 2-hour incubation period using a cell proliferation ELISA kit (Roche). In a clinical controlled, randomized, single-blind trial ePTFE tubes are implanted adjacent and subcutaneously to the two laparoscopic ports in 50 patients. One ePTFE tube receive PRF and the other ePTFE tube saline (control). On postoperative day 14, ePTFE tubes are analyzed colorimetrically on the amount hydroxyproline, as an indicator of collagen deposition, and fibroblast infiltration quantified by immunohistochemistry using a monoclonal antibody against type I procollagen (Chemicon). Patient enrollment began June 2005.

Results: The in vitro assay showed increased fibroblast proliferation (mean ± SEM in Figure) with PRF (P < 0.001) and PDGF-BB (P < 0.001) compared with control (FBM). In a preliminary clinical trial, the number of fibroblasts correlated to the amount of hydroxyproline in ePTFE tubes. PRF appeared to increase both fibroblast infiltration and hydroxyproline accumulation in ePTFE tubes.

Discussion: The platelet-rich fibrin (PRF) exhibited fibrogenic properties both in vitro and in vivo and may be a useful adjuvant in wound management.

V 36-3

A cytokine study investigating the temporal changes in cytokine levels in acute wound fluid

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Tissue repair is described as a complex progression of events, which is orchestrated by cell-cell and inter-cell mediated communications involving cytokines, lymphokines, cellular released enzymes, immune cells, and cells in situ. Acute wounds heal in an orderly and efficient manner characterized by four distinct phases: haemostasis, inflammation, proliferation, and tissue remodeling. The temporal characterization of these chemical signals will elucidate a biochemical profile of normal wound healing and will help identify the defective parameters when compared to chronic or delayed wounds. In this study, we have used donor site wounds (harvesting of skin grafts for reconstructive surgery) as a clinical model of acute wound healing and have examined the change in cytokines, proteases, and their inhibitors with time post-wounding. Split thickness donor skin graft sites heal within 7 to 10 days and produce harvestable amounts of wound fluid over the first 5 days. These wound fluid samples were collected and a panel of cytokines, proteases and inhibitors measured by ELISA and by activity assays. Results demonstrate that PDGF (AA & AB), EGF, TGF-B1 and IL-10 are abundant early in the repair process but steadily decline with time. In contrast, TGF-alpha, VEGF, TNF-alpha and KGF show a modest increase with time while IL-8 and GM-CSF levels dramatically increase over time. High levels of MMP-2 and MMP-9 were detected throughout the time of fluid collection. These results provide a more comprehensive insight into the biochemical changes which occur in acute wound healing and are more indicative of the sequence of events which occur in a dermal wound over other acute wound fluid studies where mastectomy drainage fluid has been used. Future studies will correlate the temporal changes in cytokines, proteases and various inhibitors with those in non-healing wounds thereby ascertaining the altered signals and identifying potential therapeutic targets to stimulate healing.

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V 36-4

A basic fibroblast growth factor successfully improves wound healing with artificial skin substitute and skin grafting

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Acute wounds caused by the severe and extensive infection such as alpha-hemolytic streptococci or MRSA may be life-threatening in immuno-compromised hosts such as steroid users or those with veno-stasis in the lower legs. On the other hand, the burn wounds are sometimes delayed for various reasons and lead to the hypertrophic scars, which cause functional as well as aesthetic problems. For 10 immediately-developing extensive wounds, artificial skin substitutes composed of dried bi-layer membranes of outer silicone membrane and inner porcine-tendon derived collagen layer (Pelnac[®], Gunze Co., Ltd., Kyoto, Japan) were immediately after extensive and meticulous debridement and for 10 delayed burn wounds, thin split-thickness (9-10/1,000 inches) grafting after extensive enough debridement. While the skin substitute integrated into the wound bed for maximally three weeks and grafted skins in burns are healed by three weeks, total 20 micrograms of the basic fibroblast growth factors (bFGF) (Trafermin[®], Kaken Pharmaceutical Co. Ltd, Tokyo, Japan) were applied by the 27-Gage syringe daily. For the artificial skin substitutes, the outer membranes were removed and thin split-thickness skin grafting (9-10/1,000 inches) was performed and wound healed uneventfully. The bFGF-treated skin texture was significantly softer compared to control by both clinical skin hardness scores (grading scales from 0 to 3) and a durometer (Teclock[®], GS-701N, Tokyo, Japan)($p < 0.01$)(figures 1-2), which is following the international standards of SRIS 0101 and is able to score ranging 519mN to 8,379mN (55-855 gf). Therefore, the artificial skin substitute with bFGF and thin-split thickness skin grafting with bFGF improve the healed skin texture (figure 3). In histology, the bFGF-treated wounds demonstrated more organized rete ridges and dermal architectures while there are more randomized dermal arrangements in control (figure 3-b).

Figure 2-a

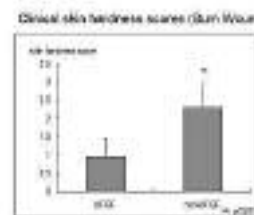


Figure 2-b

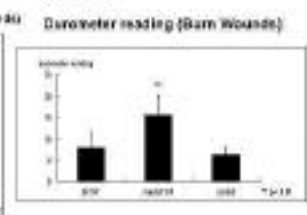


Figure 3-a



Figure 3-b



V 36-5

Growth factor and biochemical characterization of platelet-rich plasma (PRP) for wound healing

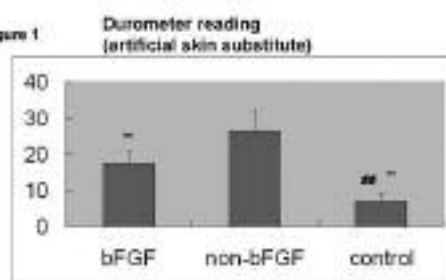
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Aim: Platelet concentrate, also known as platelet-rich plasma (PRP), is used increasingly in the form of autologous platelet gel (APG) to accelerate wound healing and to help heal difficult wounds. This study was undertaken to characterize the contents and properties of PRP prepared using an automated, table-top centrifugation device.

Methods: PRP (6 mL) was prepared, from blood (60 mL) donated by healthy volunteers, using the Medtronic[®] Magellan[®] Autologous Platelet Separator. Cellular contents of the PRP were measured by performing a complete blood cell count. By comparing cell counts in the PRP to those in the initial blood, concentration levels were determined. The quality of PRP was assessed to ensure that the separation process did not cause trauma, activate cells, or initiate clotting. Hemolysis was assessed by measuring the level of free hemoglobin in the plasma. Fibrinogen was assayed using a coagulation analyzer to ensure that no clotting occurred. Leukocyte activation was measured by an assay for PMN Elastase. Platelet activation and viability were measured

Figure 1



—: $p < 0.01$, compared to non-bFGF
■: $p < 0.01$, compared to others

using flow cytometric techniques to evaluate whether the separation process affected platelet functionality. Growth factor (PDGF, TGF- β , VEGF, bFGF and EGF) levels were measured using ELISAs (enzyme-linked immunosorbent assays), while a cytokine array was used to detect and semi-quantitatively measure the various cytokines.

