Regenerating matrix-based therapy for chronic wound healing: a prospective within-subject pilot study

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ABSTRACT

The aim of this study was to determine whether a skin-specific bioengineered regenerating agent (RGTA) heparan sulphate mimetic (CACIPLIQ20) improves chronic wound healing. The design of this article is a prospective within-subject study. The setting was an urban hospital. Patients were 16 African-American individuals (mean age 42 years) with 22 wounds (mean duration 2·5 years) because of either pressure, diabetic, vascular or burn wounds. Two participants each were lost to follow-up or removed because of poor compliance, resulting in 18 wounds analysed. Sterile gauze was soaked with CACIPLIQ20 saline solution, placed on the wound for 5 min, then removed twice weekly for 4 weeks. Wounds were otherwise treated according to the standard of care. Twenty-two percent of wounds fully healed during the treatment period. Wounds showed a 15·2–18·1% decrease in wound size as measured by the vision engineering research group (VERG) digital wound measurement system and total PUSH scores, respectively, at 4 weeks ($P = 0·014$ and $P = 0·003$). At 8 weeks there was an 18–26% reduction in wound size ($P = 0·04$) in the remaining patients. Wound-related pain measured by the visual analogue pain scale and the wound pain scale declined 60% ($P = 0·024$) and 70% ($P = 0·001$), respectively. Patient and clinician satisfaction remained positive throughout the treatment period. It is concluded that treatment with CACIPLIQ20 significantly improved wound-related pain and may facilitate wound healing. Patient and clinician satisfaction remained high throughout the trial.

Key words: Glycosaminoglycans • Heparan sulphate • Wound healing • Wound pain

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INTRODUCTION

Skin breakdown, be it because of pressure, diabetic or vascular ulcers, is a significant problem worldwide. Despite extensive research, this secondary medical complication has met with unsatisfactory treatment solutions, and continues to pose a medical hazard for persons, decaying health, activity, function, life quality, well-being and longevity (1–3).

Pressure ulcers, in particular, place a significant burden on the individual and society. In a US-based study of pressure ulcer occurrence in the acute hospital setting, prevalence ranged from 14% to 17% (from 1999 to 2002) and

Key Points

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- despite extensive research, this secondary medical complication has met with unsatisfactory treatment solutions, and continues to pose a medical hazard for persons, decaying health, activity, function, life quality, well-being and longevity

Key Points

- this study sought to examine whether a skin specific regenerating therapy (RGTA), which is a bioengineered structural analogue of epithelial heparan sulphate glycosaminoglycan (HS GAG), now commercially available in Europe under the trade name CACIPLIQ20, can restore natural wound healing to chronic non healing wounds when applied topically
- multiple preclinical studies on a variety of wound models including chronic ulcer, acute skin excision, radiation, thermal burn and ischaemic pressure ulcer suggest that these biopolymers may improve the speed and quality of skin repair by stimulating revascularisation
- this study also examined related psychosocial aspects of wounds, including the treatment value of CACIPLIQ20 in the context of patient, caregiver and medical staff satisfaction with the proposed intervention
- hence, the primary aims were to determine whether: (i) application of CACIPLIQ20 improves wound healing, (ii) application of CACIPLIQ20 alleviates wound-related pain and (iii) use of CACIPLIQ20 is perceived positively by patients and clinicians
- the study was based on a prospective within subject design with each participant serving as his or her own control; therefore no control group was used

incidence ranged from 7% to 9% (2000–2004) (4). Similarly, the National Pressure Ulcer Advisory Panel (NPUAP) estimates that pressure ulcer prevalence in US hospitals is 15% with an incidence of 7% (5). Likewise, in a summary guideline of 5947 patients in Belgium, Italy, Portugal, Sweden and the UK produced by the European Pressure Ulcer Advisory Panel (EPUAP) (6), an overall pressure ulcer prevalence of 18.1% was found (7). Populations with even higher incidence and prevalence rates include those receiving palliative care in home hospice (8,9), critical paediatric patients (10) and those with limited mobility (e.g. spinal cord injury) (11,12).

