

Efficacy of Oral Cicaglocal for Wound Healing and Pruritus Alleviation in Patients with Epidermolysis Bullosa: A Single-Arm Clinical Trial

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ABSTRACT Introduction: Epidermolysis bullosa (EB) is a rare dermatosis causing mucocutaneous fragility, which can culminate in secondary afflictions such as contractures. This disease can adversely impact the lives of sufferers with pruritus.

Objective: This study was conducted to assess the effects of Cicaglocal in improving wound repair and pruritus intensity in EB patients.

Method: This single-arm non-randomized trial was carried out in 2024 on 12 EB patients. The recruited patients administered one capsule of Cicaglocal daily for 28 days. Intensities of pruritus and pain were measured with the visual analogue scale. Also, patients' improvement was assessed utilizing clinical global impression of improvement and patient global impression of improvement. Furthermore,

dimensions of ulcers were measured. These examinations were implemented on the first day, prior to the start of taking Cicaglocal, and after four weeks. We used the IBM™ SPSS Statistics application (version 20.0) for statistical analyses.

Results: Patients included six females and six males of Persian ethnicity, with an average age of 20.17 ± 11.99 years. Despite no remarkable change in the count and length of the ulcers, the width of wounds (median width: 9.5 mm to 4.5 mm, $P=0.042$) and magnitude of pruritus (median: 8.5 to 4.5 mm, $P=0.026$) exhibited a statistically significant decrease after four weeks of treatment. Moreover, three and two patients developed gastritis and esophagitis, respectively.

Conclusion: Cicaglocal was a relatively efficient medication for relieving pruritus and enhancing wound healing in EB patients. However, we highly recommend more studies on these issues.

Introduction

Epidermolysis bullosa (EB) refers to a group of genetic dermatoses rarely involving individuals and is distinguished by mucocutaneous fragility as well as by blister formation. EB presents with a wide array of manifestations and consists of more than 30 subtypes. Diagnosis of EB is made through clinical and electron microscopy evaluation along with immunohistopathological investigations. According to the national epidermolysis bullosa registry (NEBR), the combined prevalence of all major types of EB was 11.07 cases per million people in 2002, and the incidence was 19.6 cases per million live births. EB patients are vulnerable to a number of problems such as pseudosyndactyly, contractures, malnutrition, and esophageal stricture as well as to cancers like squamous cell carcinoma [1-3].

Pruritus is among the most intrusive problems involving EB patients, which accordingly impacts their quality of life significantly [4,5]. Notably, a vicious cycle constituted by itching-scratching may exacerbate the blister formation in EB patients [6]. In this context, some patients or their caregivers, as well as researchers, turn to herbal products or natural remedies to alleviate pruritus and enhance the rate of wound healing [7,8].

Cicaglocal is a supplement composed of bromelain (the main active ingredient), Centella asiatica extract, sodium hyaluronan, vitamins such as B2, B3, B7, C, and D3, in addition to minerals, including iron, zinc, and copper [9]. Bromelain, a mixture of enzymes with proteolytic and fibrinolytic activities, exhibits a broad continuum of effects, including angiogenesis regulation, immune modulation, and antioxidation. This has proven safe in surgical wound healing [10]. Centella asiatica extract has been utilized for the management of keloid, ameliorates wound healing and angiogenesis, and demonstrates anti-inflammatory effects [11]. Hyaluronic acid (HA), while deemed a major constituent of skin extracellular matrix (ECM), plays a pivotal role in the tissue regeneration process [12]. Vitamins C, B complex, and D3

hold imperative roles in wound healing [13-15]. Micronutrients like zinc and copper are other contributors to wound repair [16, 17].

The effects of Cicaglocal on pruritus and wounds caused by EB have not thoroughly been investigated. Additionally, no study directly examining the effects of bromelain, sodium hyaluronan, or Centella asiatica extract on EB patients was found in an extensive search of scientific databases, including PUBMED, Scopus, and Web of Science.

Objectives

To the best of our knowledge, no clinical trial has yet examined the effects of Cicaglocal on EB patients. The current study was conducted to determine the presumptive healing and mitigating effects of Cicaglocal on ulcers and pruritus, respectively, in EB patients.