Results: The PRP contained more than 6 times higher platelet concentration compared to the initial blood. PDGF, TGF- β , VEGF, bFGF and EGF levels were all significantly increased compared to baseline levels in the whole blood. In general, these levels correlated to the increase in platelet concentration. In addition, other pro-angiogenic and wound healing cytokines were detected. Centrifugal preparation of the PRP did not cause significant trauma to the blood components. Platelets were not activated by the separation process and remained functional. Fibrinogen remained at physiologic levels and leukocytes were not activated.

Discussion: This characterization study identifies and quantifies various components of PRP that may be responsible for its effectiveness in wound healing. The measurement of growth factors and cytokines enables us to better understand how they may influence treatment efficacy.

V 36-6

The soluble variant of the vascular endothelial growth factor receptor VEGFR-1: a novel mediator in wound healing

Der lösliche VEGFR-1 Rezeptor (sVEGFR-1): ein neuer Mediator in der Wundheilung

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The endothelial cell-specific mitogen vascular endothelial growth factor-A (VEGF-A) is a potent regulator of angiogenesis during wound healing. The soluble form of the VEGF receptor VEGFR-1 (sVEGFR-1) is a strong and specific inhibitor of VEGF-A signaling and has been characterized as a potent inhibitor of angiogenesis. In the present study we investigated the hypothesis whether sVEGFR-1 plays a role during tissue repair and we evaluated the expression of sVEGFR-1 in healing and non-healing human wounds. RT-PCR analysis indicates that the full length receptor VEGFR-1 and its splice variant sVEGFR-1 are expressed in normal skin and non-healing wounds. ELISA and western blot analysis demonstrate that sVEGFR-1 is released at low levels in wound fluid obtained from normal healing wounds averaging 2.2 ± 2.0 ng/ml ($n = 11$), and at significant higher levels in chronic non-healing wounds with a mean sVEGFR-1 concentration of 9.3 ± 3.2 ng/ml ($n = 16$) ($p < 0.001$). Only in those chronic wounds, which eventually entered a phase of granulation tissue formation and finally wound closure, wound healing progression correlated significantly with a decline in sVEGFR-1 levels ($r=0.92$; $p < 0.0005$). Northern analysis of cultured HUVE cells exposed

to wound fluid indicate, that wound fluid obtained from chronic non-healing wounds contains mediators that are able to enhance the expression of sVEGFR-1 mRNA. This report suggests that sVEGFR-1 represents a regulatory molecule during wound repair. Our findings contribute to a better understanding of the pathophysiology underlying chronic non-healing wounds and indicate a predictive value for sVEGFR-1 levels for differentiating healing and non-healing wounds.

Der vaskuläre Endothelzellfaktor (VEGF) stellt ein Schlüsselmolekül in der Regulation der Wundangiogenese dar. Der lösliche VEGF Rezeptor VEGFR-1 (sVEGFR-1) ist der bisher einzig bekannte endogene VEGF-spezifische Inhibitor. In unterschiedlichen Angiogenesemodellen wurde gezeigt, dass sVEGFR-1 einen sehr potenten Angiogeneseinhibitor darstellt. Die Rolle von sVEGFR-1 in der Wundheilung ist bisher nicht bekannt. Um dieser Frage nachzugehen haben wir die Expression von sVEGFR-1 in heilenden und nichtheilenden humanen Wunden untersucht. Mittels RT-PCR Analyse konnten wir die Expression von VEGFR-1 und sVEGFR-1 im Gewebe heilender und nichtheilender Wunden nachweisen. Die Konzentration von sVEGFR-1 in Wundseren nicht heilender Wunden ist signifikant gegenüber der Konzentration in heilenden Wunden erhöht. Der Heilungsprozess chronischer Wunden korreliert signifikant mit der Abnahme der sVEGFR-1 Konzentration im Wundserum. Im Gegensatz zum Sekret heilender Wunden, konnte durch das Sekret nichtheilender Wunden die Expression von sVEGFR-1 in HUVE Zellen induziert werden. Unsere Untersuchungen deuten auf eine Rolle für sVEGFR-1 in der kutanen Wundheilung hin. Wie sVEGFR-1 auf zellbiologischer Ebene die Endothelzellfunktion während der Wundheilung reguliert ist derzeit unklar. Unsere Untersuchungen führen jedoch zu der Hypothese, dass eine erhöhte sVEGFR-1 Konzentration die VEGF vermittelte Angiogenese und somit die Ausbildung eines funktionellen Granulationsgewebe im Milieu der chronischen Wunde einschränkt. Darüber hinaus werfen unserer Untersuchungen die interessante Frage auf, ob die sVEGFR-1 Konzentration im Wundsekret als Indikatormolekül für heilende versus nicht heilende Wunden, bzw. ihrem Therapieerfolg, dienen kann.

V 37

Innovative methods of wound treatment

Innovative Methoden der Wundbehandlung

V 37-1

ChitoSkin: A new chitosan-based wound dressing for healing especially chronic wounds

ChitoSkin: Eine neue Chitosan-basierte Wundauflage zur Heilung insbesondere chronischer Wunden

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ChitoSkin is a 1:1-complex of chitosan and of gelatine from swine, chitosan is poly-glucosamine. The water-soluble chitosan with its positively charged ammonium group is unique, and because of this property, it binds not only gelatine, but also other anionites. In general, chitosan has many interesting properties regarding wound healing. It can be produced out of crab shells(chitin) and mushrooms. ChitoSkin can take up the 50 fold amount of its weight of water or exsudate, and by the special production(freeze drying) it has a porosity of about 100 µm, which provides a matrix(template) for 3-dimensional tissue growth. Thus ChitoSkin has a proper adhesion to the wound surface, but it does definitely not stick to the surface and is easily removed. ChitoSkin can bind metal ions. It also binds matrix-metallo-protease(MMP), albumine and thrombine. The molecular components of ChitoSkin are also integral parts of the main natural matrix substances, like hyaluronic acid, heparin, keratan- and dermatan- sulfate. So ChitoSkin simulates the natural intercellular matrix, which is necessary for regular tissue growth. Investigations reveal, that chitosan has hemostatic potential and anti-bacterial effects, it activates macrophages and fibroblasts, it stimulates angiogenesis, it inhibits inflammation, it promotes intercellular matrix growth, and it induces regular collagen deposition, avoiding scar formations in tissue. These properties make ChitoSkin effective in all (4) phases of wound healing. Thus, ChitoSkin is a universal and bio-regulatory wound dressing. Comparative clinical studies with a collagen pad in burns (39 cases) and in diabetic chronic wounds (68 cases), show that the adhesion was better, the frequency of necessary redressing was lower by 50 %, that the granulation was two times quicker, and that the epithelialisation was accelerated by 30 %. These studies also demonstrate a substantial improvement of compatibility (pain,

burning, itching) and of side effects(allergic dermatitis). With its pronounced bio-regulatory properties the universal wound pad ChitoSkin stands for a new (3.) generation of wound dressing.

