Topical Probiotics in a Soybean Concentrate for Diabetic Foot Ulcers: A Prospective, Multicentre, Double-Blind, Randomized Controlled Trial

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Study Protocol and Statistical Analysis Plan

This multicentre, prospective, double-blind, two-arm, parallel-group randomized clinical trial was conducted between January 2022 and June 2024 to evaluate the efficacy of a topical probiotic formulation in a soybean concentrate compared with placebo in the treatment of diabetic foot ulcers (DFUs) (ClinicalTrials.gov Identifier: A11002001). Participants were randomized to receive twice-daily application of either investigational product (bottle A) or placebo (bottle B), both administered directly to the wound in addition to standard care. The contents of each bottle were prepared off-site, and both investigators and participants were blinded to treatment allocation.

The trial was conducted across three hospitals in Taiwan—Dalin Tzu Chi Hospital (Chiayi County), Taichung Tzu Chi Hospital (Taichung City), and Hualien Tzu Chi Hospital (Hualien City)—by three senior plastic surgeons, each with expertise in DFU wound management. The study was conducted in accordance with the principles of the Declaration of Helsinki (2013) and Good Clinical Practice guidelines. Ethics approval was obtained from the Institutional Review Boards of each participating centre. All participants provided written informed consent prior to enrolment. The trial was conducted and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Study Population

Eligible participants were adults with a diagnosis of diabetes mellitus and a non-healing DFU measuring greater than 1 cm^2 in area, without exposed bone or tendon. Full inclusion and exclusion criteria are shown in Table 1.

Randomization and Intervention

Block randomization in blocks of 8 was used to assign participants to 1 of 2 groups: Group 1 received bottle A (topical probiotic in soybean concentrate) and Group 2 received bottle B (placebo). Both groups received secondary dressing with standard wound care with wet-to-dry dressings. The assigned topical treatment was applied directly to the ulcer twice daily throughout the treatment phase.

Outcomes and Data Collection

Baseline demographic data, medical history, comorbidities, current treatments, and wound characteristics were recorded at enrolment. Participants were evaluated weekly or biweekly for up to 24 weeks or until complete wound healing, whichever occurred first. At each visit, wound surface areas were measured and documented using standardized digital photography. Adverse events were assessed and documented at each visit. Debridement, when necessary, was performed as part of routine clinical care and recorded.

The **primary outcome** was the proportion of wounds achieving complete healing within 24 weeks. Complete wound healing was defined as full re-epithelialization without drainage or dressing requirements. Wound healing was assessed jointly by the treating plastic surgeon and wound care nurse. Due to resource constraints, independent blinded assessors were not employed.

Secondary outcomes included percentage reduction in wound area, wound recurrence rates, incidence and nature of adverse events, and the need for additional surgical intervention. Participants who achieved wound healing were followed at 2- and 12-weeks post-healing to monitor for recurrence or complications.

Unblinding of treatment allocation was permitted only in the case of a serious adverse event (SAE) in which treatment knowledge was required for patient safety. All unblinding events were documented and reviewed by the data monitoring committee. Otherwise, treatment codes remained concealed until study completion.

Statistics

All analyses were performed using IBM® SPSS® Statistics V25. Continuous variables were summarized using means and standard deviations. Categorical variables were expressed as frequencies and percentages. Paired *t* tests were used to evaluate differences in continuous variables. Chi-square (χ^2) tests were applied for comparisons of categorical variables. Survival outcomes were assessed using Kaplan–Meier analysis and Cox proportional hazards regression modelling. All tests were two-sided, and p values < 0.05 were considered statistically significant.