Chronic wounds are a particularly challenging clinical problem which place significant financial burden on the health care system (13) and result in prolonged suffering for the patient. A chronic or non healing wound is defined as one that has not improved significantly in 30 days or has not completely healed by 60 days. Further, the longer a wound remains open, be it acute or chronic, the likelihood of healing and responsiveness to treatment decreases (14). Impaired vascular perfusion because of diabetes mellitus (15), venous hypertension (16) and chronic pressure secondary to immobility (17) are common aetiologic factors in chronic non healing wounds.

This study sought to examine whether a skin-specific regenerating therapy (RGTA), which is a bioengineered structural analogue of epithelial heparan sulphate glycosaminoglycan (HS GAG), now commercially available in Europe under the trade name CACIPLIQ20 (18), can restore natural wound healing to chronic non healing wounds when applied topically. Multiple preclinical studies on a variety of wound models (19) including chronic ulcer (20), acute skin excision (21), radiation (22), thermal burn (23) and ischaemic pressure ulcer (21,24) suggest that these biopolymers may improve the speed and quality of skin repair by stimulating revascularisation. This study also examined related psychosocial aspects of wounds, including the treatment value of CACIPLIQ20 in the context of patient, caregiver and medical staff satisfaction with the proposed intervention. Hence, the primary aims were to determine whether: (i) application of CACIPLIQ20 improves wound healing, (ii) application of CACIPLIQ20 alleviates wound-related pain and (iii) use of CACIPLIQ20 is perceived positively by patients and clinicians.

METHODS

The study was based on a prospective within-subject design with each participant serving as his or her own control; therefore no control group was used. The study was approved by the MedStar Health Institutional Review Board. All study personnel were certified in and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the MedStar IRB. All participants were recruited from the wound care clinics or wound service at either Washington Hospital Center or National Rehabilitation Hospital, both located in Washington, DC. At the time of enrolment, potential participants must have met the following inclusion and exclusion criteria: pressure, diabetic, vascular or burn wound present for at least 6 weeks and free of necrotic tissue; 18 years of age or older; medically stable with physician approval to participate; and Pressure Ulcer Scale for Healing (PUSH) Score of at least 4 at baseline. Exclusion criteria included necrosis, a highly purulent wound, or concomitant treatment with a gold-, silver- or copper-based wound care product.

The treatment protocol involves coating the wound twice weekly with the HS mimetic (CACIPLIQ20), which is composed of a sterile solution of polycarboxymethylglucose sulphate, or PCGMS, in saline. Sterile gauze saturated with CACIPLIQ20 is placed on the wound for 5 min. After 5 min, the CACIPLIQ20-soaked gauze is disposed of and the wound is treated and dressed according to the standard of care. Participants received the intervention twice weekly for up to 4 weeks (eight sessions), unless the wound healed before the eighth treatment. Additionally, patients were asked to return to the clinic once weekly for two post-intervention follow-ups. At the conclusion of the intervention period, several participants requested continuation of treatment if their wound(s) had not healed. An amendment to the protocol was approved by the MedStar IRB and six participants with seven wounds continued extended treatment, ranging from 14 to 20 additional intervention sessions. These sessions were analysed separately.

Main outcome measures

Primary endpoints included quantification of wound healing, wound-related pain and satisfaction with treatment (see Table 1 for a summary of the assessment schedule). Adverse event data were collected at each patient's visit.

Wound size and appearance

Wound size and appearance were measured weekly using the PUSH (Pressure Ulcer Scale for Healing) score and the vision engineering research group (VERG) Videometer Wound Measurement & Documentation digital wound measurement system (VERG VeV MD, VERG Inc. Vision Engineering Research, Winnipeg, Manitoba, Canada). At baseline and every other visit (once per week) study personnel measured length, width and depth of the wound. Exudate amount and tissue type were also monitored, which were all combined in a single PUSH score, per clinical standard of care at the participating institutions.