ChitoSkin besteht aus einem 1:1-Komplex von Chitosan und Schweine-Gelatine; Chitosan selbst ist poly-N-Glucosamin. Diese wasserlösliche Substanz ist mit seinen positiven Ladungen in Form von Ammonium-Gruppen einzigartig und bindet daher nicht nur Gelatine, sondern auch andere Anionite. Insgesamt besitzt es eine Reihe interessanter Eigenschaften hinsichtlich der Wundheilung. Chitosan lässt sich aus Krebschalen(Chitin) und Pilzen gewinnen. ChitoSkin kann das 50-fache seines Gewichts an Wasser oder Exsudat aufnehmen, und es besitzt durch die Art der Herstellung(Gefriertrocknung) eine Mikro-Porosität von etwa 100 µm, die dem Gewebe zum 3-dimensionalen Wachstum eine Matrix in Form einer Schablone bietet. Demgemäß besitzt ChitoSkin zur Wundfläche eine sehr gute Adhäsion, jedoch verklebt es nicht mit der Wunde und kann einfach entfernt werden. ChitoSkin kann aufgrund seiner molekularen Struktur (Schwer-)Metall-Ionen und außerdem Matrix-Metall-Proteasen(MMPs), Albumin und Thrombin binden. Die Monosacchrid-Bausteine von ChitoSkin sind zugleich integrale Bestandteile der natürlichen Matrix-Substanzen, wie Heparin, Hyaluronsäure, Keratan- und Dermatan-Sulfat, sodass die Gewebe- Zellen an der Grenzfläche zur Auflage ein molekulares physiologisches Milieu vorfinden. Die natürliche interzelluläre Matrix interagiert mit den Zellen und ist für ein reguläres Gewebewachstum unerlässlich. Untersuchungen haben ergeben, dass Chitosan hämostatisch und anti-mikrobiell wirkt, Makrophagen aktiviert, Fibroblasten stimuliert, die Angiogenese fördert, die Entzündung hemmt, die interzelluläre Matrixbildung steigert und für eine regelrechte Kollagenbildung ohne Narben im Gewebe sorgt. Diese Eigenschaften machen ChitoSkin in allen 4 Phasen der Wundheilung förderlich wirksam; ChitoSkin ist daher eine universelle und bio-regulative Wundauflage. In klinischen Vergleichsstudien mit einer Kollagen-Wundauflage an Verbrennungswunden (39 Fälle) und diabetischen Wunden (68 Fälle) wurde gefunden, dass die Adhäsion besser ist, dass ein Bandwechsel halb so oft erforderlich war, dass die Granulation doppelt so schnell auftrat und dass die Epithelialisierung etwa 1/3 der Zeit schneller eintrat. Die gleichen Studien zeigten, dass sowohl die Verträglichkeit (Schmerzen, Brennen, Jucken) als auch die Nebenwirkungen (allergische Dermatitis) deutlich seltener auftraten. Mit seinen ausgeprägten bio-regulatorischen Eigenschaften steht das universelle ChitoSkin für eine neue dritte Generation von Wundauflagen.

V 37-2

Steigerung der Hypoxietoleranz von Zellen durch Vakuumtherapie am Beispiel der HIF-1 α - (Hypoxia inducible factor-1 α) Expression

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Einleitung: Im Rahmen der zielgerichteten Geweberekonstruktion mit und ohne tissue engineering Verfahren durch Modulation der Wundheilung hat sich die Vakuumtherapie als ein nicht-invasives Verfahren zur Förderung der Wundheilung etabliert. Der genaue Wirkmechanismus der Vakuumtherapie ist jedoch bislang weitestgehend unbekannt. Aufschluss über die Gewebeoxygenierung bietet möglicherweise die Bestimmung der Expression von HIF-1 α . Bei HIF-1 α (Hypoxia inducible factor-1 α) handelt es sich um einen DNA-bindenden Komplex und physiologischen Regulator der Expression von VEGF. Dieser wird insbesondere bei Gewbehypoxie und mechanischer Dehnung von glatten Gefäßmuskulzellen vermehrt exprimiert.

Methodik: Im Rahmen des allgemeinen Wunddebridements wurden mit schriftlichen Einverständnis der Patienten aus dem Wundrand und dem Wundgrund vor der Vakuumversiegelung sowie 4 Tage nach kontinuierlicher 125 mmHg Soganzwendung Biopsien entnommen. Die untersuchten 15 Patienten litten unter postoperativen oder posttraumatischen Wundheilungsstörungen. Ausgeschlossen wurden Patienten mit schweren Wundinfektionen, chronischen Grunderkrankungen. Die zuvor durch HE-Färbung als Granulationsgewebe identifizierten paraffinfixierten Schnitte wurden mittels HIF-1 α (Hypoxia inducible factor-1 α) angefärbt. Aus fünf zufällig ausgewählten Areale von 1,0 \times 10 (-4) mm [2] erfolgte die semiquantitative Auswertung der Schnitte durch lichtmikroskopische Auszählung der angefärbten Zellkerne bei 200facher Vergrößerung durch einen verblindeten Beobachter.

Ergebnisse: Die histologische Untersuchung des Granulationsgewebes zeigte nach der Vakuumtherapie insgesamt eine leichte Abnahme der Kapillardichte bei gleichzeitiger Zunahme ausgeprägter kollagener Strukturen. Vor der V.A.C-Therapie zeigten sich die Zellkerne in der Anzahl als auch in der Farbintensität stärker durch HIF-1 α anfärbbar. Unter der Vakuumtherapie kam es dagegen zu einer signifikanten Abnahme der angefärbten Zellkerne.

Diskussion: Der signifikante Abfall an durch HIF-1 α angefärbten Zellkernen nach kontinuierlicher lokaler topischer negativer Druckbehandlung kann als ein Anzeichen für eine verbesserte Gewebeoxygenierung gedeutet werden. In dieser Studie konnte somit erstmals der klinische Eindruck einer gesteigerten Gewebeoxygenierung nach Vakuumtherapie direkt im Gewebe verifiziert werden. Dieses Bild wird unterstützt durch die in anderen Studien bereits nachgewiesene Steigerung Mikrozirkulation unter Vakuumtherapie. Die Modulation der Sensibilität von Zellen durch Beeinflussung der Hypoxietoleranz kann für den Einsatz im tissue engineering von entscheidender Bedeutung für die Umsetzung der TE Konzepte in die klinische Praxis sein.

