Wound Care Research Review™

Making Education Easy

Issue 4 - 2012

In this issue:

Abbreviations in this issue:

b-FGF = basic fibroblast growth factor
IL = interleukin
NIR = near-infrared
NPWT = negative pressure wound therapy
PU = pressure ulcer
TNF = tumour necrosis factor
VAS = visual analogue score

Welcome to the fourth issue of Wound Care Research Review.

Quality of life is an important measure in wound care, and in this issue we look at an article addressing the ramifications of negative pressure wound therapy on social life. Also included is an assessment of laser irradiation use in debriding biofilm, several novel approaches to diabetic foot ulcers, and a review of a 3-year training program in China that is helping Chinese medical professionals efficiently manage chronic wounds.

If you have colleagues or friends within Australia who would like to receive our publication, send us their contact email and we will include them in the next issue. We hope you find the selections for this issue interesting, and we look forward to receiving your comments and feedback.

Kind Regards,

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Topical morphine gel in the treatment of painful leg ulcers, a double-blind, placebo-controlled clinical trial: a pilot study

Authors: Bastami S, et al.

Summary: The aim of this study was to evaluate the analgesic effect of topically applied morphine on chronic painful leg ulcers. Twenty-one patients were assigned to receive either morphine or placebo in a randomised, placebo-controlled, crossover pilot study. Each patient was treated four times in total. Pain was measured by the visual analogue score (VAS) before application of gel, directly after and after 2, 6, 12 and 24 hours. Although an overall, clinically relevant, reduction of pain was observed upon treatment with morphine, the difference was not statistically significant. Morphine reduced pain scores more than placebo on treatment occasions 1 and 2. The difference was statistically significant only 2 hours after dressing on the first treatment occasion.

Comment: There's a growing awareness of the impact of other aspects of leg ulcers upon the quality of life of the patient. Issues such as pain and odour control are increasingly in the literature. This study failed to show a significant difference in pain following topical morphine application; only reaching statistical significance 2 hours after the first dressing. The researchers may not have allowed enough time for the morphine to be absorbed and have an effect locally. Removal of a dressing is often the most painful part – it's difficult to see how topical treatments could be effective for this phase of dressing.

Reference: Int Wound J. 2012 Aug;9(4):419-27.
http://onlinelibrary.wiley.com/doi/10.1111/j.1742-481X.2011.00901.x/abstract

Laser irradiation effect on *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms isolated from venous leg ulcer

Authors: Baffoni M, et al.

Summary: This study aimed to investigate the laser action as a possible biofilm eradicating strategy, in order to attempt an additional treatment to antibiotic therapy to improve wound healing. In this work, the effect of near-infrared (NIR) laser was evaluated on mono and polymicrobial biofilms produced by two pathogenic bacterial strains, *Staphylococcus aureus* PECHA10 and *Pseudomonas aeruginosa* PECHA9, both isolated from a chronic venous leg ulcer. Laser effect was assessed by biomass measurement, colony forming unit count and cell viability assay. It was shown that the laser treatment had not affected the biofilms biomass neither the cell viability, although a small disruptive action was observed in the structure of all biofilms tested. A reduction on cell growth was observed in S. aureus and in polymicrobial biofilms.

Comment: Biofilms are one of the 'topics du jour' in wound healing. They're a little like possums (protected in Australia, a pest in New Zealand) – some clinicians want them eradicated and some want them protected. Like possums, they are tenacious and don't like moving once established. Their removal may cause damage to underlying tissue, and provide the opportunity for the entry of more pathological species. This in vitro study is an attempt to laser debride the biofilm without damage to underlying tissue. Near-infrared laser, in this study, was ineffective against the mass or viability of the biofilm.

Reference: Int Wound J. 2012 Oct;9(5):517-24.
http://onlinelibrary.wiley.com/doi/10.1111/j.1742-481X.2011.00910.x/abstract

A prospective pilot study of ultrasound therapy effectiveness in refractory venous leg ulcers

Authors: Escandon J, et al.

