Use of autologous conditioned serum dressings in hard-to-heal wounds: a randomised prospective clinical trial

Objective: In this study, we aimed to assess both the efficacy and tolerability of autologous conditioned serum (ACS) as an innovative wound dressing in the local management of hard-to-heal wounds.
Method: In this single-blinded randomised controlled trial, patients with hard-to-heal wounds were randomly assigned to receive either ACS treatment or normal saline (NS) dressings. The treatment was applied once a week for three weeks with a final assessment at three weeks from the first ACS application.
Results: A total of 30 patients took part in the study. Analysis of wound assessment data demonstrated statistically significant differences for wound surface area and Pressure Ulcer Scale for Healing scores (area score, exudate and tissue) from baseline to the end of the study in patients who received the ACS dressing, but not in patients who received the normal saline dressing. There were statistically significant differences in changes in: the wound surface area at week three (–6.4±2.69cm^2 versus +0.4±2.52cm^2); area score at week three (–2.2±1.08 versus +0.2±0.86); exudate at week two (–1.2±0.70 versus +0.0±0.45) and at week 3 (–1.3±0.72 versus –0.1±0.63); tissue at week two (–1.1±0.35 versus +0.0±0.53) and at week three (–1.8±0.65 versus –0.1±0.63); and the PUSH total score at week one (–1.6±0.98 versus +0.4±1.22), week two (–3.2±0.86 versus +0.4±0.98) and week three (–5.3±1.17 versus –0.0±1.33) between the ACS and NS groups, respectively.
Conclusion: This trial revealed a significant decrease in wound surface area as well as a considerable improvement in wound healing in the ACS dressing group.
Declaration of interest: The trial is registered at the Iranian Clinical Trial Registry database (No. IRCT20100720004422N7). Funding was received from the Deputy of Research, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. The funding body had no role in the design of the study, collection, analysis, or interpretation of the data, or writing of the manuscript. The authors have no conflicts of interest to declare.

autologous conditioned serum • chronic • diabetes • hard-to-heal • pressure ulcer • Pressure Ulcer Scale for Healing • PUSH • randomised controlled trial • ulcer • wound • wound care • wound dressing • wound healing

Hard-to-heal wounds are among the most common complaints of patients referred to general and vascular surgeons, orthopaedists, infectious disease specialists and dermatologists. Chronic disorders, including diabetes, cardiovascular diseases (CVD), hypoxia, malignancy, immunosuppression, local vascular disease, infection and repeated trauma are the common causes of hard-to-heal wounds.[1] The prevalence rate for hard-to-heal wounds is between 1–2% of the general population and 8.5% of older people in industrialised countries.[2–4]

The burden of managing hard-to-heal wounds is rising fast globally, because of growing healthcare costs, an ageing population, and a drastic increase in the prevalence of diabetes and obesity.[5] Besides the physical, emotional and social perspectives, costly medical treatments also place a significant financial burden on the health system.[6]

The wound healing process is a dynamic response to damage, which includes the following stages:

- Coagulation and haemostasis (0–several hours post-injury)
- Inflammation (2–5 days)
- Proliferation (3–14 days)
- Maturation (3 weeks to 2 years).[7]

It requires an interaction among different cell types, building proteins and growth factors.[8] However, if the natural wound healing process is disrupted, the wound can become hard-to-heal due to a lack of growth factors and cytokines that play a role in the wound healing process.[9]

Hard-to-heal ulcers are lesions that do not usually heal within three months due to an underlying pathological condition(s), and can also indicate an imbalance between chronic traumatic factors (such as those injuries caused by overuse of the affected limb) and poor restorative responses.[10] Ulcers are categorised into the following four classes: pressure ulcers (PUs); diabetic ulcers; venous ulcers; and arterial insufficiency ulcers.[11]

Wound care methods include traditional treatments, such as debridement followed by wound dressings and

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application of topical treatment agents, which are often slow and time-consuming processes.[9] Preparing the wound bed to support re-epithelialisation has long been used in the treatment of wounds of different aetiology. Of note, a common approach to wound preparation is DIME: debridement of nonviable tissue; inflammation and infection management; moisture control; and environmental and re-epithelialisation evaluation.[12,13]

Conventional debridement is one of the main procedures in preparing wound beds as bacteria and toxins are often concentrated in necrotic tissue.[14] Removing the necrotic tissue can also decrease the bacterial load, abnormal cells and local oedema, as well as regularising the microenvironment of the surface of the wound.[15]

The production and promotion of modern wound dressings are based on the therapeutic concept of the moist wound environment, and have greater benefits in comparison with the traditional dressing methods, such as gauze, cotton pads and bandages.[16] The most commonly applied modern wound dressings in clinical practice are hydrogels, hydrocolloids, alginates, foams and films.[17] The application of therapeutic agents consists of growth factors and antimicrobial drugs, which principally focus on stimulating the healing process and preventing infection, and plays a crucial role in the management of all types of wounds. However, there still exists a need to discover new therapeutic drugs for topical treatment.

