ORIGINAL ARTICLE

Thai Novel Cost-Effectiveness Biocellulose Dressing: Clinical Trial Phase I, Randomized Controlled Trial

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Background: Biocellulose wound dressings offer flexibility, high tensile strength, and water-retention properties, resulting in a cool and painless dressing experience. However, their usage has been limited due to high costs. In 2020, the PTT Research and Development Department introduced "Innaqua®," a novel biocellulose wound dressing that excels in fluid absorption capacity, desorption, wound dressing surface, and wound moisturization. This product is particularly suitable for developing countries, as it combines low cost with high effectiveness, thereby enhancing treatment accessibility. However, it lacks clinical studies.

Objective: To evaluate the clinical safety of Innaqua® for human use.

Materials and Methods: A randomized controlled trial, clinical safety study was conducted with 63 healthy volunteers. Skin irritation and allergic reactions were analyzed.

Results: Clinical safety studies of Innaqua® indicated non-inferiority in terms of erythema at 4.8% versus 4.8% (p=0.012) and allergic reactions at 3.2% versus 4.8% (p=0.004) compared with Bactigras®. No edema occurred with either wound dressing.

Conclusion: Innaqua® is a biocellulose wound dressing researched and developed in Thailand. It creates an optimal environment for wounds. The present study demonstrated clinical safety in human use. Innaqua® emerges as a new, cost-effective option for biocellulose wound dressing, catering to a broader population.

Keywords: Biocellulose; Innaqua; Thai; Allergy; Safety

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According to the Wound Healing Society, a wound results from the disruption of normal anatomical structure and function[1]. It is estimated that 3% of people over 65 years of age suffer from a cutaneous lesion at any given time[2]. Local factors associated with the wound healing process include adequate oxygenation, stimulation of angiogenesis, promotion of moisturization, and proper fluid absorption[3]. There are a range of methods to control the wound moisture environment, from local dressings to vacuum-assisted wound dressing systems[4]. In addition to these properties, an ideal wound dressing should be elastic, sterile, non-occlusive, non-allergenic, and easy to apply[5,6]. One such material mentioned is 'biocellulose'.

Biocellulose, synthesized by *Acetobacter xylinium*, was first discovered by Brown in 1886[7]. It possessed flexibility, high tensile strength, and water-retaining properties that contributed to a cool and painless dressing[8]. These functionalities create a more favorable environment for wound healing compared to traditional dressings. Biocellulose dressing shows significantly better outcomes in various wound types. The healing time was twice as fast for patients with partial thickness loss of skin from acute traumatic injury when using biocellulose compared to normal dry dressings[9]. In diabetic ulcers, biocellulose outperforms petroleum gauze, showing a healing rate 1.7 times faster[10]. It also has favorable outcomes in the chronic wound healing process and burn wounds[11,12].

Despite the increasing popularity of biocellulose for its superior wound healing functions, its high

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cost hinders accessibility for many patients[13]. Innaqua® is a hydrogel composed of pure water and nanocellulose fiber developed by the PTT Research and Development Department, Thailand. It is believed to provide moisturization, eliminate necrotic tissue, and relieve pain in the dressing area. Moreover, its lower price compared to original biocellulose products makes it more accessible for low to middle-income societies.

In 2020, preclinical studies were conducted in an animal model at Naruesuan University Center for Animal Research and found Innaqua® to be safe. However, Innaqua® lacks clinical trial phase I. Therefore, the aims of the present study were to evaluate the clinical safety of the product in terms of allergies and irritation in healthy volunteers.

Material and Methods

Sample size and study protocol

The safety test of the present study dressing in healthy volunteers was approved by the Ethics Committee for Research Involving Human Subjects at Siriraj Hospital, 796/2564(IRB3). It was a prospective, randomized, controlled study conducted between December 2021 and February 2022 in the Division of Trauma Surgery, Department of Surgery, Siriraj Hospital, Thailand.

Before initiating the clinical trial phase I for this biocellulose wound dressing (Innaqua®), safety assessments were performed in experimental animals, confirming its safety. From a literature review, Muangman et al. reported allergic reactions to Bactigras®, which the authors used for comparison with Innaqua®[14]. The study indicated an erythema reaction rate of 1.2%. For population calculation in this study, the nQuery Advisor program (MOT1-1) was utilized with parameters including 1.2% erythema skin reaction from Bactigras®, proportion discordant 1.01, test significance level 0.05, equivalent limit difference for non-inferiority test 0.010, expected difference 0.0, and 80% power of the test.