V 37-3

Die Wertigkeit der Ultraschall assistierten Wundreinigung in der ambulanten Behandlung chronischer Wunden – eine prospektive klinische Studie

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Einleitung: Die Behandlung chronischer Wunden ist nach wie vor uneinheitlich. Ist die Therapie auf die Identifikation und Beseitigung der zu Grunde liegenden Erkrankung, wie der arteriellen und/oder venösen Perfusionsstörung, dem Diabetes mellitus oder dem posttrombotischen Syndrom ausgerichtet, ist die lokale Therapie neben verschiedenen occlusiven und semioclusiven Wundaufgaben im Wesentlichen auf das wiederholte chirurgische Debridement ausgerichtet. Als modernes Verfahren erlaubt die niederfrequente Ultraschall-Dissektion (NUD) das schmerzarme Wund-Debridement bei chronischen Wunden. Ziel der vorliegenden Studie ist es, die Wertigkeit der Methode in der ambulanten Therapie chronischer Wunden zu beurteilen.

Methodik: Prospektive monozentrische Studie an 40 konsekutiven ambulanten Patienten mit mindestens einer chronischen Wunde der unteren Extremität. NUD über 10 Wochen einmal wöchentlich bei zweitägigem standardisiertem Verbandswechsel.

Ergebnisse: In die derzeit laufende Studie wurden seit April 2004 einundzwanzig Patienten eingeschlossen. M/W = 11/10, Durchschnittsalter 62 bzw. 65 Jahren vergleichbar. Anamnesedauer bei Erstvorstellung 96 Monate (5–418). Ätiologie 8 \times venös, 5 \times diabetisch, 3 \times arteriell, 5 \times sonstige. Bis Studieneinschluss waren 12 Patienten im Vorfeld mindestens einmal chirurgisch wunddebridiert. Nach Protokoll behandelt wurden 18 Patienten, drei Patienten wurden nach Studieneinschluss ausgeschlossen (einmal bei positivem Tumornachweis, zweimal Patientenwunsch). 18 von 21 Patienten konnten vollständig ausgewertet werden. Nur ein Patient musste auf Grund lokaler Komplikationen zweimalig intermittierend stationär aufgenommen werden. Innerhalb der Behandlungsdauer konnten drei Patienten zur Abheilung gebracht werden. Bei 12 Patienten waren die Wundverhältnisse deutlich gebessert, so dass entweder die spontane Abheilung oder die kurzfristige Spalthautdeckung angestrebt werden konnte. In keinem Fall der ambulanten Behandlung erfolgte die begleitende antibiotische Therapie.

Schlussfolgerung: Die ambulante NUD ist eine schnelle, kostengünstige und für den Patienten sichere Therapieoption in der Behandlung chronischer Wunden im unteren Extremitätenbereich. Begleitend zur Therapie der ursächlichen Erkrankung ermöglicht der Sonoca 180 die umfassende Wundtoilettage. Das Ultraschalldebridement kann als ambulante Maßnahme wiederholte stationäre Aufenthalte für chirurgische Wunddebridements ersetzen. Evidenzbasierte Daten hierzu stehen bisher aus. Prospektive, multizentrische Untersuchungen müssen folgen.

V 37-4

Manganese superoxide dismutase overexpression significantly enhances the contractile activity of a human dermal fibroblast cell line in the free floating collagen lattices

Überexpression der Mangan-Superoxid-Dismutase erhöht das Kontraktionsvermögen von humanen dermalen Fibroblasten im Kollagengel

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Manganese superoxide dismutase (MnSOD) is located in mitochondria and represents the first line of antioxidative defense against superoxide radicals produced as byproduct of oxidative phosphorylation and during tissue repair. In fact, MnSOD expression is induced during cutaneous wound healing. Superoxide anions are dismutated by MnSOD to hydrogen peroxide, which is subsequently detoxified by catalase and glutathione peroxidase. Strong individual differences in the spontaneous activity and inducibility of MnSOD have been suggested to confer differences in the individual susceptibility for skin aging and wound healing disturbances. Fibroblasts stably overexpressing MnSOD with defined capacity for the removal of superoxide anions and concomitant accumulation of hydrogen peroxide were generated as tools (1) to evaluate the role of increased MnSOD activities in term of fibroblast interaction and organization of its surrounding extracellular matrix and (2) to further dissect the role of distinct reactive oxygen species overproduced at defined subcellular sites in growth factor release and signaling mechanisms underlying collagen lattice contraction. A stably transfected cell clone with an 4.6-fold overexpression of MnSOD and vector transfected control cells were seeded into a collagen lattice and contraction was monitored over time as a model for wound contraction. A time-dependently enhanced contraction of collagen lattices was observed in MnSOD overexpressing fibroblasts compared to control cells. Using a specific ELISA for Transforming Growth Factor β 1 (TGF β 1), we found significantly higher TGF β 1 concentrations in supernatants of collagen lattices with stably MnSOD overexpressing fibroblasts compared to control cells. Exogenous application of recombinant TGF β 1 resulted in an enhanced contraction of lattices populated with control cells, while preliminary data show that neutralizing antibodies against TGF β 1 could partly decrease contraction of collagen lattices seeded either with control cells or MnSOD overexpressing cells. Collectively, our data provide evidence that MnSOD overexpression in human dermal fibroblasts with H₂O₂ accumulation leads to an enhanced release of TGF β 1 which subsequently may at least in part be responsible for the increased contraction of collagen

lattices. These results will help to better understand the role of antioxidant enzymes in wound healing and may provide therapeutic approaches to balance antioxidant deficiencies in pathological states of tissue repair.