A number of other modern methods are used in wound healing. Notably, negative pressure wound therapy (NPWT) has demonstrated greater medical efficacy in the treatment of diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) compared with the standard wound therapy.[18,19] Other innovative wound healing modalities include bioengineered skin substitutes, extracellular matrix proteins, hyperbaric oxygen (HBO_2) therapy, ultrasound and regenerative therapy.[9,20]

Autologous conditioned serum (ACS) is an experimental medical procedure in which a patient's own blood is extracted, manipulated and then injected back into his/her body as an anti-inflammatory drug.[21] ACS is exclusively obtained from the patient's own blood and, because it is cell-free, varies from platelet-rich plasma (PRP), which is an alternative autologous blood therapy.[22] The efficiency of ACS is attributed to high concentrations of interleukin (IL)-1 receptor antagonist (IL-1ra), anti-inflammatory cytokines (IL-4, IL-10 and IL-13) and growth factors (for example, transforming growth factor (TGF)-b and insulin-like growth factor (IGF)1), which differentiate ACS from PRP. Growth factors and cytokines are suggested for use in improving the healing process of soft tissue and skin. ACS contains more growth factors than PRP, and has been shown to have better effects on the wound healing process.[23] PRP, whole blood and ACS are promising new treatment modalities.[22]

Several studies have confirmed the beneficial effects of individual growth factors, for example, platelet-derived growth factors (PDGFs), fibroblast growth factors (FGFs) and granulocyte–macrophage colony stimulating factor (GM–CSF), on the wound healing process in both animal and human models.[24–27] However, the efficacy of ACS, as a representative of biological treatment with multiple growth factors, besides IL-1ra and anti-inflammatory cytokines, in the management of hard-to-heal wounds has not yet been verified. Therefore, in this trial, we aimed to determine the efficacy of an ACS wound dressing in the treatment of hard-to-heal wounds of different aetiologies.

Methods

Study design and setting

This was an open-label, parallel-group, randomised controlled trial performed to determine the efficacy and safety of ACS wound dressing in comparison with normal saline dressing, as a control, in the treatment of hard-to-heal wounds.

The study was conducted in two universities affiliated to outpatient clinics (Shohada and Imam Reza) between February 2019 and March 2020. Patients with hard-to-heal wounds referred to outpatient clinics were continuously recruited in the study using the non-probability convenience sampling method in terms of the eligibility criteria.

Study sample and ethical approval

Patients with hard-to-heal wounds of different aetiologies and the following characteristics were included in this trial:

- Both sexes aged between 18–80 years old
- Had wounds classified as either grade I or II based on wound depth (dermis as grade I, subcutaneous tissue as grade II)[28] of a duration >3 months
- A willingness to participate in the study.

