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CASE REPORT

Effect of probiotic supplementation on wound healing in postoperative patients: A case report and literature review

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Abstract

Background: Delayed wound healing, particularly in chronic wounds, is a significant global public health issue. The World Health Organization (WHO) reports that over 6 million people in the United States experience delayed wound healing annually, resulting in a healthcare cost of $25 billion USD. Probiotics, known for their anti-inflammatory properties, have potential in influencing skin immunity by facilitating the transfer of cytokines and immune cells from Peyer's patches to the skin. Nevertheless, the precise impact of probiotics on postoperative wound healing remains an area with limited research.

Objective: Determine the effectiveness of probiotic supplements in wound healing in patients with surgical wounds

Method: Literature search is done by advanced searching on Pubmed, Cochrane, Scopus, and EBSCOhost with eligibility criteria determined by the author.

Results: There were three articles relevant to clinical questions and eligibility criteria that had been established, consisting of one systematic review article from the randomized controlled trial (RCT) study and two RCT articles. The SR/MA article includes good-quality RCT studies. The SR/MA article showed insignificant results on the effect of probiotic administration on healing. The RCT article showed significant results on the effect of probiotics on surgical wound healing, but the confidence level was low in one of the articles.

Conclusion: Probiotic supplementation on wound healing in postoperative patients is not conclusive. This can be affected by the type of probiotic strain, dosage, duration of administration, and location of the surgical wound.

Keywords: probiotic, wound healing, surgical wound

Case scenario

A 41-year-old woman came to the emergency room with complaints of an open surgical wound after incisional hernia repair after 2 weeks of SMRS. The patient said that the wound initially opened a little, then got bigger, and finally all opened after 1 week of SMRS. Initially, the wound oozed pus from the stitches and drain marks. Since all the stitches were open, pus could no longer come out and pooled in the wound. Within 1 week the patient also complained of fever and pain in the surgical wound. From the physical examination found compos mentis awareness, blood pressure 108/67 mmHg, pulse 86 x/minute, respiratory rate 18 x/minute, SpO2 99% and temperature 36.5 ℃, body mass index 57.5 kg/m2, at physical examination distended, visible surgical scars in the median infra umbilical open with a size of 8 x 4 cm, based on organ impressions, pus and odor present, necrotic tissue present, no active bleeding. There was an open drain with a size of 2.5 cm x 1.5 cm, no pus and active bleeding, normal bowel sounds, supple, VAS 1-2 tenderness, and other physical examination within normal limits. Laboratory

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examination results showed Hb 8.8 g/dL, leukocytes 10,060/µL, platelets 375,000/µL, sodium 136 mg/dL, potassium 3.6 mg/dL, chloride 102.1 mg/dL, GDS 155 mg/dL and Albumin 2 mg/dL. The patient has received therapy for wound problems. In addition, the patient has been given nutrition as needed. The clinic's nutrition specialist plans to provide probiotic supplements to help heal wounds on the skin. The effect of probiotic supplementation is still being debated, so the authors want to find further evidence regarding the effectiveness of probiotic supplementation in the skin healing process in postoperative patients.

Introduction

Delayed wound healing has become a global public health problem, especially in chronic wounds. According to the World Health Organization (WHO), more than 6 million people are affected by delayed wound repairs each year in the United States at a cost of $25 billion (USD) to the Health system.[1] Chronic wounds impact the quality of life (QoL) of nearly 2.5% of the total population in the United States and the management of wounds has a significant economic impact on health care.[2] Caring for surgical wounds presents numerous difficulties, including the patient's underlying health conditions, the surrounding environment, and potential complications. Skin wound healing is a dynamic and highly regulated process of cellular, humoral, and molecular mechanisms that begins immediately after injury and can last for years. Any tissue damage to the normal anatomical structures with successive loss of function can be described as a wound.[3] Wound healing can be divided into four phases, namely hemostasis, inflammation, proliferation, and tissue remodeling.[4] Various things can affect disturbed wound healing. Patients with comorbid problems such as diabetes, vascular disorders, smoking, malnutrition, obesity, infection, immobilization, and administration of immunosuppressants.[4,5] Wound management begins with an assessment of the etiology of the wound and a patient-centered approach to managing systemic and lifestyle factors. Local management often begins with debridement, the removal of necrotic, infected, or hyperkeratotic tissue by surgery or less invasive modalities.[6]