Sixty-three healthy volunteers aged between 18 and 60 years, capable of following instructions, were recruited. Participants were excluded if they had a known history of allergy to biocellulose-containing dressing material or had taken antihistamines or corticosteroids within 2 weeks prior to the study. Withdrawal criteria included volunteers unable to follow up in time. Termination criteria included those experiencing severe allergic reactions such as Stevens-Johnson syndrome or those unwilling to participate. Volunteers who had allergic reactions would be evaluated by medical doctors and consulted for internal medicine and skin specialists in severe cases.

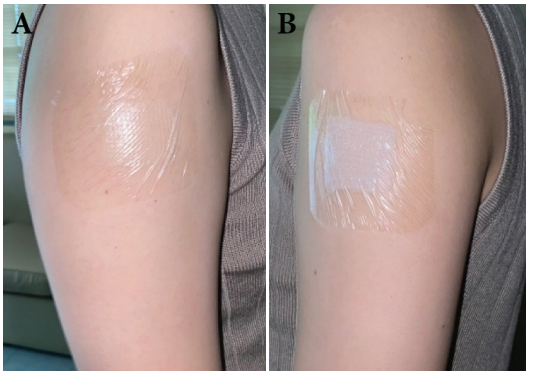

Figure 1. The application of Bactigras® and Innaqua® on upper arms: (A) Bactrigas®, (B) Innaqua®.

All volunteers received information and instructions about the present study, and consent was obtained following ethical committee guidelines. At the study's commencement, the skin on both upper arms of the volunteers was cleaned using a sterile cotton ball soaked with a normal saline solution. Volunteers received Innaqua® or Bactigras® by a random drawing. Subsequently, Innaqua® or Bactigras® in patch of 3×3 cm^2 were applied to the skin and secured with Tegaderm® film (Figure 1). Volunteers were instructed to avoid using skincare products or medication on the test site during the study.

The dressing was changed on day 3 of the study, and skin reactions were measured and data collected using the Acute Dermal Irritation/Corrosion Grading of Skin Reactions from the Organization for Economic Co-operation and Development 2015[15] and the Modified Scale for Reading Repeated Open Application Test Results from the European Society of Contact Dermatitis Patch Test Guideline 2015[16].

Outcome measurements

The Acute Dermal Irritation/Corrosion Grading Of Skin Reactions classified irritating reactions into two categories, erythema and edema, both graded on a scale of 0 to 4 for the severity of the reaction.

The modified scale for reading repeated open application test results defined allergic reactions to contact material on normal skin based on four characteristics, involved area of application, erythema, papules, and vesicles. A score equal to or greater than 5, with a maximum score of 17,

was defined as an allergic reaction for each wound dressing.

Statistical analysis

Data preparation and analysis were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) and R software, a language and environment for statistical computing from the R Foundation for Statistical Computing, Vienna, Austria (URL: https://www.R-project.org/). Quantitative data were expressed as mean and standard deviation (SD) or median and range (min, max) as appropriate. Number and percentage were described for qualitative data. The Mann-Whitney U test was used to compare non-normally distributed quantitative data between the two groups. Qualitative data were compared using Yates' test or Fisher's exact test. All significance tests were two-tailed, and a p-value less than 0.05 was considered significant. A non-inferiority test of two correlated proportions and a one-sided 95% confidence interval (CI) of the correlated proportions difference between Innaqua® and Bactigras® were performed.

Results

Sixty-three volunteers were recruited for the present study. No participants were excluded from the data analysis. The demographic data of the volunteers are described in Table 1.

There was no inferiority of erythema observed in Innaqua® compared with Bactigras® at 4.8% versus 4.8%, one-sided 95% CI of difference of –6.8 to 100 (p=0.012). Regarding edema, no occurrences were reported for both Innaqua® and Bactigras® wound dressings. In terms of allergic reactions, assessed using the modified scale for reading repeated open application test, the results indicated non-inferiority of allergic reactions in Innaqua® compared with Bactigras® at 4.8% versus 3.2%, one-sided 95% CI of difference of –5.5 to 100 (p=0.004) (Table 2).

The only statistically significant factor for erythema reaction in both Innaqua® and Bactigras® irritation was allergic rhinitis, which may be partially related to immunologic responses, with rates of 25.0% and 1.8%, respectively (p=0.04), and 38.0% and 0%, respectively (p=0.001). As for the Modified scale for reading repeated open application test allergic score, allergic rhinitis was associated with a higher risk of Bactigras® allergy, with a median 2.25 versus 0.5 (p=0.001) but had no significant effect on Innaqua® allergy, with a median of 0.5 versus 0 (p=0.115) (Table 3).

