Dermatol Ther (Heidelb) (2023) 13:299–314
https://doi.org/10.1007/s13555-022-00852-5

ORIGINAL RESEARCH

# Application of Comfort Therapy under eCASH Concept in Acute and Chronic Wound Treatment

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Received: October 9, 2022 / Accepted: November 2, 2022 / Published online: December 6, 2022


## ABSTRACT

***Introduction***: Given the new ideas on wound care offered by the eCASH (early Comfort using Analgesia, minimal Sedatives, and maximal Humane care) and the substantial differences in clinical treatment between acute and chronic wounds, we aimed to investigate the effect of comfort therapy under the eCASH concept on analgesic sedation and accelerated wound healing in patients with acute or chronic wounds.

***Methods***: This randomized clinical study was conducted in two parts: acute wounds and chronic wounds. Patients with acute wounds were allocated into the acute wound control group (AWCG) and the acute wound experimental group (AWEG). Patients with chronic wounds were allocated into the chronic wound control group (CWCG) and two experimental groups, in which they received intermittent negative pressure therapy (IPTEG) and continuous negative pressure therapy (CPTEG). On the basis of the standard treatment for patients in the control group, eCASH therapy was used in the experimental groups. In addition, pain intensity and procedural anxiety were evaluated using the visual analogue score (VAS) and the Hamilton Anxiety Scale (HAM-A). In addition, clinical effects were assessed on the basis of the size of the surface area, rate of healing, and concentration of pro-inflammatory factors (IL-1, IL-6, TNF-α) and growth factors (VEGF, bFGF, TGF-β1).

***Results***: Compared with the control group, the VAS score and HAM-A score in the experimental groups were significantly decreased after intervention ($P < 0.05$). After intervention, the levels of IL-1β, IL-6, and TNF-α in AWEG, IPTEG, and CPTEG were significantly lower than those in AWCG. In addition, the levels of VEGF, bFGF, and TGF-β1 in IPTEG and CPTEG were significantly higher than those in CWCG ($P < 0.05$).

***Conclusion***: These results indicated that comfort therapy under the eCASH concept has a significant effect on ameliorating the pain and anxiety of patients, reducing the inflammatory reaction during the period of wound healing in the treatment of acute and chronic wounds.

***Clinical Trial Registry***: The trial has been registered in the Chinese Clinical Trial Registry (ChiCTR2200057981).

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**Keywords:** Comfort therapy; Continuous negative pressure therapy (CNPWT); eCASH; Hamilton Anxiety Scale (HAM-A); Intermittent negative pressure wound therapy (INPWT); Visual Analogue Score (VAS); Wound care

**Key Summary Points**

***Why carry out this study?***

The concept of early Comfort using Analgesia, minimal Sedatives, and maximal Humane care (eCASH) provided a new idea for wound care.

There were substantial differences in clinical treatment between acute and chronic wounds.

***What was learned from the study?***

Comfort therapy under the eCASH concept has a significant effect on ameliorating the pain and anxiety of patients in the treatment of acute and chronic wounds.

This study provides a nonpharmacological treatment reference for patients suffering from acute and chronic wounds.

## INTRODUCTION

According to the healing process, wounds are divided into acute and chronic, and their prevalence rate is increasing by 9% and 12% per year, respectively, in the UK [1]. Acute wounds are defined as those that develop suddenly and heal quickly, such as surgical incisions, burns, or trauma. If an acute wound covers an excessive injury area, infections and disorders in blood flow and nutrition to the area may lead to a chronic wound [2]. There is no unified definition of chronic wounds, nor is there a time frame for their healing [3]. Almost all chronic wounds start as minor cuts or scrapes and then stop at some stage and linger [3–5]. The aging population has increased the rate of chronic refractory wounds and the demand for treatment [6]. Pressure ulcers, diabetic feet, and vascular ulcers have become three major diseases in older inpatients [7], and the annual expenditure for them in the USA has risen to approximately $25 billion [8]. With the aging population and the change in the disease spectrum, patient wounds have become a significant social public health problem [9].

Wounds cause pain, and common treatments such as debridement, dressing change, scab cutting, skin grafting, and physical therapy cause additional pain [10]. In addition, pain in wound treatment is closely related to anxiety, which aggravates it [11]. Pain is harmful to the physical, psychological, family, and society of patients with acute and chronic wounds. Improper pain treatment also affects wound healing and disease recovery, so its effective management is essential. However, recent studies have shown that pain management in hospitals is unsatisfactory [12]. Medical staff often neglect to assess the intensity, characteristics, or effects of pain on psychosocial relationships, and music and other adjunctive analgesia have not been routinely used in hospitals [13]. The current people-oriented modern medical model gives more attention to the humanized connotation of wound treatment and puts forward higher requirements for treating wound pain. In traditional analgesia therapy, there are significant individual differences in pain, and it is challenging to measure patients' demand for drugs. It is easy to cause adverse reactions, and it is difficult to control moderate and severe pain effectively. Therefore, it is necessary to find methods that minimize patient pain, promote comfort, and have few side effects. However, there is a lack of practical research on pain management and nursing wards in mainland China [14] and in the standard management process.

In 2016, Vincent [15], former Chairman of the European Critical Care Medicine Association, proposed the new painless comfort concept of early Comfort using Analgesia, minimal Sedatives, and maximal Humane care (eCASH) to provide a new way to approach wound treatment. On the basis of the idea of eCASH, this study established a painless comfort ward

in the burn unit, aiming to determine the best practices for combined intervention in the treatment of pain anxiety in those with acute or chronic wound treatment and to provide a reference for its further optimization and the promotion of ward management.

# METHODS

## Study Design

This randomized controlled trial (RCT) was registered in China (ChiCTR2200057981). The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee at The Affiliated Hospital of Jiangnan University (Z201710/18 Dec. 2017). Informed consent was obtained after explaining the study protocol to patients in Chinese.

