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Combination Therapy with rhGM-CSF Gel and Collagen Sponge for Pediatric Deep Dermal Burns: A Randomized Clinical Study

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Abstract

The goal of this investigation was to assess the therapeutic benefits of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) gel, medical collagen sponge, and the joint application of rhGM-CSF gel together with medical collagen sponge on deep second-degree burns affecting the head, face, or neck in infant patients. 108 infants presenting with deep second-degree burns on the head, face, or neck were assigned by random allocation to one of three arms: an rhGM-CSF arm, a medical collagen sponge arm, and an arm receiving rhGM-CSF combined with medical collagen sponge. Comparisons and analyses were performed for the time required for scab dissolution, the duration of wound closure, the rate of positive bacterial cultures, and the Vancouver Scar Scale ratings. The analyzed data indicated that both the period for scab dissolution and the time to wound healing were reduced in the combination arm relative to the rhGM-CSF alone and medical collagen sponge alone arms, with the observed difference reaching statistical significance ($P < .05$). The proportion of positive bacterial findings was also lower in the rhGM-CSF plus medical collagen sponge arm than in the two monotherapy arms ($P < .05$). At the 3-month follow-up, the measurements on the Vancouver Scar Scale—covering thickness, pliability, pigmentation, and vascularity of the scar—were more favorable in the rhGM-CSF plus medical collagen sponge arm compared with the arms using rhGM-CSF or medical collagen sponge independently ($P < .05$). Combining rhGM-CSF gel with medical collagen sponge yields marked efficacy in the management of deep second-degree burns of the head, face, or neck among infants. This regimen helps control infection, accelerate scab dissolution and wound repair, and reduce scar overgrowth and abnormal pigmentation, supporting its value for broader clinical adoption and dissemination.

Keywords: Collagen sponge, rhGM-CSF gel, Pediatric, Dermal burns

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Introduction

Worldwide, it is projected that hundreds of thousands of individuals lose their lives to burn injuries annually, and infants are at elevated risk as a consequence of caregiver oversight or deficient safety consciousness, making burns the fifth most common source of nonfatal injuries in children [1]. Additionally, financial status appears to play a role in burn incidence, with developing regions and low-income countries exhibiting a higher prevalence [2]. In China, the incidence of infant burns is increasing. Infant burn injuries are typically severe, particularly when they involve the face and neck, and are linked to grave complications and a poor outlook. Hence, early and appropriate intervention improves prognosis and reduces financial strain.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a multifunctional cytokine that regulates the biological activities of granulocytes and macrophages. Under normal homeostatic conditions, GM-CSF is not required for baseline myelopoiesis. When tissue damage or inflammatory processes occur, however, GM-CSF is released from numerous cell types to drive neutrophil proliferation and monocyte maturation, processes that support tissue repair [3]. In experimental animal models, either topical or systemic delivery of GM-CSF significantly accelerates wound closure timelines [4, 5]. Moreover, this agent has been introduced into clinical practice for the treatment of burn wounds and has shown notable efficacy as a recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) gel [6]. It has also been documented that rhGM-CSF gel can be safely administered to pediatric burn cases without provoking adverse drug events [7], thereby representing an alternative modality for the care of burned infants.

Medical collagen sponge, as designated, is a biomaterial composed predominantly of type I collagen, which is biocompatible with human tissues and does not elicit immune rejection [8]. In everyday clinical application, the medical collagen sponge is utilized as a supplementary product to facilitate wound repair [9]. Whether medical collagen sponge offers genuine effectiveness in the treatment of infant burn wounds remains uncertain. In this study, we compared the clinical outcomes of rhGM-CSF gel alone, medical collagen sponge alone, and concurrent rhGM-CSF gel plus medical collagen sponge for deep second-degree burn injuries of the head, face, or neck in infants.

Materials and Methods

Patients

Altogether, 108 infant patients diagnosed with deep second-degree burns involving the head, face, or neck were recruited from January 2020 through January 2022. Each child's guardian received details about this trial, consented to the child's enrollment in the research, and provided signed informed consent. Photographs of the affected children appearing within this manuscript were released with the guardians' approval. Permission to publish the case specifics was secured through guardian-informed consent. The study complied with the Declaration of Helsinki and was sanctioned by the Ethics Committee of Wenzhou Medical District, NO—906 Hospital, Joint Logistics Support Force of the PLA (906ECA-2020-001).