The PUSH tool is a quick, reliable measure to monitor the change in pressure ulcer status over time in the clinical setting. Since its initial development, the tool has been validated by two multi-site retrospective studies (25,26) and a pilot study conducted by Centers for Medicare and Medicaid services (27). It has also been validated for use in chronic lower extremity vascular and diabetic ulcers (28,29).

The VERG VeV MD digital wound measurement system is a software-based system using automated image recognition based on a mathematical algorithm. An off-the-shelf digital camera is used to take digital images under standardised lighting and distance conditions. A standardised colour and size target orientation card recognisable to the VERG VeV MD software is placed next to the wound before the image is taken. The centre of the target plate card is labelled with the date, participant and wound ID, and session number. Images are downloaded to a laptop computer loaded with the VERG VeV MD software. Using the software, the wound edge is manually traced onto the image and the software calculates the wound dimensions. All photos were taken and wound edges were traced by one investigator to limit user error.

Wound-related pain

Wound-related pain was measured via the wound pain scale (WPS) and the Visual Analogue Pain Scale (VAPS). The WPS was developed to measure wound-specific pain symptoms in a 'yes–no' format (aching, cramping, sharp, shooting, electric shock, hypersensitivity, throbbing, tingling) and provides a global measure of wound-specific pain on a numerical scale from 1 to 10. Level and intensity of pain was measured using the VAPS with a 1–10 scale.

Patient and clinician satisfaction

To monitor for patient and clinician satisfaction with the treatment, two 6-item Likert-type questionnaires ranging from 'Strongly Agree' to 'Strongly Disagree' were developed for both patients and clinicians (PatSat and ClinSat, respectively). Two open-ended questions were provided for the possibility of qualitative analysis of patient's experiences compared with other wound care treatments.

Data analysis

Paired *t*-test and a repeated measures General Linear Model, Friedman ANOVA and

Table 1 Study outcome measures and assessment schedule

		Frequency of assessment	
Outcome domain	Assessment	Visit #	Measurement interval
Wound size and appearance (tissue type and exudate amount)	1. PUSH score	Every other visit	Weekly
	2. Digital (VERG) photos	Every other visit	Weekly
Wound-related pain	3. Visual analogue pain scale	Every other visit	Weekly
	4. Wound pain scale	Every other visit	Weekly
Satisfaction with the treatment	5. Patient satisfaction	Visit 2, final treatment session and follow-up	Three total measurements
	6. Clinician satisfaction	Visit 2, final treatment session and follow-up	Three total measurements

PUSH, Pressure Ulcer Scale for Healing; VERG, Vision Engineering Research Group Advanced Wound Measurement System.

Key Points

- sixteen African-American individuals with at least one wound characterised as a pressure ulcer, diabetic ulcer, vascular ulcer or burn (the burn was a result of chemotherapy) met the screening criteria and were enroled
- two participants dropped out prior to completion of Session 8, and two participants were discontinued from the study because of poor hygiene, compliance and wound care, leaving a total of 18 wounds analysed

Wilcoxon Signed-Rank Test were used to assess change over time in wound size via the PUSH score and change in pain score through consecutive Sessions 1–8. Paired *t*-tests were used to assess change in wound size via the PUSH score and change in pain. Wilcoxon signed rank test was used to assess change in wound size via the VERG digital wound measurement system. Analysis of patient and clinician satisfaction with the treatment was performed using a non parametric chi-square-based measure. The analyses compared baseline versus treatment assessments of basic outcome variables. To further study the effect of treatment, a 2-week post-treatment period was used. An alpha of 0.05 was determined to be significant a priori.