## Setting and Participants

The subjects of this study were patients with acute or chronic wounds who received inpatient treatment in wards A1 or A2 of the Burn Plastic Surgery Department, The Affiliated Hospital of Jiangnan University, from 2019 to 2020. The allocation of participants was done by a pain specialist who was not involved in the study design and implementation. Demographic data were obtained from the files of patients, patients themselves, or their families.

## Inclusion Criteria

- Common burns or other acute wounds (burns covering less than 10% of total body surface area (TBSA).
- Chronic wounds that persisted at least 4 weeks or more and had a difficult time healing [3, 4].
- Patients with complaints of intolerable pain or a visual analogue score (VAS) score greater than 3.

## Exclusion Criteria

- Wounds with active bleeding, exposure of large blood vessels or nerves, or localized tumors that were unlikely to tolerate debridement.
- Patients with mental illness.
- Diabetic patients with unstable blood glucose control in the past 2 weeks.

## Assignment of Groups

### *Randomization*

After completing baseline data collection, participants with acute or chronic wounds were randomly assigned following a simple randomization procedure (computerized random numbers) to the control or the experimental group. Gray, sealed, opaque, numbered envelopes were used. The intervention nurse opened the envelope and allocated the participant to the respective group.

### *Blinding*

Before the experiment, patients were only informed of the principle, purpose, and method of eCASH comfort therapy but were not informed of group assignment. Owing to a modification of the A2 ward environment, the study was not blinded to the participants or the staff conducting the intervention.

## Groups and Interventions

Owing to differences in the clinical treatment of acute and chronic wounds, the study was conducted in two parts: acute wounds and chronic wounds. In both parts, the control and experimental groups used wound treatment based on the principles of best clinical practice (standard treatment), that is, after mechanical debridement, the wound was sterilized with iodophor, covered with Vaseline gauze (Vaseline) and sterile gauze, and secured with bandages. Compared with the control group, patients in

the experimental group received eCASH treatment on the basis of standard wound treatment.

In the acute wounds part, patients were randomized into two groups: the acute wound control group (AWCG) and the acute wound experimental group (AWEG). In the chronic wounds part, patients were randomized into three groups: the chronic wound control group (CWCG) and two experimental groups. In addition to standard treatment and eCASH, patients in two experimental groups received an intermittent negative pressure therapy (IPTEG) and continuous negative pressure therapy (CPTEG), respectively.

### Negative Pressure Therapy for Chronic Wounds

Since chronic wounds heal slower, negative pressure wound therapy is used to treat them. Specific methods: after the necrotic tissue was debrided, wounds were covered with a foam dressing based on the size, sealed with a biofilm, and connected to the negative pressure center of the hospital [16].

CPTEG uses the Kulovy negative pressure drainage device (Fine-based Biologics Co., Ltd) with negative pressure suction 24 h a day for 12 days. IPTEG adopts an intelligent negative pressure therapy instrument (Depus Medical Equipment), and the negative pressure mode is intermittent (treatment for 5 min, stop for 2 min).

### Comfort Therapy Under the eCASH Concept

The comfort therapy under the eCASH concept was used as a treatment intervention for experimental groups. The eCASH includes a multidisciplinary approach, preferred analgesics, minimizing sedation, promotion of comfort, focus on humanistic care, and exercise.

### Multidisciplinary Approach

The intervention was conducted by a multidisciplinary team of (1) nurses specializing in wound management, (2) burn orthopedic surgeons, (3) pain physicians, and (4) rehabilitation therapists. The need for analgesia and sedation treatment was assessed comprehensively by the teams at the early stages. Explanations were provided to family members who provided approval for eCASH analgesia, sedation, humanistic nursing, and management strategies.

### Early Analgesia and Minimal Sedation

Pain management is a top priority in implementing eCASH. Clinicians assessed the severity of pain early, and dynamic and combined pharmacological and nonpharmacological approaches were used to reduce pain. In parallel, researchers evaluated and monitored patient opioid use and adverse drug reactions and provided timely feedback to multidisciplinary teams about the severity of pain-targeted drug analgesia. When the VAS score was $< 3$, patients were given an ibuprofen sustained-release capsule of 0.1 g for analgesia. When the score was 3–5, 0.2–0.3 g of ibuprofen analgesia or 100 mg indomethacin anal plug was given. When the score was 6–7, severe pain required opioid analgesics, and dezocine 5 mg intramuscular injection was used. Dezocine 5 mg intramuscular was used when the score was $> 5$ to 7 and the patient had severe pain requiring opioid analgesia. When the score was $> 7$–10, patients developed extreme pain and were given dezocine 10 mg intramuscular or tramadol 100 mg intramuscular. During the treatment, the nursing staff provided timely feedback on patient complaints. If the pain remained, inhaled nitric oxide gas and butorphanol micropump were considered.

In eCASH, sedation is not necessary if analgesia is adequate. The principal sedative drug

used was dexmedetomidine, which was titrated on the basis of the degree of sedation. In parallel, music therapy, video playing, and other methods of empathic sedation were adopted.

### Humanistic Care

Humanistic care is a core component of eCASH. Clinical staff frequently and appropriately communicated with patients and explained the care components, time and space orientation, noise reduction, avoidance of unnecessary restraints, sleep promotion at night, mental stimulation, occupational therapy, and cognitive training. Team members patrolled the unit at least twice a day. Doctors were responsible for wound assessment and diagnosis of stress injury and provided wound management measures. The wound nurses were responsible for dressing changes, nursing, and health education of wounds. Rehabilitation therapists were responsible for creating an exercise program.

