Study of Trolamine-Containing Topical Emulsion for Wound Healing After Shave Biopsy

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The efficacy and safety of trolamine-containing topical emulsion (Biafine®) for enhancing wound healing after shave biopsy were evaluated in a single-center, open-label, single-group study. Fifteen participants applied trolamine-containing topical emulsion twice daily to the entire wound area for 4 weeks. Twelve of 15 participants (80%) completed the study. Wound healing was evaluated at weeks 1, 2, and 4. After 1 week of treatment with trolamine-containing topical emulsion, wound size was reduced by half. Complete healing occurred by week 4. Intention-to-treat (ITT) analysis of the investigator's global assessment (IGA) of efficacy (primary end point) over time showed trolamine-containing topical emulsion was moderately to very effective in 80% of participants (12/15) at week 1, 86.7% (13/15) at week 2, and 80% (12/15) at week 4; corresponding figures for the per-protocol analysis were 85.7% (12/14), 100% (13/13), and 100% (12/12), respectively. Treatment was well-tolerated with mild or moderate application-site signs (ie, erythema, erosion, inflammation, crusting) present during the first 2 weeks of treatment; mild or moderate subjective symptoms (ie, irritation, itchiness, burning, tenderness, pain) were present predominantly during the first 2 weeks of treatment. One participant withdrew from the study because of application-site erythema/burning probably related to trolamine-containing topical emulsion. These data indicate that 4 weeks of treatment with trolamine-containing topical emulsion promotes rapid healing and is safe and well-tolerated in patients who undergo shave biopsies.

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Skin biopsies, including shave, punch, and excisional biopsies, are common diagnostic procedures. Shave biopsy is the least invasive. It does not require suturing. It is safe, simple to perform, and economical. However, as with all physical modalities, shave biopsies cause disruption of the epithelium and dermatologists continue to be challenged with identifying a topical agent that expedites the healing process without the risk for antibiotic resistance and contact dermatitis.

Trolamine-containing topical emulsion (Biafine®) is a water-based emulsion with both occlusive and hydrating properties that has been used extensively in Europe and the United States for the management of multiple conditions affecting skin integrity, including superficial wounds, full-thickness wounds, minor abrasions, pressure sores, dermal ulcers, dermal donor and graft site management, first and second degree burns, and radiation dermatitis.[1] Macrophages are involved in several aspects of wound healing, including phagocytosis, cellular recruitment and activation, angiogenesis, regulation of matrix synthesis, and wound debridement.[2] Trolamine-containing topical emulsion promotes wound healing via the recruitment of increased numbers of macrophages to the wound site, with an

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increase in the IL-1:IL-6 ratio that enhances granulation tissue formation.[3] Additionally, the occlusive properties of trolamine-containing topical emulsion may help to protect the wound from external contaminants that could lead to secondary infection, and its hydrating properties may assist in creating a moist environment for optimal healing.

Studies and clinical observations have shown that trolamine-containing topical emulsion has clinical benefits in the prevention of radiation dermatitis[4] and the healing of actinic keratosis treatment sites after cryosurgery[5] as well as wounds that require healing by second intention after dermatologic surgery.[6] This observational study investigated the efficacy and safety of trolamine-containing topical emulsion for enhancing wound healing in participants who underwent shave biopsies.

Methods

A single-center, open-label, single-group study was conducted in outpatients who underwent shave biopsies of clinically suspected lesions on the head and neck. The wounds studied were varied in size and depth. Participants were eligible for inclusion if they were aged 18 to 85 years and able to provide written informed consent. Exclusion criteria included allergy or sensitivity to any component of the test medication; medical condition that, in the opinion of the investigator, contraindicated participation; recent alcohol or drug abuse; history of noncompliance or unreliability; and participation in an investigational drug study within the preceding 30 days.