Die Mangan-Superoxid-Dismutase (MnSOD) ist mitochondrial lokalisiert und spielt als antioxidatives Enzym eine entscheidende Rolle beim Abbau von Superoxidanionen, die als Nebenprodukte bei der oxidativen Phosphorylierung und während der entzündlichen Phase der Wundheilung auftreten. Während der Wundheilung kommt es zur Induktion der MnSOD-Expression. Durch die MnSOD werden Superoxidanionen zu Wasserstoffperoxid dismutiert, welches dann durch die Katalase und die Glutathionperoxidase weiter entgiftet wird. Individuelle Unterschiede in der Spontanaktivität und der Induzierbarkeit der MnSOD werden als prädisponierende Faktoren für Hautalterung und Wundheilungsstörungen vermutet. Wir haben eine humane dermale Fibroblastenzelllinie mit stabiler MnSOD-Überexpression, gesteigertem Abbau von Superoxidanionen und entsprechender Anreicherung von Wasserstoffperoxid generiert, um (1) die Bedeutung erhöhter MnSOD-Aktivität bei der Zell-Zellinteraktion und bei der Organisation der umgebenden extrazellulären Matrix und (2) um die Bedeutung von bestimmten reaktiven Sauerstoffspezies in definierten subzellulären Kompartimenten bei der Freisetzung von Wachstumsfaktoren und Signalmechanismen im Rahmen von Wundkontraktion zu untersuchen. Ein stabil transfizierter Fibroblastenzellklon mit einer 4.6-fachen Überexpression der MnSOD und vektortransfizierte Kontrollfibroblasten wurden in ein Kollagengel aus Kollagen I eingesät. Die Kontraktion der Kollagengele dient als Modell für die Wundkontraktion und wurde zu verschiedenen Zeitpunkten gemessen. Hierbei zeigte sich eine verstärkte Kontraktion der Kollagengele mit MnSOD überexprimierenden Fibroblasten – im Vergleich zu Kollagengelen mit Kontrollzellen. Mit Hilfe eines für TGF β 1 spezifischen ELISAs fanden wir signifikant höhere TGF β 1 Konzentrationen in den Überständen der Kollagengele mit MnSOD-Überexpression – im Vergleich zu Überständen von Gelen mit Kontrollzellen. Exogene Zufuhr von rekombinantem TGF β 1 führte zu einer gesteigerten Kontraktion, während neutralisierende Antikörper gegen TGF β 1 zumindest teilweise die Gelkontraktion vermindern. Zusammenfassend lässt sich sagen, dass die MnSOD-Überexpression in humanen dermalen Fibroblasten mit entsprechender Anreicherung von H₂O₂ zu einer verstärkten Sekretion von TGF β 1 führt, welches anschließend, zumindest teilweise, für die gesteigerte Kontraktion der Gele verantwortlich sein könnte. Diese Ergebnisse werden dazu beitragen, die Bedeutung antioxidativer Enzyme bei der Wundheilung besser zu verstehen und könnten therapeutische Ansätze mit sich bringen, deren Ziel es wäre, das antioxidative Gleichgewicht in pathologischen Wunden wiederherzustellen.

V 37-5

Water-filtered Infrared A (wIRA) for the improvement of wound healing in acute and chronic wounds**Wassergefiltertes Infrarot A (wIRA) zur Verbesserung der Wundheilung bei akuten und chronischen Wunden**

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Introduction: Aim of this review is to summarize some clinical studies – mostly prospective, randomised, controlled studies – concerning water-filtered infrared A (wIRA) for the improvement of wound healing in acute and chronic wounds. Wound healing and infection defense (e. g. granulocyte function) depend on a sufficient energy supply (and on sufficient oxygen) quite decisively. Water-filtered infrared A (wIRA) as special form of heat radiation with a high penetration ability into the tissue and with a low thermal burden to the surface of the skin is able to improve three energetically meaningful factors of wound healing – oxygen partial pressure, tissue temperature and tissue blood flow – by thermal and non-thermal effects on the uncovered wound (wIRA radiator in 25 cm distance).

Methods and results: A prospective, randomised, controlled study with $n = 20 + 20 = 40$ patients with chronic venous lower leg ulcers showed with additional irradiation three times a week 30 minutes with visible light (VIS) and wIRA during maximal 6 weeks a significantly and relevantly more rapid wound healing (18 vs. 42 days till complete wound closure) as well as a significantly and relevantly lower consumption of analgesics. Another prospective study with $n = 10$ patients with effortful thermographic follow-up showed a complete healing of before therapy refractory lower leg ulcers in 7 and an ulcer reduction in 2 of 10 patients, a clear reduction of pain (e.g. from 15 to 0 pain tablets per day), and a normalization of the thermographic image (before the beginning of the therapy typically hyperthermic border of the ulcer with relative hypothermic ulcer floor). Another prospective, randomised, controlled study with $n = 21 + 24 = 45$ severely burned children in a child surgical department showed advantages of wIRA (VIS + wIRA vs. VIS). Another prospective, randomised, controlled study with $n = 46 + 48 = 94$ patients of a surgical university hospital showed, after abdominal surgery, with 20 minutes irradiation twice a day a significant and relevant pain reduction combined with decreased consumption of analgesics, improved wound healing, in 2 cm of tissue depth an increase of the tissue temperature (2.7 degrees centigrade) and of the oxygen partial pressure (30 %) and a trend to a lower rate of wound healing disturbances (VIS+wIRA vs. VIS).

Discussion: wIRA can decrease pain considerably and accelerate the wound healing or improve a stagnating wound healing both in acute wounds – even without a disturbance of wound healing – and in chronic wounds problem wounds including infected wounds.

Einleitung: Ziel dieser Übersichtsarbeit ist, einige – hauptsächlich prospektive, randomisierte, kontrollierte – klinische Studien hinsichtlich wassergefiltertem Infrarot A (wIRA) zur Verbesserung der Wundheilung bei akuten und chronischen Wunden zusammenfassend darzustellen. Wundheilung und Infektabwehr (z. B. Granulozytenfunktion einschließlich antibakterieller Sauerstoffradikalenbildung) hängen ganz entscheidend von einer ausreichenden Energieversorgung (und von ausreichend Sauerstoff) ab. wIRA als spezielle Form der Wärmestrahlung mit hohem Penetrationsvermögen ins Gewebe bei geringer thermischer Oberflächenbelastung vermag über thermische und nicht-thermische Effekte drei energetisch bedeutsame Faktoren der Wundheilung – Sauerstoffpartialdruck im Gewebe, Gewebetemperatur und Gewebedurchblutung – meßtechnisch belegt zu verbessern. wIRA ist ein kontaktfreies, verbrauchsmaterialfreies, leicht anzuwendendes Verfahren mit guter Tiefenwirkung, das der Sonnenwärmestrahlung auf der Erdoberfläche in gemäßigten Klimazonen nachempfunden ist. Die Bestrahlung der unbedeckten Wunde erfolgt typischerweise aus ca. 25 cm Abstand mit einem wIRA-Strahler.