### Promotion of Comfort

Comfort therapy was patient-centered, considered family members, and provided high-quality care for diet and living as well as aspects of psychological, emotional, and social needs. The unit was equipped with a central thermostat to ensure that the temperature and humidity in the unit were appropriate to prevent cold stimulation of the wound. At the same time, a suspension bed, standard dressings, and warm sock covers were used to ensure practical and comfortable wound care. In addition, the eCASH unit played soothing music and videos from 9:00 until 10:00 and again from 14:00 until 15:30 during dressing changing periods every day.

### Early Rehabilitation Exercise

Patients were encouraged to participate in exercise programs as early as possible after eCASH treatment, which is believed to be essential for physical recovery. The unit is located opposite the rehabilitation treatment room and equipped with two rehabilitation therapists, ensuring that patients receive early practical and personalized functional training guidance.

### Family Engagement

On the basis of a regular visitation system, family members were encouraged to participate in the rehabilitation of patients actively. They used videos to teach the patient families to pivot turning skills. During treatment, family members and medical staff were as likely to


**Fig. 1** On the equipment, the researchers have equipped the unit with sofas, desks and chairs, stereos, and LCD televisions, which can facilitate the daily activities of patients and their families and create a good family atmosphere. At the same time, the unit is equipped with central temperature control equipment, a suspension bed, standard functional dressing, an air pump, and warm socks to ensure a comfortable treatment environment and effective wound care. The researchers redesigned the layout of the units: the unit's logo is a pair of hands holding hope, and the unit's color scheme is warm pink and dark green to help calm. There are three beds in the unit to facilitate peer communication among patients

have anxiety and tension as the patients [17]. Units were also equipped with sofas, desks, chairs, and LCD televisions to facilitate daily activities and patient visits with their families and create a favorable atmosphere (Fig. 1).

### Measures

After admission, pain intensity and anxiety of patients with acute wounds were evaluated before, during, and after three debridement dressing changes. The physiological healing mechanism of chronic wounds was destroyed, and the treatment was different from that of acute wounds. The dressing of negative pressure wound therapy occurred every 7 days. Therefore, the pain intensity and anxiety level of patients with chronic wounds before treatment, 7 days, and 14 days after treatment were evaluated. The same procedure was used to measure the indexes of acute and chronic wounds. The VAS was selected for on-site assessment of pain intensity by trained nurses. After training, physicians used the Hamilton Anxiety Scale (HAM-A) to assess patients' anxiety during communication with them. The expression levels of proinflammatory factors (IL-1β, IL-6, TNF-α) and growth factors (TGF-β1, VEGF, bFGF) were determined by ELISA after wound debridement. A digital camera was used to take photos of the wounds, which were treated for 14 days. The wound healing rate was determined using ImageJ software [(the rate of wound healing = the area of wound before treatment − the area of wound after treatment)/ the area of the wound before treatment × 100%] using a standard of complete epithelialization of the wound. Risk factors affecting wound healing were screened for by referring to diagnostic efficacy criteria for surgical diseases of traditional Chinese medicine (TCM) with wound healing rate ≥ 75% as the significant effect.

### Outcomes

The outcome measures were pain intensity, procedural anxiety, proinflammatory factors and growth factors, size of the surface area, and rate of change in surface area.

### Statistical Analysis

SPSS 20.0 was used to perform statistical analysis. The quantitative data with normal distributions were evaluated with *t*-tests and are presented as mean ± standard deviation (SD). Qualitative data are presented as *n* (%). Chi-squared tests were performed to evaluate unordered data. Rank-sum tests were used to evaluate ordered data; $P < 0.05$ was considered statistically significant. According to the two categories of wound healing, rate as dependent variables, the levels of IL-1β, IL-6, TNF-α, TGF-β1, VEGF, bFGF, and binary classification multifactor logistic regression analysis were used to analyze the risk factors of significant wound healing.

## RESULTS

### Study Participants and General Information

A total of 127 eligible patients were enrolled in the study. After enrollment, 2 patients in the CWCG and 2 in the CPTEG withdrew owing to disease progression, invalid filling of the scale, or other reasons, leaving 123 patients that were included and analyzed. There were 70 acute and 53 chronic wounds assessed and the data analyzed. In the acute wounds part, there was no significant difference in gender, age, total burn area, body mass index, smoking history, alcohol consumption, hypertension, diabetes, coronary heart disease, chronic organ dysfunction, or infectious diseases ($P > 0.05$). Similarly, there was no significant difference with chronic wounds part in wound surface area ($F = 0.062$, $P = 0.94$) and depth of wound ($F = 1.655$, $P = 0.201$) between IPTEG, CPTEG, and CWCG. Baseline characteristics for the three groups did not differ significantly either. Table 1 presents other details of the demographic and clinical characteristics of the participants.

**Table 1** Demographic and clinical characteristics of acute and chronic wounds

| Category | Acute wound | | Chronic wound | | |
|---|---|---|---|---|---|
| | AWEG | AWCG | IPTEG | CPTEG | CWCG |
| *N* | 35 | 35 | 19 | 17 | 17 |
| Male sex | 12 (34.29%) | 15 (42.86%) | 8 (42.1%) | 5 (29.4%) | 7 (41.2%) |
| Age (years) | 44.31 ± 15.89 | 45.23 ± 15.61 | 47.05 ± 11.16 | 48.53 ± 10.52 | 46.59 ± 10.35 |
| TBSA (%) | 4.69 ± 0.53 | 4.63 ± 0.55 | | | |
| Wound surface area ($cm^2$) | | | 90.03 ± 60.77 | 94.99 ± 61.12 | 96.26 ± 46.45 |
| Depth of wound (cm) | | | 1.27 ± 0.44 | 1.24 ± 0.54 | 1.55 ± 0.65 |
| BMI ($kg/m^2$) | 21.83 ± 2.15 | 22.67 ± 2.05 | 20.71 ± 2.11 | 21.68 ± 2.10 | 20.25 ± 2.72 |
| Formerly medical history | | | | | |
| Smoking | 10 (28.57%) | 8 (22.86%) | 11 (57.9%) | 9 (52.9%) | 10 (58.8%) |
| Alcohol consumption | 14 (40.00%) | 11 (31.42%) | 6 (31.6%) | 7 (41.2%) | 6 (35.3%) |
| Hypertension | 6 (17.14%) | 8 (22.86%) | 13 (68.4%) | 10 (58.8%) | 9 (52.9%) |
| Diabetes | 6 (17.14%) | 5 (14.29%) | 11 (57.9%) | 8 (47.1%) | 10 (58.8%) |
| Coronary heart disease | 1 (2.86%) | 2 (5.71%) | 4 (21.1%) | 2 (11.8%) | 1 (5.9%) |
| Chronic organ dysfunction | 3 (8.57%) | 2 (5.71%) | 5 (26.3%) | 3 (17.6%) | 4 (23.5%) |
| Other infectious diseases | 0 (0%) | 0 (0%) | 2 (10.5%) | 1 (5.9%) | 2 (11.8%) |