Summary: This open labelled pilot study of 10 refractory venous ulcers of large size aimed to determine the effect of non-contact ultrasound on wound closure, bacterial counts, expression of inflammatory cytokines and pain reduction. A control group was not used, instead the authors compared the baseline and end of treatment assessments and noted the differences. They found a significant reduction in wound area (P=0.0039) over the 4-week treatment period. They also found a decline in individual and total bacterial counts; however, these differences were not significant. For all patients, there was also a trend toward reduced inflammatory cytokine expression compared with baseline levels; however, this reduction did not reach statistical significance. There was a correlation between healing and change in cytokine expression, which showed statistical significance for tumour necrosis factor (TNF)-α P=0.0395, IL-1a P=0.0351, IL-6 P=0.0508, IL-8 P=0.0990. Pain as measured by the VAS was reduced from 4 at the baseline to 2.7 by the end of the study.

Comment: To truly be able to draw a conclusion from this study a control group is needed, where all treatments are exactly the same other than the use of ultrasound. We have no way of knowing if ultrasound contributed to the results these patients achieved or not from the data presented. The title of the manuscript calls this a pilot study, and that is appropriate. Pilot studies are akin to 'proof of concept' studies. Results obtained from them inform the methodology of subsequent, full scale studies and we would hope to see such a study in the near future published by the same authors.

Reference: Int Wound J. 2012 Oct;9(5):570-8.
http://onlinelibrary.wiley.com/doi/10.1111/j.1742-481X.2011.00921.x/abstract

Phase IIa randomised, placebo-controlled study of antimicrobial photodynamic therapy in bacterially colonised, chronic leg ulcers and diabetic foot ulcers. A new approach to antimicrobial therapy

Authors: Morley S, et al.

Summary: Sixteen patients with chronic leg ulcers and 16 patients with diabetic foot ulcers (each 8 active treatment/8 placebo) were recruited into a blinded, randomised, placebo-controlled, single treatment, phase IIa trial. All patients had ulcer duration >3 months, bacterially colonised with $>10^4$ cfu/ml. After quantitatively assessing pre-treatment bacterial load via swabbing, phenothiazin-5-ium bromide or placebo was applied topically to wounds for 15 minutes, followed immediately by 50 J/cm^2 of red light and the wound again sampled for quantitative microbiology. Wound area was measured for up to 3 months following treatment. Treatment was well tolerated with no reports of pain or other safety issues. In contrast to placebo, patients on active treatment showed a reduction in bacterial load immediately post-treatment ($p<0.001$). After 3 months, 50% (4 of 8) of actively treated chronic leg ulcer patients showed complete healing, compared to 12.5% (1 of 8) placebo patients.

Comment: Same problem, different approach. Here the investigators are using photodynamic therapy in an attempt to decrease the bacterial burden. That they do so with their therapy is evident from the results comparing bacterial burden pre- and post-treatment. Translating that into improved wound healing is not as secure a statement, given the small numbers of patients being treated here. Again, the fundamental issue is how to get rid of bacteria, and sustain that clean environment, to allow the body's natural healing processes to take over. All of this to be done without impairing natural healing or damaging the underlying patient tissues.

Reference: Br J Dermatol. 2012 Oct 15.
http://onlinelibrary.wiley.com/doi/10.1111/bjd.12098/abstract

NorLeu3-A(1-7) stimulation of diabetic foot ulcer healing: results of a randomized, parallel-group, double-blind, placebo-controlled phase 2 clinical trial

Authors: Balingit PP, et al.

Summary: This randomised, double-blind, placebo-controlled phase II clinical trial explored NorLeu(3)-A(1-7) (DSC127) safety and healing efficacy in diabetic foot ulcers. Patients with chronic, non-infected, neuropathic, or neuroischemic plantar Wagner Grade 1 or 2 foot ulcers (n=172) were screened for non-healing. Subjects were randomised to receive 4 weeks' once-daily topical treatment with 0.03% DSC127 (n=26), 0.01% DSC127 (n=27), or placebo (n=24), followed by 20 weeks' standard of care. Dose-response curves for DSC127 effect on percent of area reduction from baseline at Week 12 (40% placebo; 67% 0.01% DSC127; 80% 0.03% DSC127) and 24 (23% placebo; 53% 0.01% DSC127; 95% 0.03% DSC127) followed a log-linear pattern for both intent-to-treat and per-protocol populations. Covariate analysis compared reduction in ulcer area, depth, and volume from baseline; reductions in the 0.03% DSC127 group were greater at Weeks 12 and 24. Placebo-treated ulcers healed in a median 22 weeks vs. 8.5 weeks for 0.03% DSC127 ($p = 0.04$).