RESULTS

Sixteen African-American individuals with at least one wound characterised as a pressure ulcer, diabetic ulcer, vascular ulcer or burn (the burn was a result of chemotherapy) met the screening criteria and were enroled. The subject's average age was 42 with a mean wound duration of 2·5 years. A total of 22 wounds were treated. Two participants dropped out prior to completion of Session 8, and two participants were discontinued from the study because of poor hygiene, compliance and wound care, leaving a total of 18 wounds analysed (see participants indicated by † in Table 2).

Mean age of participants was 42 years, with a range from 23 to 89 years. Inferential analysis of the study group showed that participants were equally distributed by gender. The average wound duration was 2·5 years (range = 3 months to 10 years). Table 2 provides a description of patient demographics by wound type.

As much as 40.9% of the wounds treated were pressure wounds, 36·4% were vascular/venous wounds, 9·1% were diabetic wounds, 9·1% were post-surgery wounds and 4·5% were burn wounds resulting from chemotherapy/radiation (Figure 1).

Wound closure was accomplished in 4 (two participants) of the 18 (or 22%) wounds during

Table 2 Participant demographics

Wound type	Location	Gender	Age (years)	Wound duration (years)
Burn/chemotherapy radiation	Left foot	F	64	1·1
Diabetic	Left posterior LE	M	69	1·1
Diabetic	Right foot	M	30	0·3
Post-surgical	Upper chest	F*	76*	0·4
Post-surgical	Lower chest	–	–	0·4
Pressure	Left breast fold	–	–	0·3
Pressure	Right ischium	M	30	1
Pressure†	Left ischium	M	37	1·1
Pressure	Right ischium	M*	56*	0·5
Pressure	Left tochanteric	–	–	0·5
Pressure	Left heel	–	–	0·5
Pressure†	Sacrum	M	28	0·5
Pressure†	Left inguinal	M	23	1·1
Pressure	Sacrum	M	31	2·1
Vascular	Right lateral LE	M	66	2
Vascular	Left anterior LE	F	89	10
Vascular	Upper anterior tibia	F*	52*	0·3
Vascular	Lower anterior tibia	–	–	0·3
Vascular	Right medial LE	F*	55*	3·1
Vascular	Left medial LE	–	–	3·1
Vascular	Left tibia	F	68	10·1
Vascular†	Left LE	F	52	5·0

*Multiple wounds of the same individual.
†Dropout/removed participants.

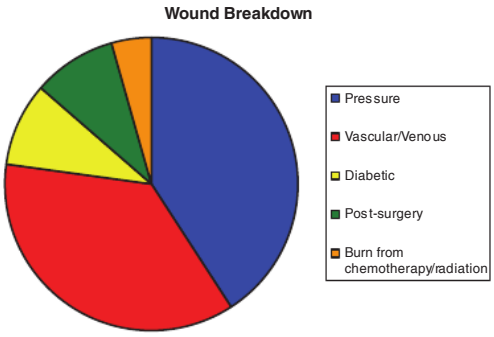

Figure 1. Distribution by wound type.

the intervention period (up to 20 treatment sessions for individual patients). The 76-year-old African-American female experienced healing of all three of her wounds, two of which were post-surgical chest wounds and the third a soft tissue pressure wound under her left breast. The two post-surgical wounds received the initially planned treatment phase of eight treatments before complete closure, while the soft tissue pressure wound healed after three treatment sessions. The second participant with full wound closure was a 69-year-old African-American male with a spinal cord injury whose wound was a diabetic ulcer to his left posterior calf who experienced wound closure after 20 treatment sessions. The diabetic ulcer had previously remained unhealed for over 1 year.

Six participants with seven wounds chose to extend their treatment, with a range of 14–20 total treatment sessions. Another seven participants (11 wounds) were not available to extend their treatment. Three of the wounds all from one participant healed during the initial treatment period requiring no further extension in treatment, one participant already extended treatment to two of his wounds therefore further treatment to the third was put on hold, two participants ended the initial treatment phase prior to the continuation being available and were lost to contact and five participants were consented after continuation approval but because of the end of the study were only treated for the initial treatment phase of 1 month (eight treatments).