Values are represented as mean ± standard deviation (SD) or frequency (%) *Significant
*AWEG* acute wound experimental group, *AWCG* acute wound control group, *IPTEG* intermittent negative pressure therapy experimental group, *CPTEG* continuous negative pressure therapy experimental group, *CWCG* chronic wound control group

### Comparison of Pain Intensity and Procedural Anxiety Between the Control Group and Experimental Group

Before treatment, there were no significant differences in VAS and HAM-A scores between the experimental and the control groups for acute or chronic wounds ($P > 0.05$), indicating comparability between groups. In terms of pain intensity, the VAS score of AWEG was significantly lower than that of AWCG during and after each debridement and dressing change ($P < 0.05$). VAS scores of IPTEG and CPTEG after 14 days of treatment were also lower than those of CWCG ($P < 0.05$), and VAS scores of CPTEG were significantly lower than those of IPTEG ($P < 0.001$). In terms of procedural anxiety, HAM-A scores of AWEG were significantly lower than those of AWCG during and after each treatment ($P < 0.05$). IPTEG and CPTEG also had lower anxiety scores than CWCG after 14 days of treatment ($P < 0.05$). Tables 2 and 3 present the detailed results.

### Comparison of the Concentration of Pro-inflammatory Factors and Growth Factors between the Control Group and Experimental Group

Analysis of proinflammatory factor concentrations in experimental acute and chronic wound groups were significantly lower than those in the control groups after 14 days ($P < 0.05$). The

**Table 2** Comparison of intensity and procedural anxiety of each time for acute wound patients

| | Time period | AWEG ($n$ = 35) | | AWCG ($n$ = 35) | |
|---|---|---|---|---|---|
| | | VAS | HAM-A | VAS | HAM-A |
| The first wound treatment | Before the treatment | 6.60 ± 1.38 | 7.43 ± 2.00 | 6.91 ± 1.34 | 7.43 ± 2.24 |
| | During the treatment | 3.40 ± 0.98* | 5.43 ± 1.69* | 8.34 ± 1.21 | 8.34 ± 1.83 |
| | After the treatment | 1.69 ± 1.16* | 3.34 ± 2.30* | 7.00 ± 1.24 | 10.46 ± 1.58 |
| The second wound treatment | Before the treatment | 2.74 ± 0.89* | 5.03 ± 1.34* | 5.80 ± 0.99 | 8.94 ± 1.39 |
| | During the treatment | 2.00 ± 0.94* | 5.09 ± 1.25* | 8.40 ± 1.09 | 9.57 ± 1.17 |
| | After the treatment | 1.46 ± 0.89* | 3.97 ± 1.38* | 6.37 ± 1.35 | 10.43 ± 1.44 |
| The third wound treatment | Before the treatment | 1.74 ± 0.66* | 2.00 ± 1.09* | 3.11 ± 0.76 | 4.63 ± 1.35 |
| | During the treatment | 1.00 ± 0.69* | 1.66 ± 1.03* | 5.89 ± 1.05 | 5.09 ± 1.38 |
| | After the treatment | 0.63 ± 0.55* | 0.97 ± 0.75* | 3.26 ± 0.82 | 4.26 ± 1.36 |