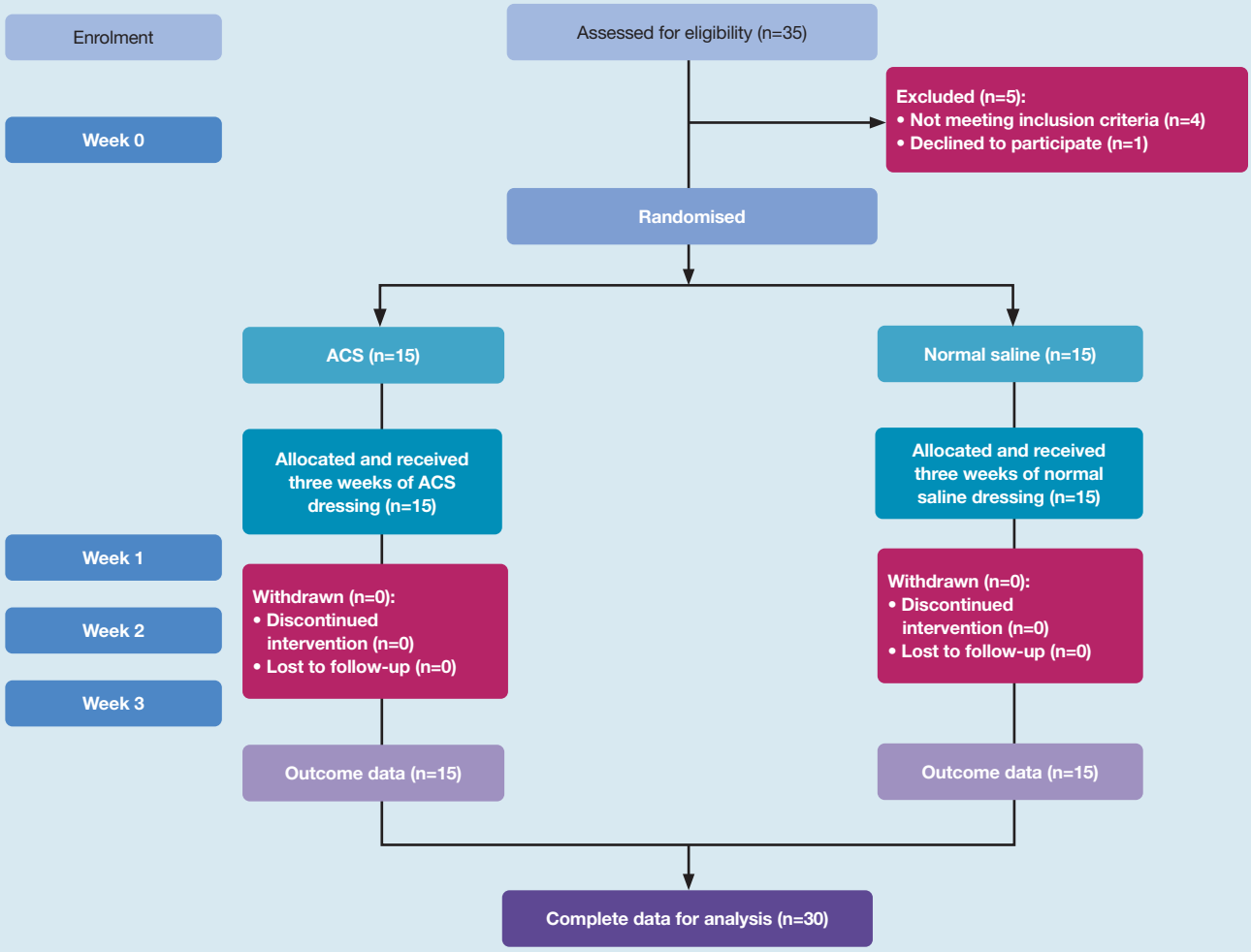
Participants were excluded if:

- They were smokers
- Had a wound with bacterial, viral or fungal infection according to the wound infection criteria of Gardner et al.[29]
- Had any coagulation disorders or platelet conditions
- Had severe vascular disorders
- Were taking systemic steroid-containing medications
- Were using corticosteroid ointment near the wound area
- Were unable to collaborate with the requirements of the trial.

None of the participants were pregnant or breastfeeding.

Each one of the included patients received information on the study purpose and intervention, and then signed the informed consent form before beginning the trial. The study was performed according to the terms of the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.

Fig 1. Flow diagram of study patients. ACS—autologous conditioned serum



REC.1398.154). The trial was registered at the Iranian Clinical Trial Registry database (No. IRCT20100720004422N7). In addition, CONSORT guidelines were followed (Fig 1).

Baseline demographic characteristics of patients (including age and sex), anthropometric indices and clinical findings were assessed at baseline. Wound data (type and size) were investigated and documented before the start of the trial. Moreover, the participants' weight and height were measured using standard scales (Seca 813 digital scale and Seca 206 roll-up measuring tape, respectively). Body mass index (BMI) was calculated by dividing the weight (in kg) by the square of height (per m^2).[30]

Patients' medical documents were obtained from previous hospital admissions and then studied by a member of the investigation team who was unaware of the trial arms and to which group patients would be allocated, to evaluate any complication related to the patients' wounds, such as infection.