Table 1. Demographic data of participants

Variables	
Age (years); mean±SD	37.2±11.9
Age group; n (%)	
18 to 29 years	25 (39.7)
30 to 39 years	15 (23.8)
40 to 49 years	11 (17.5)
50 to 60 years	12 (19.0)
BMI (kg/m^2); mean±SD	24.3±4.1
BMI; n (%)	
<18.5	3 (4.8)
18.5 to 24.9	39 (61.9)
25 to 29.9	13 (20.6)
30 to 34.9	8 (12.7)
Sex; n (%)	
Male	17 (27)
Female	46 (73)
Underlying disease; n (%)	
Arrhythmia	1 (1.6)
DLP	2 (3.2)
DM	3 (4.8)
HT	4 (6.3)
HBV infection	2 (3.2)
OSA	1 (1.6)
PCOS	1 (1.6)
Rheumatoid arthritis	1 (1.6)
Thyroid	3 (4.8)
Allergic rhinitis	8 (12.7)

BMI=body mass index; DLP=dyslipidemia; DM=diabetes mellitus; HT=hypertension; HBV=hepatitis B virus; OSA=obstructive sleep apnea; PCOS=polycystic ovarian syndrome; SD=standard deviation

Table 2. Unfavorable outcomes between Innaqua® and Bactigras® in 63 volunteers

	Innaqua n (%)	Bactigras n (%)	Difference (one sided 95% CI)	Non-inferiority test (p-value)
Erythema	3 (4.8)	3 (4.8)	0.0% (–6.8 to 100)*	0.012**
Allergy score ≥5	3 (4.8)	2 (3.2)	1.5% (–5.5 to 100)*	0.004**

CI=confidence interval

* Non-inferiority was shown, lower bound of the one sided 95% CI for the difference of unfavorable outcomes between Innaqua® and Bactigras® was lower than pre-specified non-inferiority margin of –10%.

** Non-inferiority was shown, p-value of non-inferiority test is less than the significant level of 0.05.

There were no signs of severe allergic reactions or systemic inflammation responses observed upon close monitoring of volunteers on the third day for both Innaqua® and Bactigras® usage.

Discussion

The primary concerns with novel wound dressings are the adverse effects, commonly skin

Table 3. Allergy disease associated with allergic reaction to Innaqua® and Bactigras®

	Allergic rhinitis		p-value
	Yes (n=8)	No (n=55)	
Innaqua			
Erythema irritation; n (%)	2 (25.0)	1 (1.8)	0.040
Allergy score; median (min, max)	0.5 (0, 6)	0 (0, 6)	0.115
Bactigras			
Erythema irritation; n (%)	3 (37.5)	0 (0.0)	0.001
Allergy score; median (min, max)	2.25 (0, 6)	0.29 (0, 4)	0.001

irritation, and allergic reactions. The present study demonstrated the safety of Innaqua® in healthy volunteers, showing no significant difference in skin irritation or allergic reactions symptoms in acute phase setting between the Bactigras® and Innaqua® groups. Allergic reactions to Bactigras® typically manifested as erythema and swelling at the dressing site, while Innaqua® caused papules. Although allergic rhinitis was identified as a potential factor for Bactigras® allergy, it did not correlate with allergic reaction associated with Innaqua®. Thus, it can be inferred that Innaqua® is a safe wound dressing, demonstrating non-inferiority in irritation and allergic reactions compared to the previously known safe dressing, Bactigras®.

Innaqua® emerged as a wound dressing with high absorptive quality, small pores facilitating exudate absorption, and superior moisture retention, promoting an optimal environment for wound healing. The skin irritation and allergic reaction tests in healthy volunteers confirmed the safety of this new dressing on human skin. This valuable information will contribute to the enhancement of wound dressing properties in future developments.

The present study met the expectation of clinical trial phase I of novel wound dressing material. However, further studies in subsequent phases of clinical trials including effectiveness in wound healing in diverse types of wounds in clinical usage are warranted. A larger number of patients need to be evaluated in clinical trial phase II.

Conclusion

Innaqua® stands out as a novel biocellulose wound dressing produced in Thailand with a cost-effective option. It demonstrated no significant clinical side effects and was safe for use in clinical practice.

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Conflicts of interest

All authors declare no conflicts of interest.

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