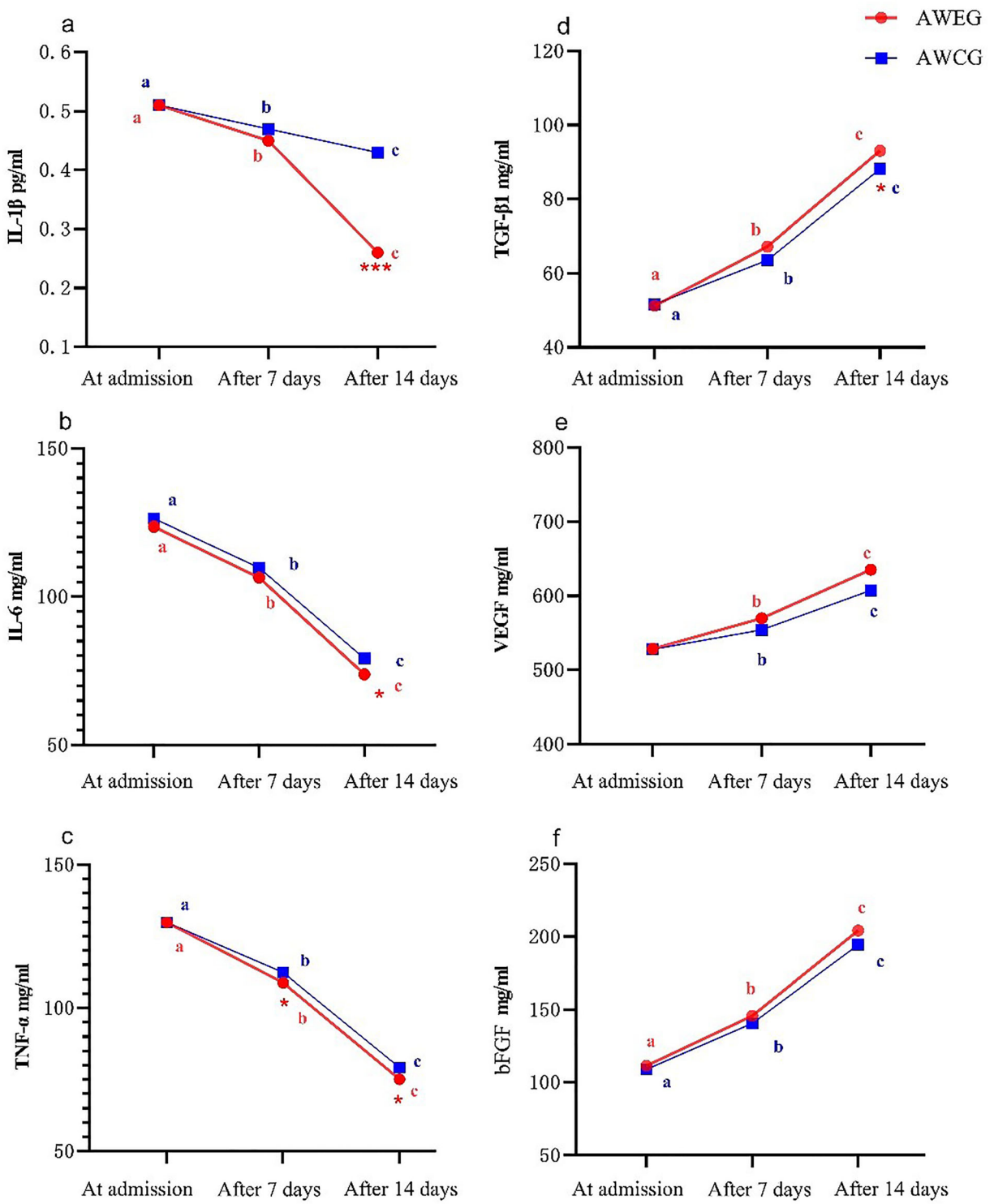
Values are represented as mean ± standard deviation (SD) *Significant

**Table 3** Comparison of pain intensity and procedural anxiety of chronic wound patients

| Group | Time period | $N$ | VAS | HAM-A |
|---|---|---|---|---|
| IPTEG | At admission | 19 | 6.26 ± 1.41 | 9.16 ± 1.95 |
| | After 7 days | | 3.95 ± 1.13 | 5.53 ± 1.71 |
| | After 14 days | | 3.47 ± 1.07*# | 3.16 ± 2.34* |
| CPTEG | At admission | 17 | 6.12 ± 1.22 | 9.29 ± 1.65 |
| | After 7 days | | 2.88 ± 0.60 | 5.24 ± 1.68 |
| | After 14 days | | 1.24 ± 0.90* | 3.53 ± 2.24* |
| CWCG | At admission | 17 | 6.82 ± 1.47 | 8.76 ± 2.31 |
| | After 7 days | | 6.12 ± 1.11 | 9.06 ± 1.75 |
| | After 14 days | | 4.29 ± 1.05 | 9.06 ± 1.64 |

Values are represented as mean ± standard deviation (SD) *Significant

TNF-α level of AWEG was significantly lower than that of AWCG 7 days after intervention ($P < 0.05$) (Fig. 2). Fourteen days after intervention, the Il-6 level of IPTEG was significantly lower than that of CPTEG ($P < 0.005$). In terms of growth factors, the TGF-β1 concentration of AWEG was significantly higher than that of AWCG 14 days after intervention ($P < 0.05$). The VEGF, bFGF, and TGF-β1 in IPTEG and CPTEG were significantly higher than those in CWCG after 14 days of intervention ($P < 0.05$) (Fig. 3). Indicators of wound healing in patients and independent risk factors were not significant for the wound groups. After 14 days of comfortable treatment with eCASH, the wound healing rate of AWEG was significantly improved compared with AWCG ($t = 2.670$, $P = 0.009$). Also, the wound healing rates of IPTEG and CPTEG were significantly higher than that of CWCG ($F = 10.864$, $P < 0.001$)


a
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c
TNF-α mg/ml
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d
TGF-β1 mg/ml
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AWEG
AWCG
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VEGF mg/ml
800
700
600
500
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f
bFGF mg/ml
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100
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◀**Fig. 2** Comparison of microscopic indexes in different intervention periods of acute wounds. **a–c** Three groups are the levels of inflammatory factors in acute wounds, **d–f** three groups are the levels of growth factors. In each part of the pictures, the differences at each time point were represented by abc letter marking method during intra-group comparison ($P < 0.05$). * was used to indicate the significant difference between the experimental group and the control group ($P < 0.05$)

(Table 4 presents the detailed results). Through correlation analysis, IL-1β was found to be an independent risk factor for lack of healing in patients with chronic wounds before intervention ($P < 0.05$). After the intervention, IL-6 and TGF-β1 were independent risk factors for lack of healing in patients with acute wounds ($P < 0.05$), while TNF-α was a protective factor for it in patients with acute wounds ($P < 0.05$). Figure 4 shows the detailed results.