Inclusive and exclusive criteria

The study's inclusion parameters encompassed the following: every participant was younger than 3 years of age; the injuries were classified as deep second-degree burns to the head, face, or neck caused by hot liquids; every participant was treatment-naïve, having received no medical care before being admitted.

The study's exclusion parameters comprised the following: patients presenting with major systemic illness or disturbances in organ performance; patients with known hypersensitivity to rhGM-CSF, medical collagen sponge, or type I collagen; patients with a tendency toward hypertrophic scarring or keloid formation.

Randomization and masking

The infants enrolled were randomly allocated to three study arms: one receiving rhGM-CSF, one receiving a medical collagen sponge, and one receiving rhGM-CSF together with a medical collagen sponge, with each arm comprising 36 subjects. A flow diagram depicted the enrollment sequence. Baseline comparison across the three arms revealed no statistically meaningful differences in age distribution, sex ratio, or burn wound surface area **(Table 1)**. The investigators were aware of the group assignment and the corresponding therapeutic regimen. Once all wounds had fully healed, the patients were followed for 3 months.

Table 1. Baseline data ($\bar{\chi}\pm s$).

Grouping	Wound area (%TBSA)	Age (years)	Male (n)/female (n)
rhGM-CSF group	6.28 ± 2.31	1.6 ± 0.7	20/16
Medical collagen sponge group	7.00 ± 2.62	1.8 ± 0.5	22/14
rhGM-CSF + medical collagen sponge group	6.67 ± 3.28	1.7 ± 0.4	19/17
F	0.61	1.20	7.00
P value	.54	.31	.12

Abbreviation: rhGM-CSF = recombinant human granulocyte-macrophage colony-stimulating factor.

Interventions

All subjects were hospitalized and placed on fundamental supportive treatment. Fluid-filled bullae were drained by puncture, whereas tiny blisters were preserved intact. The wound surfaces were disinfected using benzalkonium chloride solution. After saline irrigation, the wounds were subjected to infrared irradiation. At the same time, an intravenous infusion containing glucose, vitamin C, and latamoxef sodium was administered for volume resuscitation, oxidative stress reduction, and infection

prophylaxis, respectively. In the rhGM-CSF arm, wound care employed rhGM-CSF gel (GeneScience Pharmaceuticals Co., Ltd., China, SFDA approval number S20080003), applied strictly per the product's prescribing guidance. In the medical collagen sponge arm, wound management consisted of applying the medical collagen sponge (BIOT Biology, China; SFDA approval number 20143142302). For the combination arm, the wound was first dressed with rhGM-CSF gel, followed by a layer of medical collagen sponge gently positioned over the gel. Every wound was subsequently covered with sterile vaseline-impregnated gauze. Skilled healthcare professionals executed the entire treatment protocol.

Clinical evaluation

For this study, the measures selected to reflect the effectiveness of the differing therapeutic strategies were time to scab dissolution, time to wound healing, rate of positive bacterial detection, and the Vancouver Scar Scale (VSS).

Scab dissolving time

Noting the specific day on which the wound bed was visually clear of scab following the initiation of therapy.

Wound healing time

Noting the specific day on which full wound epithelialization was confirmed.

Bacterial positive rate

On day 7 after treatment commenced, a bacterial culture was performed using wound exudate samples.

Assessment of VSS

The VSS was a standardized scoring instrument designed to assess post-healing scar quality by evaluating scar thickness, pliability, pigmentation, and vascularity [10].

Statistical analysis

The dataset was processed through SPSS 25.0 software (IBM SPSS Statistics, USA). Depending on the results of normality testing and variance homogeneity assessment, the t-test, Mann–Whitney test, or Chi-square test was applied as appropriate. A calculated P value below 0.05 was considered statistically significant.

Results and Discussion

Comparison of the scab dissolving time

As summarized in **Table 2**, the duration required for scab dissolution in the rhGM-CSF arm averaged (8.45 ± 2.52) days, which proved shorter than the corresponding figure in the medical collagen sponge arm. Notably, the arm treated with both rhGM-CSF and a medical collagen sponge had the shortest scab-dissolution time among the three arms.

Table 2. Comparison of the scab dissolving time and healing time ($\bar{\chi}$± s).