Assignment of interventions

Patients with and without diabetes who met the study's eligibility criteria were randomly allocated into two treatment groups using a simple randomisation method of computer-generated random numbers. Accordingly, this was done by an independent statistician with the allocation ratio of 1:1 using opaque sealed envelopes comprising indicators of groups 1 and 2, in order to conceal the allocation process. In this regard, envelope 1 referred to ACS dressings, while envelope 2 indicated normal saline dressings.

This study was an open-label trial. It was not possible to blind the participants to the treatment. Furthermore, the treating physicians were not blinded to the treatment; however, the investigators providing the treatment were different from those performing wound evaluations and those who were responsible for clinical tests. Moreover, the statistician who executed all the statistical analyses was blinded to the

study groups' allocation. These investigators did not know the assignments of the patients, and could not determine the assignment by looking at the wound after dressings were removed.

Interventions

At this stage, wounds were washed, debrided and evaluated by a physician. Thereafter, laboratory tests were done to confirm that they were not infected and were appropriate for the ACS treatment. For all patients, sharp debridement with a scalpel until pinpoint bleeding formed in the depths of the lesions was applied weekly for as long as was needed, in order to eliminate as much non-viable tissue as possible. Local anaesthesia was given to patients if they felt pain.[15] To avoid damaging tissue, physiologic saline was then used at pressure to eliminate microorganisms. Pressure offloading (a removable walker cast) was also prescribed by the treating physician, depending on clinical necessity, wound appearance and position for patients with DFUs.[31,32] Subsequently, primary treatment was applied, including glycaemic control. EmsiG AM30 Air Mattress (EmsiG GmbH, Germany) was prescribed for pressure relief in those patients with pressure wounds and patients were repositioned every two hours.[33] The treatment protocol was determined based on the wound site, ischaemia, neuropathy, bacterial infection and depth (SINBAD) score. The scoring system is easy to apply in routine clinical practice.[34] Additionally, a nutritional assessment was performed by checking haemoglobin and albumin levels once a week. Patients who smoked were requested to quit smoking at least four weeks before the treatment.[35]

Group 1: Dressing containing ACS

ACS was prepared in a sterile environment using the method previously described in the literature.[36,37] From each patient, 30ml of their own blood was drawn from the antecubital vein under sterile conditions, transferred to six polypropylene syringes (5ml) containing glass beads, and incubated for six hours at 37°C. These tubes were then centrifuged on a table-top centrifuge for 15 minutes at 1500rpm and serum was aspirated. Thereafter, the ACS-soaked gauze dressing was applied to the surface of the wound bed and the activated ACS was injected into the wound border by a trained physician. The dressing and injection were applied at baseline and then once a week for a period of three weeks. This period was selected based on the results of previous studies.[38,39]

Group 2: Dressing containing normal saline (control)

The patients in the control group were all managed with normal saline solution. Standard sterile cotton gauze was soaked in normal saline and then applied directly to the wound bed. Subsequently, it was changed once a week, as directed by the treating physician, for a period of three weeks.

All the steps were performed under sterile condition for all the patients. Wound assessment was performed every 48 hours by the treating physician for any adverse wound reactions.

Main outcome measures

The main outcome measures were wound surface size and wound healing. Wound surface size was measured by a one-centimetre flexible grid, which is a standard measurement for wound size.[40,41] A two-dimensional evaluation was also applied by determining the wound's linear dimension; for example, a rectangle (length × width), a circle (diameter × diameter) or an oval (maximum diameter × maximum diameter perpendicular to the first measurement).[41]

Additionally, both wound size and appearance were estimated using the Pressure Ulcer Scale for Healing (PUSH). Accordingly, the PUSH is a rapid and reliable

Table 1. Patient-related characteristic of the study participants

Variable	ACS group (n=15)	NS group (n=15)	p-value
Age, year, mean±standard deviation	53.2±12.53	56.3±10.77	0.469*
Sex, n (%)			
Male	13 (86.7)	12 (80.0)	0.775†
Female	2 (13.3)	3 (20.0)	
Weight, kg, mean±standard deviation	72.4±6.22	78.6±5.85	0.009*
Height, cm, mean±standard deviation	167.3±5.48	169.6±5.59	0.271*
BMI, kg/m^2, mean±standard deviation	25.9±3.30	27.4±2.98	0.220*
Haemoglobin, g/dl, mean±standard deviation	12.5±2.37	11.9±2.89	0.158*
Albumin, g/dl, mean±standard deviation	2.4±0.68	2.6±0.54	0.091*
HbA1C, %, mean±standard deviation	6.5±0.76	6.7±0.92	0.507*