## DISCUSSION

Wound treatment has become a health concern receiving public attention in recent years. Wounds are caused by trauma, surgery, or acute and chronic diseases and affect millions of people worldwide. They cause physical and mental pain to patients and are heavy burden on the social and medical systems [18]. The systemic effects caused by acute wounds are hard to ignore, as well as is the fact that they can result in systemic inflammatory response syndrome (SIRS) in severe cases [19]. If acute wounds are not treated correctly, they can become prolonged and result in chronic wounds, as seen with diabetic and vascular ulcers of the lower extremities, as well as pressure and scar ulcers. Most patients with chronic wounds are middle aged or elderly, often having underlying diseases such as diabetes, heart disease, vascular disease, or other primary diseases. These individuals have a pain tolerance of wound treatment that is far less than ordinary adults. Since 2017, our department has actively implemented the comfort-therapy modalities associated with the eCASH concept when treating acute and chronic wounds. As part of this focus, we have analyzed the efficacy of comfort therapy using the eCASH concept.

This study showed that patients with acute or chronic wounds all had moderate-to-severe pain with apparent anxiety before treatment, which was also consistent with the research results of Zhou [20] and Yan [21]. Debridement and dressing changes are the main methods for wound treatment. In this process, uncovering the dressing, cleaning the wound, debridement, placing a new dressing, and other operations cause severe pain. This pain may lead to elevated blood pressure, tachycardia, and lack of oxygen due to reduced ventilation. Chronic pain can also affect immune function and wound healing. Studies have shown that pain and anxiety overlap owing to the use of the same neural circuits, and about 45% of patients with chronic pain also have anxiety [22]. Pain has a negative impact on patient physiology, psychology, family, and society and may induce post-traumatic stress disorder (PTSD) in severe cases [23]. The current treatment of pain and anxiety caused by wound treatment is usually ineffective and has side effects. However, this has yielded an opportunity to determine best practices. Here we found that compared with traditional treatment, comfort treatment could significantly relieve pain and anxiety during wound treatment ($P < 0.001$). The study established a painless comfort unit based on the concept of eCASH. An interdisciplinary team of burn orthopedic surgeons, wound specialist nurses, pain physicians, and rehabilitation therapists was established to manage patient wound problems. By adopting the concept of comfort therapy under eCASH, the team tried to achieve early analgesia to promote comfort, minimize sedation, and maximize humanistic care. The results showed that after 14 days of comfortable treatment, the wound healing rates in both acute and chronic wounds were significantly improved compared with conventional treatment. Therefore, we believe that the comfort therapy under the eCASH concept is an easy and effective program for wound patients. It can reduce pain and anxiety to some extent and indirectly promote the healing of patients' wounds through more comfortable treatment.

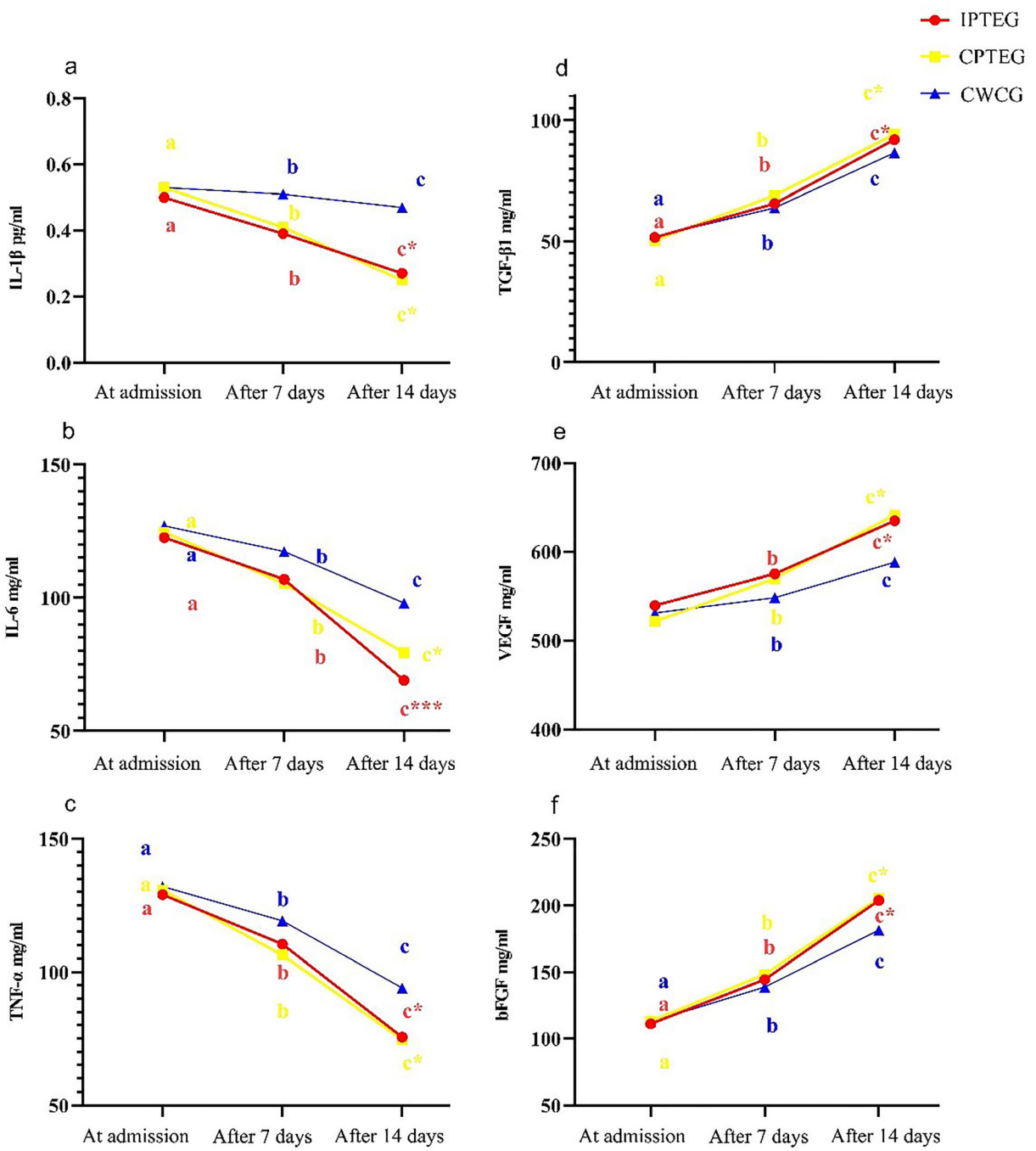


**Fig. 3** Comparison of microscopic indexes of chronic wounds in different intervention periods. **a–c** Three groups are the levels of inflammatory factors in chronic wounds, **d–f** three groups are the levels of growth factors. In each part of the pictures, the differences at each time point were represented by abc letter marking method during intra-group comparison ($P < 0.05$). For comparison between groups, * was used to indicate the significant difference between the experimental group and the control group ($P < 0.05$), and *** was used to indicate the significant difference between the experimental group and the control group ($P < 0.01$)