Comment: This is not the first study looking at this compound. It's an analogue of the angiotensin 1-7, a naturally occurring peptide. It's thought to work by inducing the proliferation of progenitor cells; accelerating vascularisation, collagen deposition, and re-epithelialisation. Other studies have shown promising results in its effectiveness in healing diabetic foot ulcers. Not only did this study show an effect with this medication, it also showed that there is a dose-response. At higher concentrations the medication was more effective, reducing healing times from 22 weeks to 8.5 weeks (for the 0.03% dose group). We await phase three trials with interest.

Reference: Wound Repair Regen. 2012 Jul-Aug;20(4):482-90.
http://onlinelibrary.wiley.com/doi/10.1111/j.1524-475X.2012.00804.x/abstract

Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes – a pilot study

Authors: You HJ, et al.

Summary: The purpose of this clinical trial study was to report preliminary findings of the efficacy and safety of the cultured allogeneic keratinocyte sheets in the treatment of diabetic foot ulcers. Fifty-nine patients with diabetic foot ulcers were randomised to either the keratinocyte treatment group (n=27) or the control group treated with vaseline gauze (n=32). Except for the application of keratinocytes, treatment of study ulcers was identical for patients in both groups. Either keratinocyte sheet or vaseline gauze was applied at the beginning of the study and weekly thereafter for a maximum of 11 weeks. The maximum follow-up period for each patient was 12 weeks. Complete ulcer healing was achieved in 100% of the treatment group and 69% of the control group ($p < 0.05$). The Kaplan-Meier median times to complete closure were 35 and 57 days for the keratinocyte and control groups, respectively.

Comment: This is akin to a skin graft onto a diabetic ulcer, except here a sheet of cultured keratinocytes is applied to the wound, rather than a split skin graft from the patient themselves. This saves the patient from the risk of donor site breakdown. The keratinocyte sheet is also presumably thinner than a skin graft would be, perhaps allowing it to vascularise more readily. The study would have been stronger if the control treatment chosen was the unit's current treatment of diabetic foot ulcers, to give a true comparison against current 'best practice'.

Reference: Wound Repair Regen. 2012 Jul-Aug;20(4):491-9
http://onlinelibrary.wiley.com/doi/10.1111/j.1524-475X.2012.00809.x/abstract

A pilot study exploring quality of life experienced by patients undergoing negative pressure wound therapy as part of their wound care treatment compared to patients receiving standard wound care

Authors: Ousey KJ, et al.

Summary: This preliminary study aimed to explore quality of life experienced by patients undergoing negative pressure wound therapy (NPWT) as part of their wound care treatment in comparison to that of patients with a wound using traditional (standard) wound care therapies. A quasi-experimental study was undertaken, with patients treated in wound care/vascular clinics with chronic/acute wounds. Quality of life impact was measured using the Cardiff Wound Impact Schedule and administered post-consent at timed intervals. Results identified no real differences in quality of life scores recorded by patients over the 12-week period. Although there was no overall interaction between the therapies used for wound healing, NPWT did have an effect on social life: during the first 2 weeks of the application of therapy, patients in the NPWT group reported an increase in the social life domain.

Comment: This is another pilot study, so has many of the same caveats mentioned above. We need to be wary of novel or expensive therapies if they don't offer a significant improvement over what is currently available. It's interesting to note patients had an improved social life if NPWT was used in the first two weeks, and I wonder if this might in part be due to odour control. Data from our paediatric burns unit suggest that NPWT may also decrease wound pain by stabilising the tissues under negative pressure. Perhaps a combination of the two effects is contributing in these patients.

Reference: Int Wound J. 2012 Oct 24.
http://onlinelibrary.wiley.com/doi/10.1111/j.1742-481X.2012.01098.x/abstract

IPARZINE-SKR study: randomized, double-blind clinical trial of a new topical product versus placebo to prevent pressure ulcers

Authors: Verdú J, et al.