Grouping	Healing time (d)	Scab dissolving time (d)	Cases
rhGM-CSF group	19.63 ± 2.65	8.45 ± 2.52	36
Medical collagen sponge group	18.25 ± 3.21*	9.68 ± 2.28*	36
rhGM-CSF + medical collagen sponge group	15.73 ± 2.47*,†	6.88 ± 1.73*,†	36
F	18.029	14.628	
P-value	< .01	< .01	

Abbreviation: rhGM-CSF = recombinant human granulocyte-macrophage colony-stimulating factor.

*Signifies a comparison against the rhGM-CSF arm, P < .05.

†Signifies a comparison against the medical collagen sponge arm, P < .05.

Comparison of healing time

Wound healing times were recorded as 19.63 ± 2.65 days for the rhGM-CSF arm, 18.25 ± 3.21 days for the medical collagen sponge arm, and 15.73 ± 2.47 days for the rhGM-CSF plus medical collagen sponge arm, in that order **(Table 2)**. These findings suggested that the concurrent utilization of rhGM-CSF gel and medical collagen sponge could meaningfully shorten the wound closure timeline.

Comparison of bacterial positive rate

Data in **Table 3** demonstrated that the count of bacterial positive cases within the rhGM-CSF plus medical collagen sponge arm was lower than counts in the two comparator arms (F = 31.24, P = .03) at the 7-day post-treatment assessment. It was additionally apparent that bacterial positive cases in the rhGM-CSF arm were fewer than those in the medical collagen sponge arm **(Table 3)**.

Table 3. Comparison of bacterial positive cases and negative cases among the three groups.

Grouping	Positive cases/negative cases
rhGM-CSF group	7/29
medical collagen sponge group	10/26
rhGM-CSF + medical collagen sponge group	3/33

F	31.24
P-value	.03

Abbreviation: rhGM-CSF = recombinant human granulocyte-macrophage colony-stimulating factor.

Comparison of VSS

At the 3-month post-treatment follow-up, VSS scores were assessed. The pigmentation score was better in the rhGM-CSF arm compared with the medical collagen sponge arm; conversely, the latter arm demonstrated more favorable pliability and vascularity scores **(Table 4)**. Strikingly, the arm that received rhGM-CSF combined with a medical collagen sponge exhibited consistently superior parameters—pigmentation, thickness, pliability, and vascularity—when compared with each of the two monotherapy arms **(Table 4)**. Overall, the combination arm achieved the highest total VSS score among the three treatment arms **(Table 4)**.

Table 4. Comparison of VSS score ($\bar{\chi}\pm$ s).

Grouping	Cases	Total score	Vascularity	Pliability	Height	Pigmentation
rhGM-CSF group	36	7.16 ± 1.61	2.01 ± 0.18	1.64 ± 0.25	1.55 ± 0.24	1.38 ± 0.18
Medical collagen sponge group	36	6.22 ± 1.92*	1.56 ± 0.22*	1.35 ± 0.32*	1.52 ± 0.13	1.49 ± 0.24*
rhGM-CSF + medical collagen sponge group	36	4.93 ± 1.56*,†	1.32 ± 0.37*,†	0.95 ± 0.13*,†	1.14 ± 0.18*,†	1.13 ± 0.06*,†
F		15.54	60.87	152.41	52.77	39.27
P-value		<.01	<.01	<.01	<.01	<.001

Abbreviations: rhGM-CSF = recombinant human granulocyte-macrophage colony-stimulating factor, VSS = Vancouver scar scale.
Compared against the rhGM-CSF arm, P < .05.
†Compared against the medical collagen sponge arm, P < .05.

Brief introduction of a typical case

A child aged 2 years presented to the hospital with scalding trauma involving the face and neck **(Figure 1)**. The injury was determined to be a deep second-degree burn covering 4% of the total body surface area. The physical examination noted swelling of the traumatized face and neck, preservation of the epidermal layer, sporadic blistering, and diminished pain perception upon stimulation. A multi-pronged management plan was implemented to address fluid restoration, oxidative stress control, infection prophylaxis, and wound-healing stimulation. Specifically, intravenous infusions of glucose and vitamin C, and latamoxef sodium, were administered as baseline support, after which the affected zone was subjected to infrared irradiation. Next, rhGM-CSF gel was spread across the wound surface, and a medical collagen sponge soaked in saline was gently placed on top of the gel. By the seventh day, the wound had partially closed and shown significant improvement **(Figure 2)**. After 15 days of therapy, the child had recovered and was discharged. At the final follow-up visit, the wound had healed satisfactorily, leaving no discernible scar on the face or neck **(Figure 3)**.