Wound size and total PUSH scores

Of the 18 wounds completing the eight treatment sessions, change in wound size measured via the PUSH tool was performed. The mean total PUSH score at Session 1 was considered baseline and was compared with the mean total PUSH score at treatment Session 8 (Table 3). The total PUSH score decreased during the treatment period from 11·72 to 9·94, representing a 15·2% decrease ($P = 0·003$).

The mean area (determined using the PUSH length × width sub-score) of the wounds decreased from 7.56 (range 2–8) at baseline to 6·28 (range 1–9) at Session 8, representing a 16·9% decrease in size ($P = 0·003$). Wound area measured via the VERG VeV MD image recognition algorithm showed a similar significant trend towards decreasing wound size from 3·3 to 2·7 by 18·1% ($t = 2·78$; $P = 0·014$).

Seven wounds were treated for an extended period of time. A post hoc sub-analysis of those receiving extended treatment sessions using the Wilcoxon signed-rank test of wound size measured by the PUSH score showed a continued decrease by 26% in the length × width (7–5·20; $P = 0·039$) and an 18% decrease in the total PUSH score (10·90–8·90; $P = 0·042$).

Wound-related pain

Wound-related pain as measured by the WPS, WPS pain intensity sub-score and VAPS is summarised in Table 4. The total WPS score decreased 70%, from 3·50 (range 0–7) at baseline to 1·05 (range 0–5) at Session 8 ($P = 0·001$). Similarly, wound-related pain measured by the VAPS decreased 60% from Session 1 (mean = 2·78, range 0–8) to Session 8 (mean = 1·11, range 0–6, $P = 0·024$). Intensity of pain decreased 65% from a mean of 5·12 (range 0–10) to 1·78 (range 0–6) at the conclusion of the treatment period ($P = 0·002$).

Table 3 PUSH score change between Sessions 1 and 8

Outcome variable (Sessions 1–8) number of wounds = 18		Baseline mean (SD)	Post-treatment mean (SD)	Wilcoxon signed-rank test value	*P*-value
PUSH adjusted scores	Width × length (cm)	7·56 (2·2)	6·28 (3·2)	3·46	0·003
	Total score	11·72 (2.8)	9·94 (4·2)	3·41	0·003

Table 4 WPS and VAPS scores change between Sessions 1 and 8

Outcome variable (Sessions 1–8)		Baseline mean (SD)	Post-treatment mean (SD)	Wilcoxon signed-rank test value	*P*-value
WPS pain score ($N = 18$)	Pain summary score (range 0–7)	3·50 (2·32)	1·05 (1.69)	4·27	0·001
	Intensity of pain (range 0–10)	5·12 (3·51)	1·78 (2·24)	3·71	0·002
VAPS pain score ($N = 18$)	Intensity of pain (range 0–8)	2·78 (2·48)	1·11 (2·08)	2·88	0·024

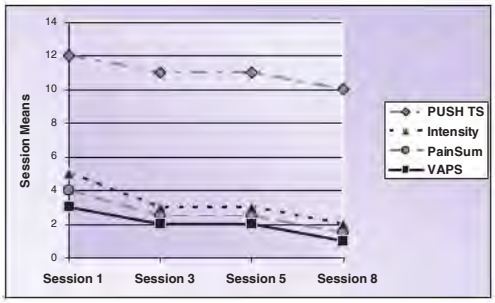

Figure 2. PUSH, WPS and VAPS scores by treatment session.

Key Points

- the therapeutic studied in this protocol, CACIPLIQ20, is a skin-specific synthetic bioengineered HS GAG mimetic which replaces HS that has been destroyed in chronic wounds, thereby reinforcing the scaffolding properties of the ECM while allowing key interactions with growth factors to reoccur

Change by treatment session is shown in Figure 2.