**Table 4** Comparison of wound healing rate among acute and chronic wound groups after 14 days of treatment

| | | *N* | Wound healing rate | *t* | *F* | *p* Value |
|---|---|---|---|---|---|---|
| Acute wound | AWEG | 35 | 74.44 ± 13.94* | 2.670 | | 0.009 |
| | AWCG | 35 | 65.58 ± 13.84 | | | |
| Chronic wound | IPTEG | 19 | 66.56 ± 18.24* | | 10.864 | < 0.001 |
| | CPTEG | 17 | 71.56 ± 15.15* | | | |
| | CWCG | 17 | 45.10 ± 19.25 | | | |

Values are represented as mean ± standard deviation (SD) *Significant

The comfort of patients is closely related to the environment and nursing care [24]. Nurses promote comfort through pain assessment, psychological intervention, comfortable postures, and health guidance. In addition, to optimize the spatial layout of the eCASH unit, we retained the multi-room layout and added an escort lounge area within the unit. The anxiety and depression of patients are improved by promoting communication between medical staff, family members, and patients to meet their emotional and social needs [25]. Studies have shown that adding natural elements to the physical environment can promote comfort and reduce the use of analgesics by "neutralizing" the sense of technology and strangeness in the ward; therefore, we added two windows and several green plants [24, 26]. The eCASH concept emphasizes the optimization of sleep. Therefore, the plan emphasized reducing nursing operations and noise from patients being admitted [24, 27, 28]. Frosted glass was placed between beds to ensure patient privacy and block out noise to promote sleep. Comfortable physical and good social environments can encourage patients to blend into the hospital atmosphere quickly to achieve the best physical and mental state. Finally, ultra-early rehabilitation training is also an essential feature of the eCASH comfort treatment program. Early functional exercise can help to improve limb function reduction caused by an acute or chronic scar contracture, and the risk is smaller than expected [29].

It is worth noting that the intermittent mode is generally believed to have a better effect than the continuous in adverse pressure treatment [30, 31], and has the advantages of fast wound healing, minor dressing changes, less pain for patients, and is a simple operation. However, the study showed that although both methods effectively relieved pain, the degree of pain in IPTEG was significantly higher than CPTEG after 14 days ($P < 0.05$). This may be owing to the intermittent mode leading to changes in foam dressing relaxation and contraction, as well as the frequent and continuous stimulation of the wound surface increasing the body's pain threshold. In addition, the intermittent mode was more likely to induce the growth of wound granulation tissue than the continuous mode [32, 33]. Overgrown tissue that grows into foam dressings can also cause pain when changing the dressings. The results showed that compared with the discontinuous mode, the new mode had a better effect on wound healing while alleviating the discomfort of patients. However, the number of patients with chronic wounds in the study was limited, which may affect the final results.

From the micro-perspective, wound repair is a complex and orderly pathophysiological process involving the interaction of various inflammatory cells, repair cells, inflammatory mediators, growth factors, and other components. The inflammatory response first occurs after trauma, and a certain degree of said response is helpful to accelerate wound healing, while an excessive amount is associated with increased mortality. Wound healing is a dynamic interaction process between various cells, growth factors, and extracellular matrix,