ACS—autologous conditioned serum; NS—normal saline; *p obtained from Chi-squared test; †p obtained from independent samples t-test

measurement tool used to screen the alteration in PU status and hard-to-heal leg ulcers over time in the clinical setting. PUSH includes three parameters and subscales as follows:

- Surface area of the wound: spans both the maximum length (vertical) and the maximum width (horizontal), in square centimetres (cm^2). To obtain the wound's surface area, the two measures are multiplied together
- Exudate amount present in the wound: measured after removing the wound dressing and before putting any agent on it. It can be categorised as 'none', 'light', 'moderate' and 'heavy', which correspond with the scores of 0 to 3.
- Wound bed tissue type: considered as the most prevalent types of tissue in the wound area, determined as follows: 'necrotic tissue' (eschar), black, brown or tan tissue that tightly coheres to the bed of the wound or edges of the ulcer and may be either tighter or weaker than the surrounding skin; 'slough', the tissue (yellow or white) that adheres to the bed of ulcer in strings or thick masses or is mucinous; granulation tissue, pink or beefy red colour tissue with a glossy, wet, and granular look; epithelial tissue, for superficial wounds, new pink or glossy tissue (skin) that develops from the margins or as islands on the surface of the ulcer; and closed/resurfaced wound, the wound is entirely enclosed with epithelium. These tissues are scored as 0 (closed wound), 1 (epithelial tissue), 2 (granulation tissue), 3 (slough), and 4 (necrotic tissue).

All the evaluations were performed at baseline (week 0), and at one, two and three weeks after the beginning of the trial.

The safety parameters of ACS over three weeks were examined by the analysis of adverse events (AEs) at each study follow-up.

Ethical approval and consent to participate

All participants provided written informed consent and endorsement was received from the Ethics Committee of the Research Vice-Chancellor of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.154).

Patients' personal data were conserved in a database to keep patient information confidential and secure. The study was also registered in the clinical trial registry under number IRCT20100720004422N7 code (https://www.irct.ir/trial/41444).

Statistical analysis

Considering the mean ulcer area difference 55.5±21.6cm^2 and 72.1±19.9cm^2 derived from a previous study by Bansal,[42] an alpha value of 0.05, power of 80%, and a 40% reduction in wound volume, the number of patients needed for each group in this present study was estimated as 14, using G*Power version 3.1. Moreover, considering a dropout rate of 10% and a 1:1 allocation ratio, the sample size was calculated as 30 patients (15 per arm).

All statistical analyses were performed using SPSS software Version 17.0 (SPSS Inc., US). The obtained data were provided as mean±standard deviation (SD) and frequency counts (n, %). Kolmogorov–Smirnov and Shapiro–Wilks tests were applied to examine normal distribution of the data. Between-group comparisons of baseline variables were also performed using the Student's t-test for continuous variables with a normal distribution, Mann–Whitney U test for continuous variables with no normal distribution, and Fisher exact test was applied for discrete variables. To assess within group changes and between group differences, two-way mixed analysis of variance (ANOVA) test (time [within subject]×group [between subjects]) and the Sidak post hoc test as an adjustment procedure were applied. The patients were assessed at baseline (week 0), and at one, two and three weeks. We illustrated effect size in terms of Cohen's d for outcome measures. In this regard, the effect sizes of 0.2, 0.5, and 0.8 were labelled as small, medium, and large, respectively.[43] A p-value of 0.05 or below was considered as statistically significant.

Results

A total of 35 participants were screened and 30 patients were randomised, having met all the inclusion and exclusion criteria. All patients completed the study and were involved in the final analysis (Fig 1). Of the patients, 15 were randomised to the ACS dressing group and 15 were enrolled into the normal saline (control) dressing group. All the participants' demographic characteristics are shown in detail in Table 1. Baseline demographics and wound characteristics were similar between the two groups, except for weight—patients in the control group had a higher mean weight, with no difference in BMI between the groups.

There was a significant interaction among the time points (baseline 0, weeks one, two and three) serving as the within-group factor and group (ACS dressing versus normal saline dressing as the control) as the between-group factor regarding the study outcomes (wound surface size, $p<0.001$; area score, $p=0.003$; exudate, $p=0.01$; and tissue: $p=0.008$). Based on the Cohen's d values, the results denoted to large effect size for the study outcomes ($d=2.36$, $d=3.01$, $d=1.77$ and $d=1.97$ for wound surface size, area score, exudate and tissue, respectively). So, we analysed the difference between the study groups at each level of the time factor.