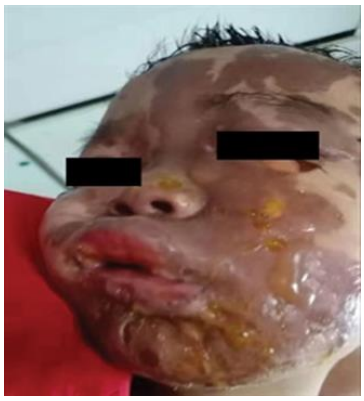

Figure 1. Clinical image captured upon hospital admission, showing a child with scalding injuries to the face and neck.

Figure 2. Image captured on day 7 of treatment with rhGM-CSF gel and medical collagen sponge. rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor. rhGM-CSF = recombinant

human granulocyte-macrophage colony-stimulating factor.

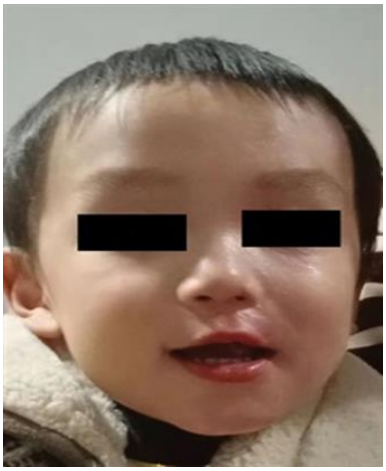

Figure 3. Image captured at the final follow-up visit of the child managed with rhGM-CSF gel and medical collagen sponge. rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor. rhGM-CSF = recombinant human granulocyte-macrophage colony-stimulating factor.

Injuries to the skin are widespread in daily life and stem from diverse intrinsic or extrinsic insults; among these, burns stand out as particularly problematic, carrying an elevated risk of infection and hypertrophic scarring [11]. Data suggest that pediatric patients constitute roughly half of the overall burn casualty population [12]. Though children's skin is equipped with a heightened regenerative drive, the developmental immaturity of their integumentary and immune systems leaves burn wounds more vulnerable to microbial invasion, thereby deepening and aggravating the initial injury, especially given the challenges of securing passive cooperation during pediatric care delivery. Hence, early-phase strategies that emphasize infection suppression and reduced inflammation are indispensable for accelerating wound closure, which in turn paves the way for improved scar appearance.

In the contemporary Chinese medical landscape, three topical growth factor preparations are used for wound care: recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF), epidermal growth factor (EGF), and fibroblast growth factor (FGF). With respect to their modes of action, rhGM-CSF acts by shaping the functional behavior of neutrophils and macrophages within the inflammatory stage—the opening chapter of the healing sequence—thereby hastening the launch of tissue repair. Its influence, moreover, spans the entire healing continuum. EGF and FGF, by comparison, are implicated mainly during the proliferative stage, which comes after the inflammatory stage. Some studies suggest that rhGM-CSF achieves better outcomes than either EGF or FGF. One recent network meta-analysis concluded that rhGM-CSF outperformed both alternatives in reducing the time required for burn wound closure [13]. It is on these grounds that rhGM-CSF was selected for the present trial. GM-CSF, which exerts a broad spectrum of biological roles within the colony-stimulating factor family, is principally recognized for driving the expansion and specialization of myeloid precursors in the context of chemotherapy- or radiotherapy-induced bone marrow toxicity or suppression [14, 15]. The molecule also proves useful in expediting wound repair [16], easing the course of sepsis [17], and restoring pulmonary function in autoimmune pulmonary alveolar proteinosis [18]. A well-established paradigm holds that neutrophils are the first responders at the wound site, arriving to ingest pathogens and debris through phagocytosis, after which macrophages clear these spent neutrophils via efferocytosis. This action limits runaway neutrophil-driven inflammation and fosters macrophage expansion [19-21]. Neutrophil activity is largely confined to the inflammatory phase of healing, whereas macrophages deliver supportive functions throughout the entire repair process, from inflammation through proliferation to remodeling [22]. At a mechanistic level, macrophages do more than carry out phagocytosis and efferocytosis: they release growth factors and proteolytic enzymes, regulate the behavior of epithelial, endothelial, fibroblastic, and myofibroblastic lineages, and remove apoptotic bodies and surplus extracellular matrix components, thereby exerting control over both scar architecture and pigmentation [22, 23]. This positions neutrophils and macrophages as indispensable orchestrators of wound repair that culminates in a superior-quality outcome.