Patient and clinician satisfaction

Patient and clinician satisfaction with the treatment remained stable throughout the course of the treatment period. Initial patient satisfaction score was 1·9 and at follow-up was 1·8 ($P = 0·546$). Initial and follow-up clinician satisfaction scores were 3·42 and 3·0, respectively ($P = 0·546$).

DISCUSSION

Therapeutic options for wound healing are numerous because of the multifactorial nature of skin breakdown and repair, characterised by damaged tissue homeostasis. Integral to wound physiology, repair and therapy is the age of the wound, with chronic and acute wounds differing substantially in their physiology and repair characteristics. *Acute* wound repair is orderly, consisting of haemostasis, inflammation, proliferation and remodelling. *Chronic* wound repair is much more complex, however. It has been proposed that chronic wounds get 'stuck' in a prolonged inflammatory phase resulting in arrested repair. Impediments to wound healing in chronic wounds include the presence of necrotic tissue, hypoxia, high bacterial burden, corrupt extracellular membrane (ECM) and senescent cells within the wound bed (30). In the case of the corrupt ECM, protease levels increase, which in turn destroy components of the ECM and damage growth factors and their receptors that are essential for healing (31,32). Hence, corruption of the ECM is a characteristic of chronic wounds and is a potential target for therapeutic options (33,34).

Recently, attention has been directed towards addressing ECM deficiencies and the role of ECM–cell interactions in wound repair and arrest (35). Our understanding of the ECM has evolved beyond it providing the structure and scaffolding for the skin. A major component of normal skin, the ECM is composed of a variety of polysaccharides, water and collagen proteins, and roles include regulation of cellular functions, lubricating cells and providing a transport system for nutrients and wastes (31). The bidirectional interactions between growth factors and the extracellular matrix are now understood to be integral to wound healing (35). Novel therapeutic interventions directed at the ECM include those that are collagen-based, non collagen ECM, biosynthetic composite scaffolds and processed native skin products (36). For example, control of matrix metalloproteinases (MMP) activity through the delivery of a collagen-rich MMP-binding material (37,38), growth factor delivery (39,40) or application of a naturally or synthetically derived ECM material is currently in testing (41). Another potential therapeutic approach targeting the ECM is to replace the heparan sulphate glycosaminoglycan (HS GAG) that has been destroyed, thus restoring tissue homeostasis and protecting the wound from further degradation.

The therapeutic studied in this protocol, CACIPLIQ20, is a skin-specific synthetic bioengineered HS GAG mimetic which replaces HS that has been destroyed in chronic wounds, thereby reinforcing the scaffolding properties of the ECM while allowing key interactions with growth factors to reoccur. When applied

topically, it penetrates into the micro-clefts of damaged ECM where it can bind to matrix proteins as heparan-binding sites become available when endogenous HS are destroyed by heparanase. Heparanase is among the first enzymes to undergo activation after tissue injury (42) and CACIPLIQ20 is a poly-glucose-based polymer engineered to be resistant to the endoglycosidase, which functions to restore the structural and functional properties of the ECM, and is the first product developed for in situ matrix therapy applied in humans (CACICOL (43,44) has been developed for use in the cornea). Hence, the underlying model is one of introduction into the ECM of a glycanase-resistant biopolymer engineered to mimic HS to improve tissue healing by halting the cycle of ECM destruction and reconstruction that characterises chronic wounds. This extracellular matrix stability is critical to the health and healing of wounds (45,46).