At baseline, there were no differences in wound surface area and PUSH area, exudate, tissue and total scores between the ACS group and the control group (Table 2). Wound surface area and PUSH area, exudate, tissue and total scores decreased significantly in the ACS group after three weeks (–6.4±0.40, $p<0.001$; –2.2±1.08, $p<0.001$; –1.3±0.72, $p<0.001$; –1.8±0.65, $p<0.001$; and –5.3±1.17, $p=0.001$, respectively). There were no significant differences in the control group

Table 2. Wound-related characteristic of the study participants

Variable	ACS group (n=15)	NS group (n=15)	p-value
Duration, months, mean±standard deviation	2.8±0.56	3.0±0.70	0.345*
Location, n (%)			
Leg	5 (33.3)	4 (26.7)	0.389†
Scalp	6 (40.0)	4 (26.7)	
Buttock	2 (13.3)	3 (20.0)	
Heel	1 (6.7)	2 (13.3)	
Thigh	1 (6.7)	2 (13.3)	
Wound type, n (%)			
Diabetic	3 (20.0)	2 (13.3)	0.389†
Pressure	6 (40.0)	5 (33.3)	
Dehisced surgical	3 (20.0)	4 (26.7)	
Burn	3 (20.0)	4 (26.7)	
Wound surface area, cm^2, mean±standard deviation	10.9±5.52	9.0±3.86	0.436*
PUSH area score, mean±standard deviation	167.3±5.48	169.6±5.59	0.271*
BMI, kg/m^2, mean±standard deviation	25.9±3.30	27.4±2.98	0.220*
Haemoglobin, g/dl, mean±standard deviation	12.5±2.37	11.9±2.89	0.158*
Albumin, g/dl, mean±standard deviation	2.4±0.68	2.6±0.54	0.091*
HbA1C, %, mean±standard deviation	6.5±0.76	6.7±0.92	0.507*

ACS—autologous conditioned serum; NS—normal saline; *p obtained from Chi-squared test; †p obtained from independent samples t-test

with regards to wound surface area and PUSH area, exudate, tissue and total scores during the study period (p=0.150, p=0.069, p=0.463, p=0.572 and p=0.926, respectively). The result of the two-way mixed ANOVA test showed that the differences in wound surface area and PUSH area, exudate, tissue and total scores in the ACS group were significantly higher than in the control group (p=0.006, p=0.005, p<0.001, p<0.001 and p<0.001, respectively) (Fig 2). However, there was no complete wound healing in either of the trial groups.

No AEs comprising rash or oedema or any other side-effects were described in either treatment group throughout the three-week follow-up period.

Discussion

The results of this study demonstrated that three weeks of ACS dressing resulted in a reduced wound surface area and improved wound healing in grades 1 and 2 hard-to-heal wounds, based on the PUSH scale.