Methods

Study Design

This single-arm non-randomized trial was conducted as a pilot study in 2024 on 12 EB patients. The patients were selected from those visited at Molecular Dermatology Research Center, and Shahid Faghihi Dermatology Clinic, which are affiliated with Shiraz University of Medical Sciences. The protocol of the study was also registered in the Iran Registry of Clinical Trials (ID: IRCT20150825023753N22, website link: <https://irct.behdasht.gov.ir/trial/74829>) on January 09, 2024.

Patient Selection

Inclusion criteria included having EB and being 5 years of age or older. Every patient holding a history of hypersensitivity to Cicaglocal or any of its ingredients or the diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency was excluded from the study.

The participants were screened through the face-to-face interview and physical examination. The chosen patients were completely informed (parents of children) about the study goals and procedures and provided (signed) written informed consent (parents of children) to participate. Furthermore, they were allowed to leave the study at any time. For children older than age 7 years, informed consent was obtained from both the patients and their parents.

Measurements of Variables

Visual analogue scale (VAS) was used for scoring the intensity of pruritus, and pain with established validity and reliability [18,19]. Dimensions of ulcers were measured with a line gauge. We also deployed clinical global impression of improvement (CGI-I) and patient global impression of improvement (PGI-I) to evaluate patients' improvement objectively and subjectively, respectively.

Intervention and Outcomes Assessment

The intensities of pain and pruritus (VAS) as well as CGI-I, PGI-I, and ulcers' dimensions were recorded twice: once before the therapy began (first day of therapy) and once after four weeks of Cicaglocal administration. Furthermore, the researchers took photographs of the ulcers at both time points after obtaining patient consent. The researchers instructed the patients to take one capsule of Cicaglocal once daily for 28 days. The researchers advised the patients with swallowing problems caused by narrowing of the esophagus, a common complication of EB, to take encapsulated powdered medication along with a spoonful of yogurt.

Cicaglocal capsules were formulated by Glocal Laboratorios and provided by Darou Darman Persian Paad.

Statistical Analysis

We employed the IBM™ SPSS Statistics application (version 20.0) for statistical analyses. The qualitative variables are reported as frequency and percentages, while the quantitative ones are expressed as mean and standard deviation (SD). Given the sample size and non-normal distribution, a non-parametric test (Wilcoxon signed-rank test) was utilized to analyze the response to treatment, with significance set at $P < 0.05$.

Results

From February 2024 to August 2024, 38 EB patients were recruited. Five patients were averse to participating in the study, and 16 individuals were excluded owing to lacking eligibility regarding the inclusion and exclusion criteria. During the course of study, five patients were withdrawn due to gastrointestinal upset. Ultimately, the study included six females (50%) and six males (50%) of Persian ethnicity, with an average age of 20.17 ± 11.99 years (Figure 1).

The greatest proportion of participants (75%) complained of itching frequently afflicting them (once to numerous times a day). Furthermore, seven out of the twelve patients (58.33%) were grappling with pruritus lasting longer than two hours. Notably, two thirds of patients experienced morning pruritus, while the remaining experienced nocturnal ones. The leading initiating factors for itching were