Methoden und Ergebnis: Eine prospektive, randomisierte, kontrollierte Studie mit $n = 20 + 20 = 40$ Patienten mit chronischen venösen Unterschenkelulzera ergab bei zusätzlich dreimal wöchentlich 30 Minuten Bestrahlung mit sichtbarem Licht (VIS) und wIRA über maximal 6 Wochen eine signifikant und relevant schnellere Wundheilung (18 vs. 42 Tage bis zum kompletten Wundschluß) sowie einen signifikant und relevant geringeren Schmerzmittelverbrauch. Eine weitere prospektive Studie mit $n=10$ Patienten mit aufwendiger thermographischer Verlaufskontrolle ergab eine vollständige Abheilung vorher therapieresistenter Unterschenkelulzera bei 7 sowie eine Ulkusverkleinerung bei 2 der 10 Patienten, eine deutliche Minderung der Schmerzen (von z. B. 15 auf 0 Schmerztabletten täglich), eine Normalisierung des thermographischen Bildes (vor Therapiebeginn typischerweise hyperthermer Ulkusrandwall mit relativ hypothermem Ulkusgrund) sowie im Einzelfall bei einem Vergleich deutliche Unterschiede zugunsten von wIRA. Eine weitere prospektive, randomisierte, kontrollierte Studie mit $n = 21 + 24 = 45$ schwerbrandverletzten Kindern in einer kinderchirurgischen Abteilung ergab eine etwas schnellere Reduktion der Wundareale, eine etwas bessere Wundbeurteilung durch den Arzt (visuelle Analogskala) sowie einen tendenziell kürzeren Krankenhausaufenthalt (VIS+wIRA vs. VIS). Eine weitere prospektive, randomisierte, kontrollierte Studie mit $n = 46 + 48 = 94$ Patienten einer chirurgischen Universitätsklinik zeigte nach abdominalen Operationen mit täglich zweimal 20 Minuten Bestrahlung eine signifikante und relevante Schmerzreduktion bei deutlich vermindertem Schmerzmittelverbrauch, eine verbesserte Wundheilung, in 2 cm Gewebetiefe einen Anstieg der Gewebetemperatur um 2,7 °C und des Sauerstoffpartialdrucks um ca. 30 % sowie tendenziell weniger Wundheilungsstörungen (VIS+wIRA vs. VIS). Weitere vergleichbare Erfahrungen bei venösen sowie bei gemischt arteriell-venösen Unterschenkelulzera sowie Dekubitalulzera.

Diskussion: wIRA kann bei akuten Wunden – auch ohne Wundheilungsstörung – sowie bei chronischen Wunden und Problemwunden einschließlich infizierter Wunden Schmerzen deutlich mindern (mit eindrucksvoller Abnahme des Schmerzmittelverbrauchs) und die Wundheilung beschleunigen oder bei stagnierender Wundheilung verbessern. Bei chronischen Wunden werden zuvor nicht erreichte Abheilungen erreicht.

V 37-6

Biological alternatives in patients with ischemic diabetic foot lesions – a new strategy for treating infections with multiresistant bacteria

Biologische Implantatalternativen beim ischämisch-diabetischen Fußsyndrom – ein neues Behandlungskonzept bei Infektionen mit multiresistenten Keimen

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According to the CORA-study the estimated percentage of diabetic patients will increase immensely during the next years. In spite of the proclamation of the St. Vincent-declaration the total amount of arteriosclerotic - induced gangrene resulting in amputation will rise, especially in cases with infections by multiresistant bacteria. Previous arterial reconstructions, aortocoronary vein bypasses, chronic venous insufficiency and av-fistulas cause a lack of sufficient autologous bypass materials. The human umbilical cord vein is a relatively infect-resistant and long-living biological

alternative with a patency rate comparable to the saphenous vein in crural and pedal reconstructions. Because of its ability to modulate the flow velocity it can be used successfully in mediasclerotic vessels as well as in arterial reconstructions with poor run-off. The human umbilical cord vein will gain an important role in the treatment of ischemic diabetic lesions. Cases considered in this paper show a follow-up to maximal nine years.

Aufgrund der Voraussagen der CORA-Studie muss in den nächsten Jahren mit einem erheblichen Zuwachs an Diabetikern in Deutschland gerechnet werden. Die Rate der AVK-assoziierten Amputationen konnte in dieser Gruppe trotz St. Vincent-Deklaration nicht reduziert werden, statt dessen steigt der Anteil an Patienten mit ischämisch-diabetischen Fußläsionen stetig an. Aufgrund des Verbrauchs von autologen Venen (vorhergehende arterielle Reconstruktionen, CVI, Shuntanlagen, ACVB) fehlt bei diesen Patienten zunehmend Venenmaterial für crurale und pedale arterielle Reconstruktionen. Die humane Nabelschnurvene stellt eine relativ infektresistente und langlebige biologische Alternative dar, die die Amputationsrate in diesem Patientengut erheblich reduzieren hilft. Aufgrund der duplexsonographisch nachweisbaren Modulationsfähigkeit ihres Flowprofils kann sie auch bei mediasklerotischen Gefäßstrecken und hohem peripherem Ausstromwiderstand verwendet werden. Sie ist zu einem wichtigen Bestandteil in der auf Diabetiker spezialisierten Gefäßchirurgie geworden und in ihren Ergebnissen dem autologen Venenmaterial gleichwertig. Die vorliegende Fallsammlung umfasst einen Zeitraum von bis zu 9 Jahren Verlaufsbeobachtung.

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V 38

Wound infection and wound cleansing I
Wundinfektion und Wundreinigung I

V 38-1

The development of infection criteria for six wound types using a delphi approach

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The development of criteria for wound infection has not kept

pace with other advances in wound care management. Historically, the criteria suggested by Celsus (30BC-45AD) still remain in use although more recently these have been superseded by additional and more subtle criteria suggested by Cutting & Harding (1994). It is now considered that infection criteria vary by indication (Cutting & White 2005) and this notion has been adopted to generate infection criteria specific to 6 wound types including; acute/surgical, arterial ulcers, burns, diabetic foot ulcers, pressure ulcers and venous leg ulcers. An international, multi-professional expert panel of 54 members was constructed. These members were divided according to their expertise into 6 specific wound type groups, resulting in 8–10 panel members per group. The objective being to achieve a consensus on infection criteria according to wound type. The process took place over

a number of 'Rounds' where data was refined and modified. The Delphi panel members were not aware whom their co-members were, all communications with the researcher being via email or airmail. The criteria generated through this process were ranked by the panel members and summary statistics were produced (mean, median, and standard deviation). The results obtained by each group included a number of expected criteria e.g. abscess and cellulitis. They also included criteria that gave further clarification of other generally accepted criteria such as friable/bleeding granulation tissue and interestingly included some hitherto rarely considered criteria, phlegmon, crepitation and ecthyma gangrenosum. Tables will be produced indicating the panels' findings for the 6 wound types. The Delphi approach is a well established methodology when seeking a consensus opinion with the advantage in this instance of generating some interesting results. This work should encourage additional debate and discussion particularly when considering clinical features and patient outcome. Following widespread empirical testing, formal validation and production of guidelines should then be undertaken.

(inter-quartile range) of 25 (17-40) Vs 12 (4-20) visits per year, $p < 0.001$). Importantly however, exclusion of diabetic patients and analysis of the proportion of visits on which patients received antibiotics did not affect the significance of the difference in antibiotic consumption.