At baseline, all participants received one 45-g tube of trolamine-containing topical emulsion and written instructions to apply the study medication in a 0.25-in thick layer over the entire wound area twice daily (morning and evening) for 4 weeks. Trolamine-containing topical emulsion was to be applied after washing the wound with soap and water, patting it dry with a soft towel, and waiting 5 minutes. After application of the study medication, participants were advised to moisten the gauze pad of an adhesive bandage and cover the wound area with the bandage, keeping it in place throughout the day (after morning application) and night (after evening application).

Participants were evaluated at baseline (visit 1; week 0) and at weeks 1, 2, and 4. Photographs of the wound area were taken at each visit and the investigator determined the wound size (length and width in millimeters). The primary end point was the investigator's global assessment (IGA) of efficacy using a 4-point scale (0=not effective; 1=slightly effective; 2=moderately effective; 3=very effective). The application site also was assessed for the level of erythema, erosion, inflammation, ulceration, crusting, swelling, infection, necrosis, peeling, contact dermatitis, hyperpigmentation/hypopigmentation, and scarring using a 4-point scale (0=none; 1=mild; 2=moderate; 3=severe). Participants were asked about the presence of adverse events (AEs), if they had missed any applications of study medication since the previous visit, and if they were using any concomitant medication/treatment. They also were asked to evaluate the presence and severity of irritation, itchiness, burning, tenderness, and pain using the same 4-point scale described above (0=none; 3=severe).

All participants were informed in accordance with the International Conference on Harmonisation guidelines and Good Clinical Practice and provided signed written consent before inclusion in the study. The protocol was approved by the institutional review board.

Formal justification of the sample size was not provided for this study. Descriptive statistical analyses were conducted on the intention-to-treat (ITT) population.

Results

Fifteen participants (9 males and 6 females) entered the study (Table 1). Participants were aged 21.6 to 84.9 years (mean [SD], 55.9 [19.5] years). Of the

Table 1.

Participant Demographics

Characteristic	ITT Population (N=15)
Age, y	
Range	21.6–84.9
Mean (SD)	55.9 (19.5)
Median	54.9
Gender, n (%)	
Male	9 (60)
Female	6 (40)
Race, n (%)	
White	15 (100)

Abbreviations: ITT, intention to treat; SD, standard deviation.

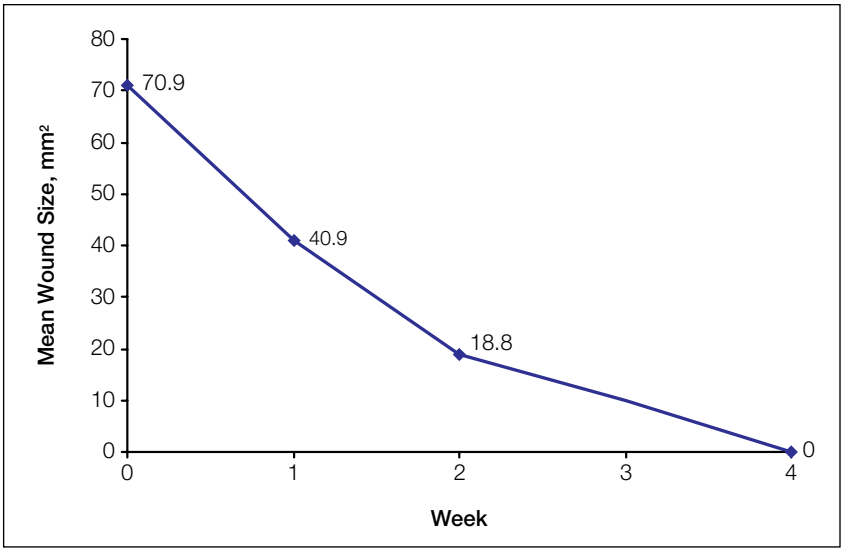

Figure 1. Change in wound size over time with trolamine-containing topical emulsion treatment.