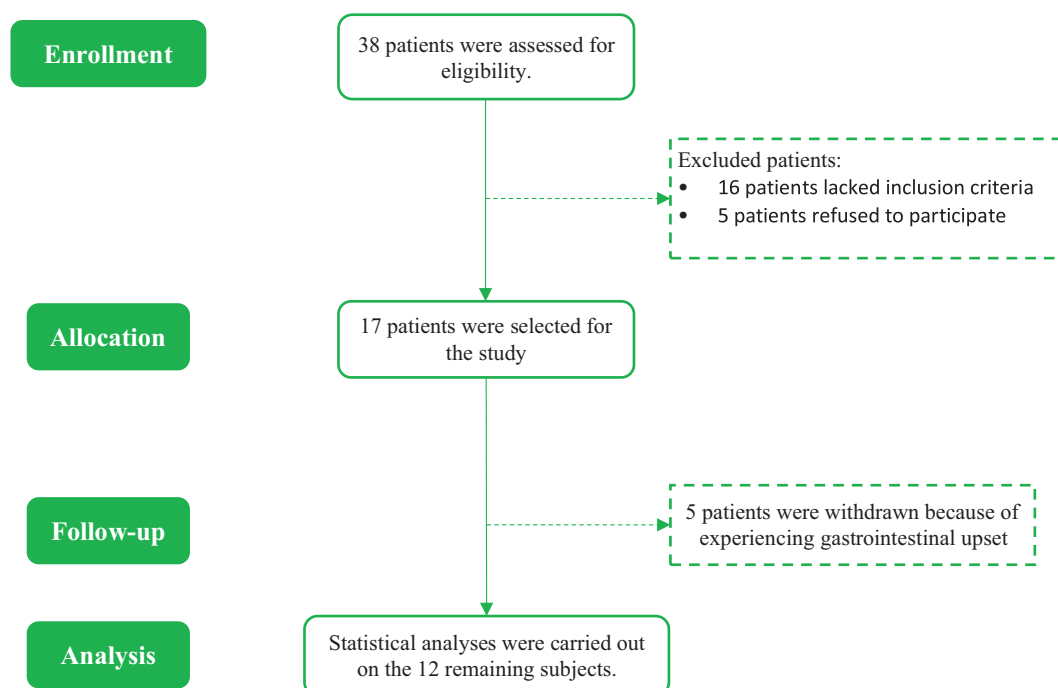


Figure 1. CONSORT flow diagram demonstrating enrollment, allocation, follow-up, and analysis.

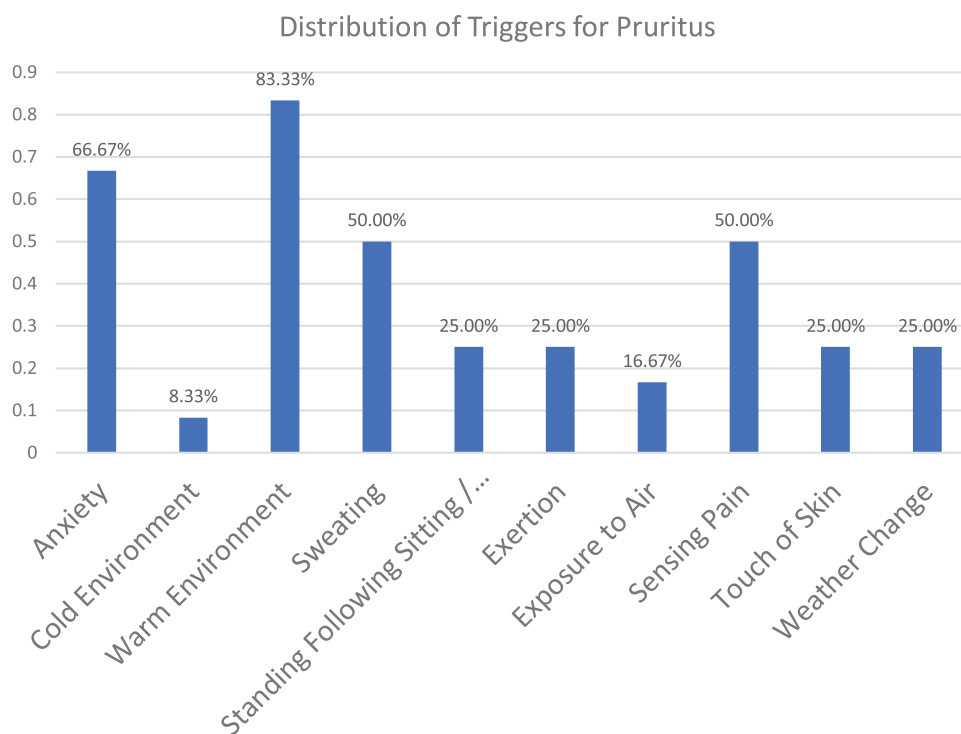


Figure 2. Distribution of triggers for pruritus in patients with epidermolysis bullosa.

Table 1. Frequency distribution of consequences of pruritus.