The purpose of this study was to determine whether CACIPLIQ20 improves healing, reduces pain and is associated with patient and clinician satisfaction in the treatment of chronic skin breakdown caused by pressure ulcers, diabetic ulcers, vascular ulcers or burns. Preliminary studies support nanobiopolymers engineererd to mimic HS and to protect heparan-binding growth factors (described as RGTA, for ReGeneraTing Agents) have been shown to promote healing both in in vitro and in vivo models (24,47,48). In in vitro models, synthesised RGTA has been shown to enhance angiogenesis via modulation of vascular endothelial growth factor (VEGF) (47–49) and modulate collagen-type expression via FGF-2 or TGF-β1 (50). When administered in vivo, RGTA promote angiogenesis in acute ischaemia models of skeletal (47) or heart muscle (48). A skin-adapted RGTA, OTR4120 showed improved healing, reduced inflammation (measured as wound erythema) and improved wound quality in mice with skin necrosis induced by intradermal doxorubicin injection (51,52). Similar results were obtained in other skin injury models such as thermal (20) and irradiation (22) burns, post-surgery wounds (21) and pressure ischaemic-induced wounds (24). In the first human trial using CACIPLIQ20, 15 patients with grade 4 arterial chronic ulcers were treated with CACIPLIQ20 following the same protocol as in this study. After one month of treatment, 12 patients improved with an average wound size reduction of 35% (12–100%), and at 2 months the reduction in size was 53% ($P < 0{\cdot}001$), with five ulcers fully healed. Pain was stable or diminished in 10 of the 15 cases (67%) and there were no adverse effects reported. After 3 months 80% ulcers healed (53).

This study was conducted in the Washington, DC metropolitan area, serving a community that is predominantly underserved, poor and with low levels of literacy. The marginalised nature of this community is evidenced in the severity, duration, and types of wounds treated. Unlike other studies of *chronic* wounds (54–57), the average duration of a wound treated in this study was considerably longer (mean 2·5 years; range 3 months – 10 years, compared with 'chronicity' typically defined as greater than 4 weeks duration). Also noteworthy, six of the participants had paralysis because of spinal cord injury, a group typically at very high risk for pressure ulcers because of insensate skin (58). Of these six participants, all but one of the wounds were pressure ulcers on the sacrum or ischium, and all patients continued to mobilise on their wounds in their wheelchairs. Hence, this study sought to improve wound healing and wound-related pain in some of the most recalcitrant wounds.

In this diverse group of chronic wounds previously resistant to treatment, 22% of wounds fully healed and there was a statistically significant 15·2% decrease in wound size measured by the PUSH Tool, and an 18% decrease in wound size measured by the VERG digital measurement system, corresponding to a reduction in wound area by 3·8–5·4% per week, depending on the measure used. Hence, rate of wound healing did not reach that of a normal acute wound (10–15%), however decrease in size from Sessions 1 to 3 was 10%, approaching the rate of a normally healing wound. It would be anticipated that rate of decline of healing would decrease with time as the least severe wounds fully heal and the most recalcitrant and severe wounds remain in the treatment protocol.

Post hoc analysis of six subjects with seven wounds who requested continuation of treatment beyond the proposed eight sessions (1 month) revealed a greater rate and total wound healing (18–26%). As these subjects had requested continuation of treatment because of

Key Points

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- post hoc analysis of six subjects with seven wounds who requested continuation of treatment beyond the proposed eight sessions (1 month) revealed a greater rate and total wound healing (18–26%)

Key Points

- as these subjects had requested continuation of treatment because of perceived beneficial effects, these participants were most likely highly compliant, thereby providing a more accurate representation of true wound healing potential of this product
- further evidence of efficacy is shown by a reduced rate of healing after the treatment was removed
- wound-related pain can be as debilitating to quality of life for the patient as the wound itself, and reduction of pain has been shown to contribute to a reduction in wound-related anxiety
- the most conspicuous benefit from the CACIPLIQ20 was the profound decrease in wound-related pain in response to the treatment, which was confirmed by two measures, the VAPS and WPS
- feasibility was confirmed via a consistently high rating of satisfaction by both patients and clinicians
- the ease of application, low treatment frequency (twice per week) and ability to use other therapeutic options concurrently add to clinician and patient satisfaction
- it should be noted, however, that CACIPLIQ20 cannot be used in conjunction with any therapeutic products containing charged metal ions as the charged ions will compete with the CACIPLIQ20 for binding sites, effectively diluting or deactivating the CACIPLIQ20 solution
- this study is limited by the relatively small number of participants, and lack of randomization and controls
- while the varying wound etiologies added heterogeneity to the cohort, thereby reducing statistical power, this aspect also makes the study results more generalisable

perceived beneficial effects, these participants were most likely highly compliant, thereby providing a more accurate representation of true wound healing potential of this product. Further evidence of efficacy is shown by a reduced rate of healing after the treatment was removed.