15 participants enrolled, 12 participants (80%) completed the full 4 weeks of treatment. Three participants discontinued treatment: 2 because of AEs, only one of which was considered treatment related, and the third participant was lost to follow-up. The per-protocol population consisted of 14 participants at week 1, 13 participants at week 2, and 12 participants at week 4.

After 1 week of treatment, trolamine-containing topical emulsion had reduced the wound size by half, with complete healing reported in all participants by week 4 (Figure 1; Table 2). According to the per-protocol analysis, IGA showed trolamine-containing topical emulsion was moderately to very effective in 12 of 14 participants (85.7%) at week 1, 13 of 13 participants (100%) at week 2, and 12 of 12 participants (100%) at week 4. The following results were reported for the ITT population: IGA was moderately to very effective in 80% of participants (12/15) at week 1, 86.7% (13/15) at week 2, and 80% (12/15) at week 4 (Figure 2). Figure 3 depicts the course of healing in one participant.

No participants experienced application-site ulceration, swelling, infection, necrosis, peeling, contact dermatitis, hyperpigmentation/hypopigmentation, or scarring. However, during the first 2 weeks of treatment, mild or moderate application-site erythema, erosion, inflammation, and crusting were reported with resolution by week 4 (Table 3).

Several participants reported mild or moderate irritation (n=7), itchiness (n=4), burning (n=3), tenderness (n=10), and/or pain (n=6) during the first week of treatment. By week 4, all of these events had resolved with the exception of 4 cases of mild itchiness and 1 case of mild tenderness. Severe itchiness was experienced by 1 participant at week 2.

Six participants experienced 10 AEs during treatment; most were mild to moderate in severity and considered unrelated to treatment (Table 4). Only 1 participant had a severe AE, which included a fracture to the left knee and a crush injury to the right ankle; treatment with the trolamine-containing topical emulsion was discontinued

Table 2.

Percentage Change in Wound Size Over Time (Per-Protocol Population)

	Week 1 (n=14)	Week 2 (n=13)	Week 4 (n=12)
Mean (SD) change from baseline, %	−51.02 (31.60)	−85.03 (21.11)	−100.00 (0.00)
P value	<.0001	.0002	—

Abbreviation: SD, standard deviation.

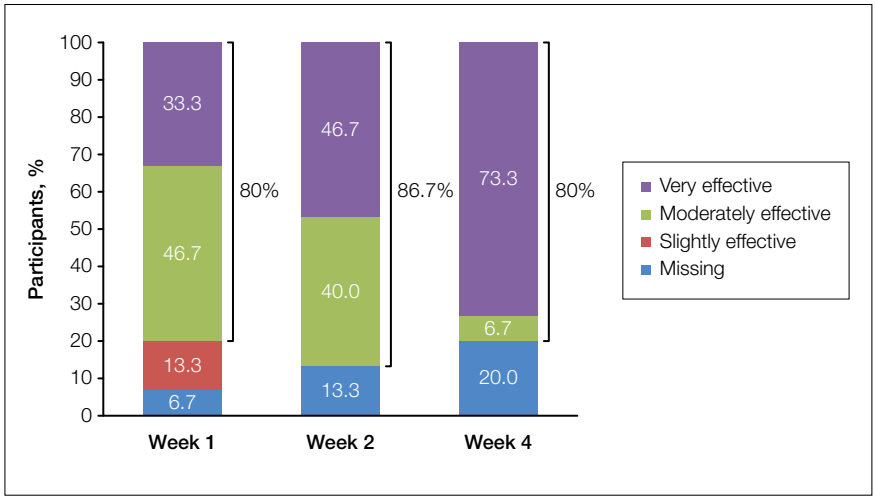

Figure 2. Investigator's global assessment of efficacy over time in the intention-to-treat population (N=15).

Table 3.