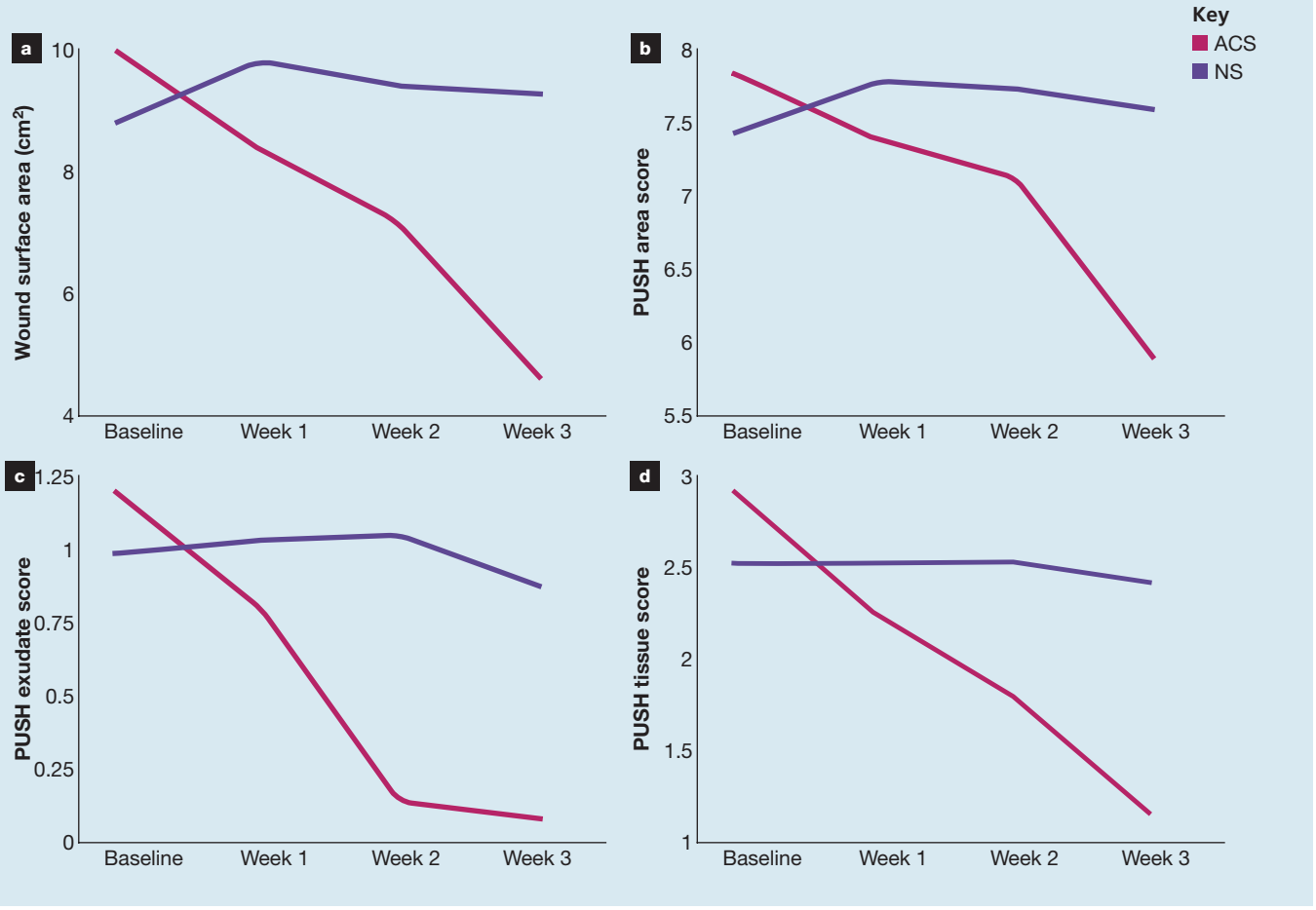
Traditional hard-to-heal wound treatments are disappointing because of their long duration, extensive AEs, considerable financial costs and unsatisfactory outcomes. The current improvements in the field of biomaterials may play a key role in the hard-to-heal wound healing process.

In hard-to-heal wounds, tissue restoration is stopped in the inflammatory phase leading to pathologic inflammation and blockage of the beginning of the healing process.[44] ACS was initially developed to advance muscle renewal in an animal model of muscle contusion[45] and to provide anti-inflammatory properties in carpal osteoarthritis in horses,[46] as well as in human subjects with knee osteoarthritis in a clinical trial.[47] ACS is derived by incubating venous whole blood at approximately 37°C. This encourages the secretion of anti-inflammatory cytokines.[48] Kerscher et al. established the efficacy and safety of microneedling with ACS in improving cutaneous elasticity and skin firmness in female patients with reduced facial skin elasticity.[49]

Blood products contain growth factors which, it has been suggested, advance the healing process and increase the repair speed in both acute and hard-to-heal wounds.[50] ACS is of particular interest because it is a derivative of the patient's own blood.[51,52] Accordingly, this enhances the product's safety, reducing the likelihood of any adverse effects, and lowering production costs.

To the best of our knowledge, this study is the first trial performed to evaluate the beneficial effect of ACS on the healing process of hard-to-heal superficial

Fig 2. Trends in main study outcomes from the beginning to last follow-up of patients in the study groups: Wound surface area **(a)**; PUSH area score **(b)**; PUSH exudate score **(c)**; PUSH tissue score **(d)**. PUSH—Pressure Ulcer Scale for Healing



wounds. Reducing the wound area is considered a good criterion for assessing the extent of healing. In the present study, wound surface area decreased from 10.9±5.52cm^2 at baseline to 4.5±3.31cm^2 after three weeks of ACS dressing (mean difference: –6.4±0.40cm^2, p<0.001). Subsequently, this led to a 2.2±1.08 point decrease in area score at week three. In the control group (using normal saline), wound surface area increased, with a mean difference of 0.4±2.52cm^2; however, it was not statistically significant.