Consequence of Pruritus	Never	Rarely	Sometimes	Usually	Always
Skin lesions development	8.33%	0.00%	33.33%	25.00%	33.33%
Social communication impairment	25.00%	16.67%	8.33%	41.67%	8.33%
Daily activities impairment	16.67%	0.00%	8.33%	33.33%	41.67%
Difficulty in falling asleep	16.67%	0.00%	25.00%	16.67%	41.67%
Early awakening	8.33%	8.33%	8.33%	16.67%	58.33%
Need for sleep aid	8.33%	25.00%	16.67%	16.67%	33.33%
Anorexia	50.00%	16.67%	8.33%	16.67%	8.33%
Anger	58.33%	8.33%	25.00%	0.00%	8.33%
Behavioral change	8.33%	0.00%	41.67%	8.33%	41.67%
Loss of concentration	25.00%	8.33%	25.00%	16.67%	25.00%

Table 2. Intensities of pruritus before and after the treatment course with Cicaglocal.

Variable	Minimum	Maximum	Median	P- Value
Prior to treatment with Cicaglocal	2	9	8.5	0.026
Following the treatment with Cicaglocal	2	9	4.5	

warm environment (83.33%), nervousness (66.67%), sweating (50%), and pain (50%), listed in the order of prevalence (Figure 2). In addition, applying topical moisturizers was the most common method to mitigate pruritus (83.33%). Tragically, early awakening was deemed the most common consistent repercussion of pruritus, of which 58.33% of participants complained (Table 1).

Changes in Wounds and Pruritus

Comparison of pre- and posttreatment severities of itching disclosed a statistically significant improvement in the median VAS score following the treatment (Table 2). Similarly, the width of ulcers demonstrated a remarkable amelioration; however, changes in ulcer counts did not follow this pattern. However, the ulcers' length generally diminished, despite no

Table 3. Count and dimensions of ulcers, pre- and posttreatment.

Variable	Before Treatment with Cicaglocal		After Treatment with Cicaglocal		P-Value
	Range	Median	Range	Median	
Ulcer count	0-1	1	0-1	1	0.157
Length of ulcer (millimeters)	50-90	50	4-35	9	0.317
Width of ulcer (millimeters)	5-40	9.5	0-20	4.5	0.042



Figure 3. Changes in wounds in 2 patients over the course of treatment with Cicaglocal. A1 and A2: Before treatment the EB patients with Cicaglocal; B1 and B2: After treatment the EB patients with Cicaglocal.

statistical significance (Table 3). Figure 3 illustrates the improvement of the wounds involving the dorsum of the trunk and hand.

Impression of Improvement

CGI-I showed that 83.33% of patients experienced improvement from the clinical perspective after the treatment course with Cicaglocal. However, based on the patients' point of view, this proportion was 75% (Table 4).

Adverse Effects

During the treatment phase, five patients developed gastrointestinal involvement, which included three cases of gastritis and two cases of esophagitis. These participants were excluded from further participation.

Discussion

First and foremost, this study showed the effectiveness of Cicaglocal in improving pruritus intensity and wounds caused

Table 4. Distribution of patients based on the impression of improvement.

Variable	No change / Exacerbation	A little better	Much better	Very better
Clinical global impression of improvement	2 (16.67%)	2 (16.67%)	6 (50%)	2 (16.67%)
Patient global impression of improvement	3 (25%)	0 (0%)	6 (50%)	3 (25%)

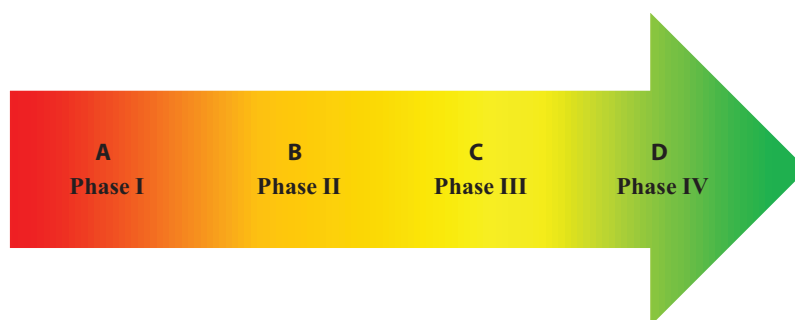


Figure 4. Phases of wound healing (listed in the order of time). A. Coagulation (Fibrin Clot Formation), B. Inflammatory Response, C. Cell Proliferation, Re-epithelialization, granulation, angiogenesis, D. Matrix remodeling, Scar formation.

by EB. Furthermore, not only did the physician observe an amelioration in patients' signs, the majority of patients also perceived that their complaints had subsided.