Investigator Application-Site Assessments

	Participants, n (%)		
Sign Severity	**Week 1 (n=14)**	**Week 2 (n=13)**	**Week 4 (n=12)**
Erythema			
None	6 (42.9)	5 (38.5)	12 (100)
Mild	6 (42.9)	8 (61.5)	0 (0)
Moderate	2 (14.3)	0 (0)	0 (0)
Erosion			
None	2 (14.3)	8 (61.5)	12 (100)
Mild	11 (78.6)	5 (38.5)	0 (0)
Moderate	1 (7.1)	0 (0)	0 (0)
Inflammation			
None	8 (57.1)	12 (92.3)	12 (100)
Mild	5 (35.7)	1 (7.7)	0 (0)
Moderate	1 (7.1)	0 (0)	0 (0)
Crusting			
None	13 (92.9)	12 (92.3)	12 (100)
Mild	1 (7.1)	0 (0)	0 (0)
Moderate	0 (0)	1 (7.7)	0 (0)

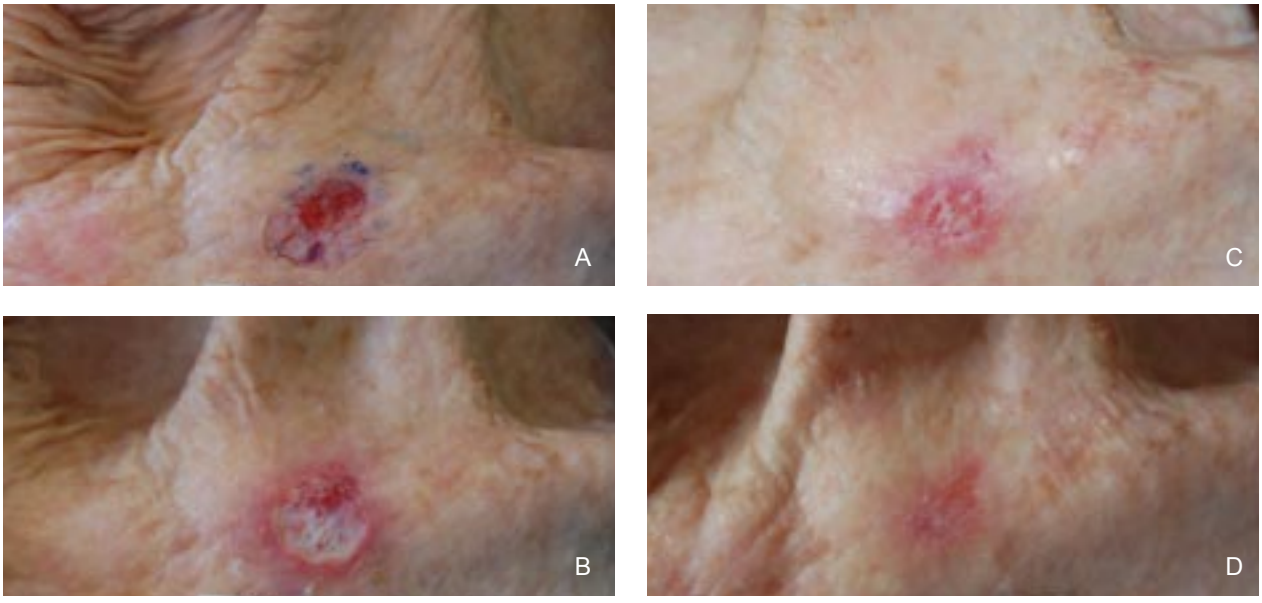

Figure 3. Lesion area at baseline (visit 1)(A), week 1 (visit 2)(B), week 2 (visit 3)(C), and week 4 (visit 4)(D) in a participant who underwent a shave biopsy. The wound site was treated with trolamine-containing topical emulsion twice daily for 4 weeks.

in this participant. One participant developed application-site erythema/burning that was considered probably related to study treatment; the trolamine-containing topical emulsion was discontinued in this participant and the reaction resolved.