Current treatment options for chronic wounds are multiple and include topical antibiotics, growth factors, vacuum-assisted closure devices, ostectomies, electrical stimulation and electromagnetic therapy, skin grafting, hyperbaric oxygen therapy (59), flap coverage for wound closure (60) and shock wave therapy (61), among others. Direct comparison between products is challenging, however, as a result of the wide variability in therapeutic mechanism of action, heterogeneity of populations, wound type and chronicity, as well as the multifactorial nature of chronic wounds. It has been suggested that reduction in wound area by 10–15% or more per week represents 'normal' healing characteristic of a healing acute wound (as opposed to stagnated healing in a chronic wound) (62,63).

Wound-related pain is a significant problem for patients, yet is rarely addressed (64). Topical opioids (65) such as morphine and diamorphine infused gels (66), as well as topical analgesics (67,68) are used to counteract wound-related pain (54,69,70) Wound-related pain can be as debilitating to quality of life for the patient as the wound itself (71), and reduction of pain has been shown to contribute to a reduction in wound-related anxiety (66) Hence, treatment of wound-related pain is a significant component of wound healing for the patient (28,29,72).

The most conspicuous benefit from the CACIPLIQ20 was the profound decrease in wound-related pain in response to the treatment, which was confirmed by two measures, the VAPS and WPS (Table 4). This is consistent with previously published data on grade 4 arterial leg ulcers (47) and on the corneal RGTA HS mimicking device, CACICOL (43,44). Lastly, feasibility was confirmed via a consistently high rating of satisfaction by both patients and clinicians (see subsections *Patient Satisfaction* and *Clinician Satisfaction* in Results). The ease of application, low treatment frequency (twice per week) and ability to use other therapeutic options concurrently add to clinician and patient satisfaction. It should be noted, however, that CACIPLIQ20 cannot be used in conjunction with any therapeutic products containing charged metal ions as the charged ions will compete with the CACIPLIQ20 for binding sites, effectively diluting or deactivating the CACIPLIQ20 solution.

This study is limited by the relatively small number of participants, and lack of randomisation and controls. While the varying wound etiologies added heterogeneity to the cohort, thereby reducing statistical power, this aspect also makes the study results more generalisable. Strengths of this study lie in the use of objective outcome measures to show clinical efficacy, rigorous conduct of the trial and the high level analytic process.

In conclusion, despite extensive research on cause and possible interventions, chronic wounds as a secondary medical complication have met with unsatisfactory treatment solutions, and continue to pose a medical hazard for persons that decay their health, activity, function, life quality, well-being and longevity. RGTA have the potential to positively influence wound healing by improving altered haemodynamics, overall ECM corruption and the growth factor trapping characteristic in chronic wounds. This study shows that partial correction of ECM function with the RGTA, CACIPLIQ20, corresponds to an improvement in chronic wound healing. CACIPLIQ20, applied topically twice per week, is safe and may promote wound healing in chronic and recalcitrant wounds that are free of heavy purulent drainage or necrotic tissue. Most notably, topical treatment with CACIPLIQ20 reduces wound-related pain and is viewed favourably by patients and clinicians. Because of the multifactorial nature of chronic wounds, combination with other therapeutics may provide additional wound healing benefit.

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Key Points

- strengths of this study lie in the use of objective outcome measures to show clinical efficacy, rigorous conduct of the trial and the high level analytic process
- this study shows that partial correction of ECM function with the RGTA, CACIPLIQ20, corresponds to an improvement in chronic wound healing

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