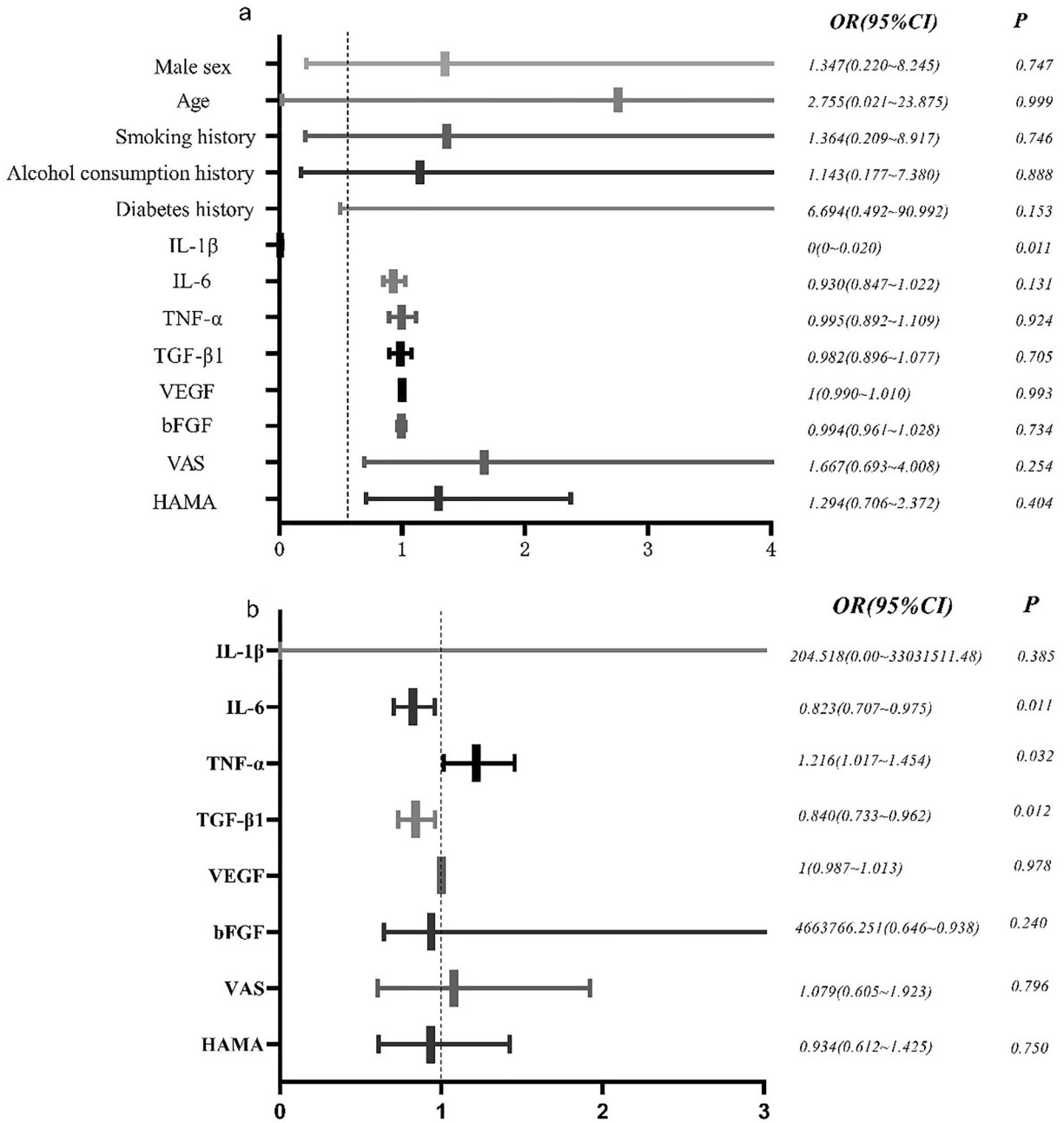


**Fig. 4** Binary logistic regression analysis was performed on the data of patients with acute and chronic wounds before and after intervention (only statistically significant data were included). The wound healing rate was more than 75% as significant healing and less than 75% as nonsignificant healing. The intervention indicators (baseline index, IL-1β, IL-6, TNF-α, TGF-β1, VEGF, bFGF, VAS score, HAM-A score) were independent variables. Independent risk factors affecting nonsignificant wound healing before and after intervention were screened. **a** Shows independent risk factors for nonsignificant healing of acute wounds after 14 days of intervention. **b** Shows independent risk factors for nonsignificant healing of chronic wounds before intervention

and the study of the growth factors is of great interest to the field of wound healing [34]. Inflammatory factors induce pain, which in turn stimulates inflammatory response [35]. In this study, the levels of IL-1β, IL-6, TNF-α, VEGF, bFGF, and TGF-β1 in different phases of acute and chronic wounds were determined after comfort treatment. The results showed that the concentrations of inflammatory factors in acute and chronic wound groups were significantly lower than those in the control groups after 14 days of treatment ($P < 0.05$). This suggests that the comfort therapy under the eCASH concept can effectively reduce wound inflammation and promote the secretion of growth factors in the middle and late periods of wound healing. Notably, after 14 days of treatment, IL-6 levels in IPTEG were significantly lower than those in CPTEG. These results suggest that intermittent negative pressure attraction mode is better than continuous in alleviating wound inflammation, which is consistent with the results of Venturi et al. [31] At the same time, intermittent negative pressure suction mode can form positive pulse regulation of blood flow and form a "shear force" to stimulate the growth of granulation tissue. However, in this study, the effect of intermittent negative pressure mode on growth factors was not significantly different from those in continuous negative pressure mode, which may be related to the small sample size. It is expected that more studies will confirm these results. TNF-α is a marker for the acute stage of the systemic inflammatory response, which induces apoptosis and necrosis, and is involved in many multi-level regulations in tissue damage [36]. However, the microscopic mechanism of inflammatory mediators in wound repair is not clear. Therefore, it remains to be known whether TNF-α inhibitors can be used to intervene in the treatment of chronic wounds.

## CONCLUSIONS

In summary, comfort therapy based on the eCASH concept has a significant effect on relieving patients' pain and anxiety and indirectly promoting the healing of patients' wounds through more comfortable treatment from a clinical perspective. Molecularly, it can effectively reduce the level of wound inflammatory factors and increase the level of growth factors after 14 days of treatment. To further verify the effectiveness of the eCASH concept for different wound types, more studies are needed for acute and chronic wounds on the basis of the existing reports, and more targeted observations should be included.

## ACKNOWLEDGEMENTS

We thank the Wuxi Health Committee (Z201710), and Wuxi science and Technology Bureau (N20192003) for their funding support. Besides, the authors are grateful to the participants of this study and the researchers.

***Funding.*** The journal's Rapid Service Fee was supported by the Wuxi Health Committee (Z201710), and Wuxi Science and Technology Bureau(N20192003).

***Author Contributions.*** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Shuting Shi, Jiayu Wei, Xiaohui Zhong and Minlie Yang. The first draft of the manuscript was written by Shuting Shi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

***Disclosures.*** All authors declare no conflicts of interest. Shuting Shi, Jiayu Wei, Guozhong Lyu, Xiaohui Zhong, Lihong Zhu, Minlie Yang have nothing to disclose.

***Compliance with Ethics Guidelines.*** This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving in study were approved by the the ethics committee of Wuxi Third People's Hospital (Renamed later as Affiliated Hospital of Jiangnan University) (No. Z201710). Written and verbal informed consent was obtained from all subjects. Verbal consent was witnessed and formally recorded.

***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.



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