Comment

In this uncontrolled study, trolamine-containing topical emulsion appeared to promote rapid healing in a small group of participants who underwent shave biopsies. Wound healing was progressive throughout the study and was apparent within 1 week of treatment, with all wounds completely healed by week 4. For the primary end point, IGA showed trolamine-containing topical emulsion was moderately to very effective in at least 80% of participants (ITT analysis) at all time points. Trolamine-containing topical emulsion was well-tolerated with predominantly only mild or moderate AEs that had mostly resolved by study end.

Although there is a paucity of evidence-based literature to guide clinicians on the optimum therapy for wound healing, it is generally accepted that a moist environment is preferred to air drying.[7,8] The ideal dressing should absorb exudates, avoid trauma to the wound during dressing removal, and be impermeable to water and contaminants.[8] Occlusive or semiocclusive dressings are the treatment of choice for healing by second intention after shave biopsies because wounds managed this way heal quickly, are easy to care for, and cause minimal pain.[9,10] Topical agents such as antibiotic ointment or petrolatum help maintain a moist environment.[9] Because of the disadvantages associated with unnecessary antibiotic use, trolamine-containing topical emulsion represents an attractive alternative to antibiotic creams, as its hydrating properties maintain a moist environment while its occlusive properties may help prevent wound contamination and the development of infection.

Wound healing involves 3 phases: inflammation, proliferation, and maturation. Macrophages play a key role in this process.[2,11] The recruitment of macrophages occurs during the inflammatory phase, with macrophages stimulating fibroblast proliferation that is essential for healing during the proliferative phase. In the proliferative phase, macrophages also promote epithelial cell multiplication and growth.[2] It appears that trolamine-containing topical emulsion is involved with a number of healing processes including macrophage recruitment, which promotes reepithelialization.[3,12] When trolamine-containing topical emulsion was compared with silver sulfadiazine and saline-soaked gauze in the treatment of superficial partial-thickness porcine burns, the reepithelialization rates were similar for all 3 treatments.[12] In a study of pure epidermal wounds in human volunteers (N=6), the exudate of wounds treated with trolamine-containing topical emulsion had significantly increased concentrations of

Table 4.

Adverse Events Reported by Participants Over 4 Weeks of Treatment

Event	No. of Events	Relationship to Treatment[a]
Mild severity		
Squamous cell carcinoma	3	Definitely unrelated
Hematemesis	1	Unlikely
Swelling of hands and feet	1	Unlikely
Moderate severity		
Application-site erythema/burning	1	Probably related
Bronchitis	1	Definitely unrelated
Seasonal allergies	1	Definitely unrelated
Severe		
Fractured left knee	1	Definitely unrelated
Crushed right ankle	1	Definitely unrelated

[a]Investigator's global assessment.

macrophages ($P<.01$ vs controls), higher levels of IL-1, and significantly lower levels of IL-6 ($P<.05$ vs controls), resulting in a significant increase in the IL-1:IL-6 ratio ($P<.05$ vs controls).[3] These findings indicate that trolamine-containing topical emulsion is chemotactic for macrophages and may enhance granulation tissue formation. The action of trolamine-containing topical emulsion in dermal wound healing also was demonstrated in a human skin model of experimental irradiation. In this study, histochemical and biochemical modifications induced by irradiation and modified by trolamine-containing topical emulsion included a reduction in the percentage of dilated vessels, reduced dermal edema, restoration of CD34 expression in endothelial cells, increased epithelial cell proliferation, decreased collagen synthesis, and reduced IL-1α levels.[13]

The current study has a number of limitations. First, it was a study in a small participant population. Second, it was a single-group trial with no control arm that compared the current standard of care. Therefore, a larger randomized, placebo-controlled, double-blind study will be necessary for more definitive conclusions.

Conclusion

The results from this study indicate that trolamine-containing topical emulsion promotes significant healing in a safe and well-tolerated manner in patients who undergo shave biopsies and can be an alternative to topical antibiotic use without the risk of antibiotic resistance and contact dermatitis.

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