Wound repair is a sophisticated process which can be divided into subsequent stages, illustrated in Figure 4 [17]: i) fibrin clot formation (hemostasis, occurs within seconds to one hour); ii) inflammatory response (within minutes to days); iii) cell proliferation, re-epithelialization, granulation and angiogenesis (begins 18–24 hours after wounding and lasts from days to weeks); iv) matrix remodeling and scar formation (5–7 days after injury and can persist for months to years).

This mixture of enzyme (Bromelain) is yielded from pineapple (*Ananas Cosmosus*); it can activate natural killer cells and enhances generation of granulocyte-macrophage-colony stimulating factor, interleukin-2 (IL-2), and IL-6. This also reduces T-helper cell activation. Hence, bromelain lowers most of the inflammatory mediators, thereby exerting anti-inflammatory effects. Interestingly, bromelain exhibits fibrinolytic effects and averts thrombus formation. [20]. Thus, bromelain holds potential to maintain blood flow to the wounded area.

Bromelain's proteolytic properties allow the elimination of proteins causing edema and swelling. It should not be overlooked that this property can enhance wound healing through facilitating the elimination of injured tissue and the expansion of healthy cells [10]. Bromelain lowers plasma kininogen, thereby inhibiting the generation of kinin, an agent inducing pain [21].

The enzymatic debridement with bromelain can facilitate recuperation of blood perfusion and heightens expression of

transforming growth factor beta (TGFβ) [22]. TGFβ1 plays roles in skin homeostasis via suppressing keratinocyte proliferation and regulating its differentiation. TGFβ signaling emerges as a critical factor in wound closure [23].

Centella asiatica extract promotes collagen synthesis and fibroblast proliferation after injury. This is also able to bolster angiogenesis, which in turn enhances wound healing. In addition, *Centella asiatica* offers an anti-inflammatory advantage through reducing pro-inflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor alpha (TNFα) [11]. Its anti-inflammatory property is underscored, considering the role of prolonged inflammation in impairing complete wound healing [24]. Importantly, this extract possesses a mast cell stabilizing property, which can justify its potential pruritus alleviating capability [25,26]. Also, given the ability of TNFα in stimulating histamine release [27], combined with the inhibitory effect of *Centella asiatica* extract on TNFα release [11] and the role of histamine in mediating itch [28], the potential mechanism of itch-suppressing activity of *Cicaglocal* is illuminated.

HA molecules make up a porous network which is crucial to cell migration, granulation tissue formation, and accordingly wound healing. The other decisive roles of HA in wound healing process include contribution to edema formation needed for cell infiltration and angiogenesis, along with abating inflammatory response through prohibition of neutrophil migration, and enhancing migration of keratinocytes and fibroblasts to the wounded site [29].

Niacin (vitamin B3) promotes cellular division in wounds. Its vasodilatory effect seems beneficial to wound

healing regarding the need for proper blood perfusion [30]. Furthermore, nicotinamide (NA), the active form of vitamin B3, ameliorates wound healing via abating inflammation, as well as an increase in fibroblast proliferation, collagen production, and vascularization [31].

Riboflavin (vitamin B2) plays the cofactor's role in flavo-protein enzymes which is involved in production of cellular energy needed for a vast diversity of processes, including repair [32]. Additionally, riboflavin has emerged as a photo-activated agent that crosslinks collagen. [33] This phenomenon can enhance the structural strength of wounded tissue. In addition, riboflavin deficiency decelerated wound contraction in rats. Moreover, riboflavin-deficient rats exhibited decreased tensile strength of wounds [34].

The vitamin D sensing receptor as well as the calcium sensing receptor have important roles in the process of activation of stem cells in response to wounding. Actually, the formation of E-cadherin/catenin complex, which is necessary to the activation and migration of epidermal stem cells, is synergistically stimulated by vitamin D and calcium [35].