Building on the preceding theoretical account highlighting the indispensable functions neutrophils and macrophages fulfill during tissue repair, GM-CSF yields favorable therapeutic outcomes across a range of wound types. Huang *et al*. [24] executed a randomized clinical experiment to explore the performance of rhGM-CSF in persistent cutaneous ulcerations—namely pressure injuries, venous ulcers, and diabetic foot wounds—with findings indicating that patients assigned to rhGM-CSF application surpassed those managed with vaseline gauze on measures of macroscopic granulation assessment, pace of wound closure, and self-reported pain intensity. In the context of frostbite lesions, a single-center randomized clinical trial demonstrated that rhGM-CSF reduced localized inflammatory activity, reduced the wound microbial load, and accelerated re-epithelialization [25]. Pooled clinical evidence from a systematic review coupled with meta-analysis signified that rhGM-CSF hastened both the speed of wound contraction and the total time to closure, free from any systemic untoward events, across adult and pediatric burn cohorts alike [6, 7]. An

investigation carried out more recently confirmed the utility of rhGM-CSF in subjects afflicted with chronic venous leg ulceration [26]. In parallel, rhGM-CSF represented a sound therapeutic candidate for attenuating hypertrophic scar development and restraining dyspigmentation once re-epithelialization had concluded [10]. Turning to the present work, rhGM-CSF gel abbreviated the interval required for eschar separation, reduced the proportion of positive bacterial cultures, and yielded a more favorable pigmentation score compared against medical collagen sponge in the management of infant burn injuries—observations tightly linked to GM-CSF's modulatory influence over neutrophils and macrophages. Even so, medical collagen sponge outstripped rhGM-CSF in terms of the rapidity of wound closure.

The fundamental building block of the medical collagen sponge is type I collagen, a structural macromolecule that confers tensile strength and provides a defensive barrier to the integument. One experimental study, employing both cell-based and whole-animal methodologies, confirmed that a depletion of type I collagen stood among the principal determinants precipitating delayed skin wound resolution in a mouse system [27]. Among individuals with diabetic foot ulcers, an upregulation of type I collagen abundance was observed to accompany accelerated wound repair [28]. As of late, sponges fabricated from type I collagen have been scrutinized and have showcased excellent host compatibility alongside reparative properties [29, 30]. Within the confines of our study, the antimicrobial capacity of medical collagen sponge lagged behind that of rhGM-CSF gel. Yet the sponge was tied to a modestly reduced wound-closure timeline. In addition, the pliability and vascularity sub-scores on the VSS instrument registered lower values in the arm receiving medical collagen sponge than in the arm receiving rhGM-CSF. Most notably, the dual therapy—rhGM-CSF deployed alongside a medical collagen sponge—achieved superior results across all endpoints measured, namely eschar separation duration, time to full closure, microbial culture positivity, and VSS ratings, relative to rhGM-CSF gel alone or the sponge alone.

Several limitations inherent to our research warrant explicit mention. The cohort size per treatment arm was on the smaller side, potentially curtailing the capacity to tease out meaningful between-group differences. Although the contrasts detected between the rhGM-CSF arm and the medical collagen sponge arm satisfied the threshold for statistical significance concerning eschar separation time, closure time, vascularity score, and composite VSS score, the magnitude of these differences remained numerically slight. In addition, the clinical evaluation was limited to a single institution; consequently, the generalizability of the dataset may be limited. Multi-center involvement, paired with substantially larger sample sizes, is required to corroborate the unequivocal therapeutic benefit of rhGM-CSF gel and medical collagen sponge in the pediatric population.

Conclusion

The evidence we present indicates that rhGM-CSF gel and medical collagen sponge each harbor their own respective clinical strengths, rooted inherently in the discrete biological actions of GM-CSF and type I collagen, and that a combined approach integrating rhGM-CSF gel alongside medical collagen sponge can meaningfully enhance both the immediate therapeutic outcome and the extended prognosis of burn injuries within a pediatric population.

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