Discussion: These data demonstrate the strong association between occurrence of chronic wounds and prescribing of antibiotics in primary care. Furthermore, wide variation in the type and duration of antibiotic therapy used in the treatment of these wounds has been demonstrated. The implications of this prescribing on antibiotic resistance prevalence have not previously been elicited. This is despite the fact that many risk factors elsewhere associated with antibiotic resistance occur in this population, including long duration antibiotic courses and use of certain antibiotics e.g. ciprofloxacin. Patients with chronic wounds are, however, also likely to be exposed to many of the non-prescribing risk factors e.g. previous hospitalisation and nursing home residency. Further work should be undertaken to identify those factors that impact on the prevalence of resistance in this specific population of patients.

V 38-2

Antibiotic prescribing for chronic skin wounds in the non-specialist, primary care setting in the UK; a potential association with antibiotic resistance?

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Aim: To characterise antibiotic prescribing for patients with chronic skin wounds in the primary care (non-specialist) setting in the UK, and to discuss the potential impact of this prescribing on the prevalence of antibiotic resistance.

Methods: Data were extracted from a large primary care database of 185,000 patients. Patients with chronic wounds were identified using the appropriate medical codes ($n=400$) and compared with randomly selected, age, sex and general practice matched control patients ($n=1600$). Chronic wounds of all aetiologies were investigated, including leg ulcers, diabetic foot ulcers, pressure ulcers and non-specified skin ulcers.

Results: Patients with chronic wounds received a significantly greater number of antibiotic courses than non-wound patients ($p < 0.001$). This increased level of prescribing was evident for flucloxacillin, co-amoxiclav, cefaclor, cefalexin, erythromycin, trimethoprim, metronidazole and ciprofloxacin ($p < 0.01$ for all). More than 10 % of the antibiotics prescribed for patients with chronic wounds in single-diagnosis visits were of duration ≥ 8 days. The patients with chronic wounds also had significantly higher prevalence of diabetes (16.5 % Vs 6.6 %, $p < 0.001$) and attended at general practice significantly more frequently than non-wound patients (median

V 38-3

Is saline solution a safe method to clean wounds?

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Aim: The aim of this work was to verify the sterility of isotonic washing solutions used in wound treatment.

Methods: We have evaluated 44 isotonic washing solutions coming from 22 health care centres. From each centre we have collected 2 aleatory samples in current use. Samples were transported at 4 °C and maintained at this temperature until its processing. In microbiological analyses, we spread 0.1 ml of the isotonic washing solutions in blood agar and in Sabouraud Chloramphenicol Agar; we have also incorporated 1 ml of the isotonic washing solutions in PCA. The transfers of the isotonic washing solutions flask were cultivated in Blood Agar. Blood Agar plates were incubated at 37 °C for 48 hours while PCA plates were incubated at 28 °C and 37 °C for 48 hours. Sabouraud Chloramphenicol Agar plates were incubated at 28 °C and 35 °C for 30 days. The identification of the microorganisms isolated was accomplished using commercial biochemical tests (BioMérieux). When the identification of the microorganisms was not possible by this method we have used acid nucleic analysis with the extraction of genomic DNA for 16S rRNA gene sequence determination, Polymerase Chain Reaction (PCR) amplification of the 16S rRNA gene and sequencing of the purified PCR products.

Results: From the 44 isotonic washing solutions analyzed, 54.5 % were contaminated. A total of 34 strains were isolated and 69.6 % of these were Gram-positive cocci, 13% were Gram-positive bacilli, 8.7 % were Gram-negative bacilli and 8.7 % were Fungus strains. The most common bacteria found (64 %) belong to human normal flora.

Conclusions: The contamination of the isotonic washing solutions is due to inadequate clinical practices. These results claim for more strict hygienic measures and the replacement of big flasks by single use bottles.

V 38-4

Wound cleansing for pressure ulcers - a cochrane review

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Introduction: Pressure ulcers are a significant financial burden to health care systems and impact negatively on the individual's quality of life. Wound cleansing is widely regarded to be an important component of pressure ulcer care. Therefore, this systematic review set out to explore the effect of wound cleansing solutions and wound cleansing techniques on the rate of healing of pressure ulcers.

Methods: The Specialised Trials Register of the Cochrane Wounds Group was searched and the bibliographies of all retrieved and relevant publications were also searched for further studies. Drug companies and experts in the wound care field were contacted to identify any further studies. RCTs, reporting an objective measure of pressure ulcer healing and comparing wound cleansing with no wound cleansing, or different wound cleansing solutions or techniques, were considered for the review. Two reviewers conducted data extraction independently. Initially a structured narrative summary of the studies reviewed was conducted. Data were analysed with Cochrane MetaView. For dichotomous outcomes, odds ratio (OR), plus 95 % confidence intervals (CI) were calculated, for continuous outcomes, weighted mean difference (WMD), plus 95 % CI were calculated. Meta analysis was not conducted, owing to the small number of diverse RCTs identified.

Results: Three RCTs were included in the review. No studies compared cleansing with no cleansing. There was a statistically significant change in Pressure Sore Status Tool scores in wounds cleansed with saline spray with aloe vera, silver chloride and decyl glucoside (Vulnopur) and those cleansed with isotonic saline ($p=0.025$). There was no statistically significant change in pressure ulcer healing in ulcers cleansed with whirlpool versus no whirlpool (OR 3.64, 95 % CI 0.98, 13.52). There was no statistically significant change in pressure ulcer healing in ulcers cleansed with water versus those cleansed with saline (OR 5.00, 95 % CI 0.17, 146.64).

Conclusions: This review identified a lack of high quality evidence available regarding cleansing of pressure ulcers. Three studies were located and only one of these studies noted a statistically significant improvement in pressure ulcer healing. Therefore, use of any wound cleansing solution or technique for the cleansing of pressure ulcers is not based on good trial evidence.

V 38-5

Patient management peculiarities in cases of anaerobic nonclostridial infection of soft tissues

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Introduction: Anaerobic nonclostridial infections (ANI) are caused by nonsporulating anaerobes (NA) and their associations with aerobes. The problem of diagnostics and surgical approach to ANI is essential because of wide-spread purulent surgical diseases, caused by NA. ANI usually has an endogenous origin. In clinical practice most important are: -gram-negative bacilli (bacteroids, fusobacteries); -gram-positive bacilli (bifidobacteries, eubacteries and others); gram-positive cocci (*Peptococcus*, *Peptostreptococcus*). The diagnostics of ANI was mainly based on the clinical data and was confirmed by bacteriological investigation. The results of bacteriological investigation were usually prepared in 5-7 days i. e. after the operation had been done. Characteristic clinical picture of the disease helped to diagnose it and start the adequate therapy before the bacteriological studies had been completed. 200 patients suffering from various purulent diseases caused were examined.

Results: Clinically an inflammatory process in soft tissues ran as phlegmoyon and could be localized in the subcutaneous fat, fascia and muscles. The age of the patients varied from 18 to 89. The aim of the work was to gather information about forms of ANI, the character of the wound discharge, the location of the focus of infection, the tendency of the purulent process to form a great number of cavities and fistules, diseases associated with ANI, surgical procedures and complications.