Ascorbic acid (vitamin C), together with iron, is involved in proline and lysine hydroxylation, the reaction which produces precursors for collagen synthesis [36]. Furthermore, there is evidence suggesting that vitamin C enhances the division and migration of dermal fibroblasts needed in wound healing [37]. Moreover, vitamin C is needed for apoptosis of neutrophils migrated to the wound during the inflammatory phase. Evidence suggests that if the neutrophils are not opportunely eliminated from the wound environment, they can release toxic contents, thereby impeding timely wound healing [38]. Importantly, the antioxidant function of vitamin C prevents oxidative damage to fibroblasts and collagen-producing enzymes during tissue repair [39].

Zinc has a wide array of roles in almost all phases of the wound repair process, including regulating membrane repair, reducing oxidative stress, and modulating inflammation along with facilitating angiogenesis and re-epithelialization. Zinc's effects on wound repair are highlighted considering the development of skin lesions and an attenuated wound repair in zinc-deficient individuals [17].

Copper enhances angiogenesis through stimulating vascular endothelial growth factor (VEGF). Actually, copper is needed to activate hypoxia-inducible factor-1 (HIF-1), an important transcription factor which regulates VEGF's expression [40].

A randomized clinical trial by Asilian et al. was performed in 2023 on 24 patients with BCC or SCC undergoing Mohs surgery. Since the first postoperative day, the patients received administered placebo or Cicaglocal, once daily, and outcomes were assessed seven and 14 days following the start of therapy. The study revealed that Cicaglocal improved the erythema of wounds considerably better than did placebo.

In addition, the Cicaglocal group demonstrated significantly higher early healing and full recovery score betterment along with patient and physician satisfaction [9]. This study was similar to the current one in terms of the studied agent and the obtained results. However, the durations of treatment course, sample sizes, and the patients' diseases differ.

Changsan et al. conducted a clinical trial in 2023 on 60 patients with clean-contaminated wounds, aiming to study clinical effectiveness of a spray film composed of *Centella asiatica* extract (Asiatic acid, madecassic acid, asiaticoside, and madecassoside) in relieving acute wounds. The testing group experienced a significant reduction in PUSH and exudate scores. Furthermore, the testing group experienced wound repair more immediately (within 4.6 ± 1.1 days of treatment onset) than the control group (4.87 ± 1.0 days) [41]. Although the examined drug was actually an ingredient of Cicaglocal, and our study resembles theirs regarding the conclusion, both studies are different in multiple aspects, including the sample size, the method, and patients' diseases.

In 2018, a study by Shoham and colleagues was carried out on 24 patients (patients had wounds of different etiologies) to investigate the safety and efficacy of bromelain-based enzymatic debridement in chronic wounds. The patients were treated with no more than 11 sequential 4-hour sessions of enzymatic debridement. Ultimately, all wounds showed an average of $68\% \pm 30\%$ debridement in about 3.5 ± 2.8 sessions. Fortunately, no adverse event was reported; however, allegedly, pain was the most common side effect. Accordingly, the authors inferred that bromelain-based enzymatic debridement of chronic wounds is potentially safe and efficient [42]. Moreover, a Cochrane review by Roehrs et al. in 2022 included trials to evaluate the effectiveness of HA in recovering chronic wounds. The authors concluded that in those with leg ulcers, HA presumptively ameliorates complete ulcer healing in comparison with neutral vehicle and may relieve pain [43].

The current study encountered variability in patient cooperation; in particular, a subset of patients did not adhere to the timely administration of Cicaglocal. Also, the study was conducted using a small sample size. Actually, a larger sample size would promote the power of the study in addition to improving the generalizability of the results. Therefore, we recommend that future studies should include a larger sample size. Furthermore, this study did not evaluate the effects of Cicaglocal on the elderly.

Conclusions

In essence, Cicaglocal demonstrated statistically significant effectiveness in reducing pruritus and promoting wound healing in EB patients. However, these results should be interpreted as hypothesis-generating due to the lack of a

control group, the small sample size of the study, and the short follow-up duration.

Ethics Approval: The study was approved by the Shiraz University of Medical Sciences' local ethics committee for biomedical research on 20 December 2023 and was allocated the approval ID IR.SUMS.MED.REC.1402.430 The study was carried out in accordance with the principles of the Declaration of Helsinki (1964).

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