Wound area usually decreases due to wound healing and connective tissue deposition during the healing process. The contractile phenomenon that pulls the epidermal layers towards each other at the wound surface, reducing the area and increasing wound healing, is the presence of both active fibroblasts and myofibroblasts in the bud tissue of granulating wounds.[53] In patients in the ACS dressing group, exudate and tissue scores decreased by 1.3±0.72 and 1.8±0.65 points, respectively, in three weeks, in comparison with a decrease of 0.1±0.63 for the same scores in the control group (p<0.001).

However, numerous investigations have established the promising effects of individual growth factors on the wound healing process. The transforming growth factor beta (TGF-b) superfamily is known as an essential mediator of tissue renovation. This multifunctional growth factor can provide pleiotropic properties during the wound healing process by adjusting cell reproduction and immigration, differentiation, extracellular matrix construction and immune regulation.[54] Of note, hard-to-heal, refractory wounds may also have an actual or practical insufficiency of TGF-b action. In addition, some previous studies have shown the beneficial impact of exogenous IGF-1 on the wound healing process, especially in combination with other growth factors.[55,56] Furthermore, liposome-mediated IGF-1 gene transfer was found to have the ability of enhancing the pathophysiology of a skin injury.[57,58] However, there are some experiments of recombinant growth factors and ACS application conducted to improve the tendon healing process in an animal model which have variable findings.[59–61]

Cytokines, such as IL-1Ra, and growth factors, such as TGF-β and IGF-1, have a short half-life after

exogenous utilisation.[59,62] However, wound healing may be improved not only by the direct connection of both the cytokines and growth factors to the receptors of the cell surface, but also by the incitement of endogenous construction of growth factors because of secondary properties.[63,64] So, the impact of ACS can possibly be improved by several sequential injections, as seen in the present trial.[65]

Hard-to-heal wounds impose a great burden on the affected patient. They cause pain, dysfunction, infection, and financial expenses, and frequently lead to sepsis or amputation. Population ageing, obesity and diabetes are quickly growing in most regions of the world. At the same time, the prevalence rates of non-healing pressure, venous, and diabetic wounds are also increasing.[66] This highlights the importance of investing in the expansion of wound management sciences as a multidisciplinary field. The complexity of hard-to-heal wounds has delayed proposing novel pharmacological approaches as alternatives to change wound parameters. Therefore, dressings are the mainstay of wound management, despite little clinical evidence.[17] However, there is great potential in the field of exogenous growth factors and cytokines.

The current research has implications for the care of patients with hard-to-heal wounds for paramedics, nurses, surgeons, and other physicians caring for these patients. The novelty of our investigation lies in our findings on the efficacious management of hard-to-heal wounds using the ACS dressing method. This investigation can be considered as the basis for further trials with a larger sample size to evaluate the superiority of ACS over traditional dressings in hard-to-heal wounds.

Limitations

There were some potential limitations to this study that should be considered, including the unavoidable unblinded design of the trial, which can introduce observer bias.[67] To minimise this bias, a single-blind trial was applied, where the individuals evaluating wounds were not aware of the type of treatment being applied.

Another major limitation was using PUSH to estimate a wound's size and appearance. This tool was developed primarily for pressure injuries (PUs) and is not suitable for other wound types.

Additionally, the sample size for this trial was small and may have been underpowered to assess the efficacy of the treatment on each type of wound.

Lack of adequate follow-up time was other limitation of this study. This trial can be considered as a pilot study. Future studies (power size calculated) by including more participants and stratifying wounds of different aetiologies are warranted to attest to the validity of this trial.

Conclusion

In conclusion, it was indicated that applying an ACS dressing for three weeks can provide an effective and safe treatment for hard-to-heal wounds. This can significantly reduce wound surface area and improve the healing process, according to the PUSH index, in a safe manner, which is likely ascribed to high concentrations of growth factors and anti-inflammatory cytokines. **JWC**

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Reflective questions

- What are the reasons for an acute wound becoming a hard-to-heal wound?
- What are the disadvantages of traditional wound dressing methods?
- What is the mechanism of action of autologous conditioned serum in wound healing?

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