Summary: This study compared the efficacy of a new topical agent (IPARZINE-4A-SKR) on preventing category I pressure ulcers (PUs) over a 2-week period, compared with a placebo. Hospital and socio-sanitary centre patients (n=194) at risk of developing a PU (Braden scale) were randomised into two groups. The product was applied on the sacrum, trochanters and heels. Six PUs (6.1%) were detected in the intervention group versus seven (7.4%) in the placebo group. Differences were not statistically significant ($P = 0.94$), relative risk =0.82 (95% confidence interval =0.29–2.36). The main limitation of the study was the sample size and, therefore, the main difficulty encountered was in determining whether the product is ineffective or simply has not been used with sufficient patients.

Comment: This study was either underpowered, in that it did not recruit enough patients to have a reasonable chance of finding a significant difference, or there is no difference to find. Without a power analysis prior to commencement we cannot be sure which is true. Had one been done, and the requisite number of patients recruited, we would have more confidence in surmising that this treatment is ineffective in preventing pressure ulcers. Of the patients in this study, 6.7% developed a pressure ulcer – a significant cost to the institution, patients, and their families.

Reference: Int Wound J. 2012 Oct;9(5):557-65.
http://onlinelibrary.wiley.com/doi/10.1111/j.1742-481X.2011.00918.x/abstract

Establishing an education program for chronic wound care in China

Authors: Yu Y, et al.

Summary: The Chinese Tissue Repair Society (CTRS) has developed a 3-year training program in wound care in China that is sponsored by the World Diabetes Foundation and the Coloplast Access to Healthcare foundation. The project focuses on training physicians and nurses in wound care for patients with diabetic mellitus and other chronic skin wounds. In the past 2 years, 1618 health care professionals, including 915 physicians and 703 nurses, have been trained. Participants are from more than 200 hospitals in 21 provinces. About 1200 patients per month, on average, have benefited from this project. In total, 13 hospitals have become training bases to continue the education program. The aim of the program is to help Chinese medical professionals efficiently manage chronic wounds, thereby shortening the wound healing time, reducing the amputation rate and treatment costs, and improving quality of life.

Comment: I hope we're entering an era where clinicians and industry can work together in a spirit of scientific endeavour without the attached strings that have previously corrupted some of the work done. On occasion both sides of the clinician/industry partnership have had other agendas, and this has led to a mistrust of industry involvement in clinical work and research. Industry is one of the few sources of funds for major programs such as this one. It's difficult to see how it would have got off the ground without sponsorship. As a result there are now 1200 patients a month benefiting from having trained wound care professionals looking after them.

Reference: Int J Low Extrem Wounds. 2012 Dec;11(4):320-324
http://ijl.sagepub.com/content/11/4/320

Quality of pediatric second-degree burn wound scars following the application of basic fibroblast growth factor: results of a randomized, controlled pilot study

Authors: Hayashida K, et al.

Summary: To evaluate the effect of application of basic fibroblast growth factor (b-FGF) on paediatric patients with deep second- degree burn wounds, 20 patients ranging in age from 8 months to 3 years with a total of 30 burn wounds from various causes were allocated either the growth factor (n=15) or an impregnated gauze treatment (n=15). Wounds still exudative after 21 days were covered with a split-thickness skin graft. Five wounds in each group required grafting. Skin/scar colour match was significantly closer to 100% in the treatment than in the control group (P<0.01). Wounds not requiring grafting were no longer exudative after 13.8 (±2.4) and 17.5 (±3.1) days in the treatment (n=10) and control group (n=10), respectively (P<0.01). After 1 year, scar pigmentation, pliability, height, and vascularity were also significantly different (P<0.01) between the groups. Hypertrophic scars developed in 0 of 10 wounds in the treatment and in three of 10 wounds in the control group, and effective contact coefficient, transepidermal water loss, water content, and scar thickness were significantly greater in control group (P<0.01).

Comment: We know that the faster your burn heals, the less likely you are to develop scarring. The majority of burns healed within two weeks will not scar; after that time there is increasing likelihood of scarring with increasing healing times. The two groups here healed on either side of this two week rule of thumb, so it's reasonable to assume this has contributed to the differences seen in scarring. It's tempting to ascribe this difference to the b-FGF but there are too many variables in such a small group to be sure. I certainly agree with the authors that further research is warranted on this treatment.

Reference: Ostomy Wound Manage. 2012 Aug;58(8):32-6.
http://www.o-wm.com/article/quality-pediatric-second-degree-burn-wound-scars-following-application-basic-fibroblast-grow