Conclusions: -90 % of patients had cellulofascio-myositis; - ANI was characterized by a peculiar clinical picture permitting correctly diagnose it and start adequate treatment before laboratory confirmation of the diagnosis; -an operative intervention should be carried out when the surgeon first suspects the anaerobic infection; - extensive dissection of all involved tissues; - proper antibacterial therapy - postoperative management should include: a) wounds treated without dressings; b) using of the open drainage.

V 38-6

Amplification of antimicrobial action by low-frequency ultrasonics**Wirkungsverstärkung antimikrobieller Substanzen durch niederfrequenten Ultraschall in vitro**C. Schulze¹, K. Breuing², S. Oesser³¹Klinikum Elmshorn, Abt. für Allgemein-, Viszeral-, Gefäß- und Unfallchirurgie, Elmshorn, Germany²Harvard Medical School, Div. of Plastic Surgery, Brigham and Women's Hospital, Boston, MA, United States of America³CRI Collagen Research Institute Kiel, Kiel, Germany

Aim: Infected chronic wounds frequently require systemic antimicrobial treatment. At the same time wound debridement is applied in order to off-load the focus of infection from necrosis and adherent bacteria. The process of Debridement itself - if performed using low-frequency ultrasonics - can contain antimicrobial properties. In this context a synergistic action of both strategies - antimicrobial and ultrasound therapy - seems very likely.

Methods: Bacterial inoculates of 10E7CFU (colony forming units) *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* oder *Streptococcus pyogenes* are incubated 4h in 10ml standard broth at 37 °C. The tenfold MIC (minimum inhibitory concentration) of either Ciprofloxacin, Cefotaxime or Tobramycin is then added to the incubates and placed at 37 °C for another 30min. Ultrasonic exposition (25 kHz, 18 W) takes place using a ball-shaped sonotrode for 0 (controls), 12 or 120 s (6 × 20 s intermittent treatment with 5 × 20 s rest). During insonification the samples are placed in an icebath (temperature inside the sample at 37 ± 4 °C). Colony counts at the onset and after bacterial reduction are estimated plating tenfold serial dilutions.

Results: Ultrasound alone exhibits antibacterial activity at sufficient exposition time of 120 s only. In contrast a short insonification of 12 s in combination to Tobramycin and Ciprofloxacin but not Cefotaxime is significantly more active than either substance alone. The highest bacterial killing rates are detected when an extended ultrasonic exposition of 120 s is combined to one of the three agents. In comparison to each antimicrobial substance alone ultrasound amplifies bacterial reduction by a factor of 57 (Tobramycin), 50 (Ciprofloxacin) and 42 (Cefotaxime) (all *E. coli*).

Discussion: A Synergism in bacterial reduction of ultrasonics and antimicrobials has not been discussed but for aminoglycosides. The data presented here depicts a significant amplification of antimicrobial activity in case of a chinolone and to a lesser extent a cephalosporine which are substances of particular clinical relevance. In wound infections with underlying impaired microcirculation and thus reduced antimicrobial availability in the wounded local ultrasonic treatment within the inflammatory focus could close a therapeutic gap. An improved penetration of the agents into bacterial cells but also a synergistic effect on cell-wall stability may count for the observed antibacterial boost.

Ziel: Verzögert heilende Wunden müssen bei Exazerbation eines Wundinfektes systemisch antimikrobiell behandelt werden. In vielen Fällen ist wie etwa beim diabetischen Fußsyndrom gleichzeitig ein lokales Wunddebridement erforderlich. Dieses Debridement kann, wenn es mit niederfrequentem Ultraschall ausgeführt wird, selbst antibakterielle Eigenschaften aufweisen. Für verschiedene Ultraschallfrequenzen wurden bereits Synergieeffekte mit Wirkstoffen der Aminoglykosidfamilie beschrieben. Mit der vorliegenden Untersuchung sollten im Modell Kombinationen aus antimikrobieller Therapie und niederfrequenter Ultraschallbehandlung auf mögliche therapeutische Vorteile hin untersucht werden.

Methoden: Bakterielle Inokulate von 10E7CFU *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* oder *Streptococcus pyogenes* werden in je 10ml Bouillon für 4h bei 37°C inkubiert. Anschließend wird die auf jeden einzelnen Bakterienstamm bezogene zehnfache minimale Hemmkonzentration der Antibiotika Ciprofloxacin, Cefotaxim und Tobramycin zugesetzt und wiederum 30 min inkubiert. Eine Ultraschallexposition erfolgt bei 25 kHz und ca.18 W für 0, 12 oder 120 s (6x20 s Ultraschall mit intermittierenden 5x20s Pause) im Eisbad bei 37 ± 4°C. Die Anzahl koloniebildender Einheiten (KBE) wird vor und nach Keimreduktion durch Anlage einer Verdünnungsreihe bestimmt. **Ergebnisse:** Ultraschall allein führt erst bei einer Expositionszeit von 120s zu einer relevanten Keimreduktion gegenüber der Ausgangskeimzahl. Bereits eine 12 s kurze Ultraschalleinwirkung führt bei Inkubation mit Ciprofloxacin und Tobramycin, nicht jedoch Cefotaxim zu einer Keimreduktion, die signifikant über der Wirkung des Antibiotikums allein liegt. Eine kombinierte Anwendung der mit 120 s längeren Ultraschallexposition plus Inkubation mit einem der drei antimikrobiellen Wirkstoffe zeigt für alle Keimspezies die effektivste Keimeliminierung. Die antibakterielle Wirkung wird z.B. für *E.coli* und Tobramycin um Faktor 57, Ciprofloxacin Faktor 50 und Cefotaxim Faktor 42 gegenüber dem alleinigen Wirkstoff gesteigert.

Diskussion: Während für Aminoglykoside ein Synergismus mit Ultraschallapplikation bereits beschrieben wurde, ist eine Wirkungsverstärkung der praktisch relevanteren Substanzen Cefotaxim und Ciprofloxacin als Vertreter verbreiteter Stoffgruppen insbesondere in Kombination mit dem in der Wundbehandlung eingesetzten niederfrequenten Ultraschall bislang nicht beschrieben. Die beobachtete Wirkungsverstärkung erhält aus der Tatsache besondere Bedeutung, dass im Wundbett mit erniedrigten Wirkspiegeln antimikrobieller Wirkstoffe gerechnet werden muß. Eine lokale Applikation von Ultraschall im eigentlichen Infektfokus könnte unter derart erschwerten Bedingungen therapeutisch wertvoll sein. Als Mechanismus der beobachteten Synergieeffekte kommt neben einer verbesserten Bakterienzellenpenetration auch eine vermehrte Verletzbarkeit der Bakterienzellwände in Frage.