Apart from amino acids, vitamins and minerals that play a role in the wound healing process with anti-inflammatory effects, probiotics have also been studied to have anti-inflammatory effects. Probiotics are living microorganisms which, when consumed in adequate amounts, confer a health effect on the host. Probiotics primarily impact the inflammation phase, which plays a significant role in wound healing impairment. Recent studies in both humans and animals have shown a clear advantage in wound healing when probiotics are applied, influencing the inflammatory response through mechanisms involving oxytocin. Bacteriocins are antimicrobial peptides produced by both gram-positive and gram-negative bacteria. The gut is considered the major immune organ, with gut-associated lymphoid tissue (GALT) being the most complex immune compartment. Cytokines and immune cells from Peyer's patches can be transported via circulation to the skin, where they can modulate immunity and enhance defense mechanisms, providing a possible link in gut-skin communication.[7,8] Studies have shown that immune modulation derived from probiotic bacteria may be due to the release of anti-inflammatory cytokines in the gut. Nonetheless, the specific molecular interactions between probiotics and hosts are not well defined. The most widely used probiotics in humans are Lactobacillus (L.), Bacillus (B.), and Bifidobacterium (BB.), but also the genus Saccharomyces (S.) which is widely adopted in commercial products.[8] However, the specific role of probiotics in postoperative wound healing has not been widely studied.

Given the high state of inflammation in postoperative patients and there is still debate about the effectiveness of probiotic supplementation in wound healing, further evidence is needed regarding the effectiveness of probiotic supplementation in wound healing in postoperative patients. While laboratory and animal experiments suggest that probiotics could enhance skin healing, it is crucial to thoroughly examine the extent of evidence available in human studies.

Clinical questions

The target population in this study was postoperative patients. The factor studied as a therapy is the relationship of probiotic supplementation to wound healing in patients. The clinical question that we compiled was "Can probiotic supplementation accelerate wound healing in postoperative patients?"

P: Postoperative adult patients
I: Probiotic supplementation
C: Placebo
O: Wound healing

Methods

A literature review was conducted by two authors independently for English literature review of four databases Pubmed, Cochrane Library, ProQuest, and EBSCOhost. The search was carried out using advanced searching until March 2023 by combining the MesH Terms and abstracts/titles of each PICO component and using the boolean operator "OR" to increase sensitivity and "AND" to increase specificity as indicate in Table 1. The keywords used are “Probiotic*”, “wound healing*”, “surgical wound*”, “surgical incision”, “wound, surgical”, “surgical, wound”, “Incisions, Surgical”. From each selected publication, information about the main author’s name, year, study design, population characteristics, intervention, probiotics used, control group, and main results were extracted as indicate in Table 2. To assess the quality of the studies included in the literature review, critical assessment tools and levels of evidence are based on the Oxford Center for Evidence-Based Medicine was used.

Eligibility criteria

Inclusion criteria including patients undergoing surgery, received oral probiotic, study design was systematic review, meta-analysis, randomized controlled trial or clinical trial and has duration of wound healing and wound area outcome, publications in the last 10 years and was written in English. Exclusion criteria including research not conducted on humans, full-text *article* not available, articles in languages other than English.

Results

The results of the papers obtained in this study are shown in **Figure 1**, **Table 1**, **Table 2**, **Table 3**, and **Table 4**.

Discussion

The systematic review conducted by Togo et al.[9] aimed to compare the effects of oral or enteral probiotic supplementation on the wound healing of oral or skin wounds between the intervention group and the placebo-controlled group. Out of the 22 included studies, only 7 studies (n=6268) provided information on the effects of probiotic supplementation on surgical wound healing. The subjects were divided into two groups, totaling 348 subjects. The intervention involved oral probiotics or lozenges with a dosage of 2-15x109 CFU/day, administered before treatment, during treatment, or for up to 12 weeks. The outcomes assessed included the need for debridement, wound healing time, wound area, and clinical wound condition scores. The systematic review revealed a significant reduction in the need for debridement among pediatric patients receiving probiotic therapy. Positive results were also observed in surgical wounds and diabetic ulcers, with a higher incidence of wound complications in the control group.

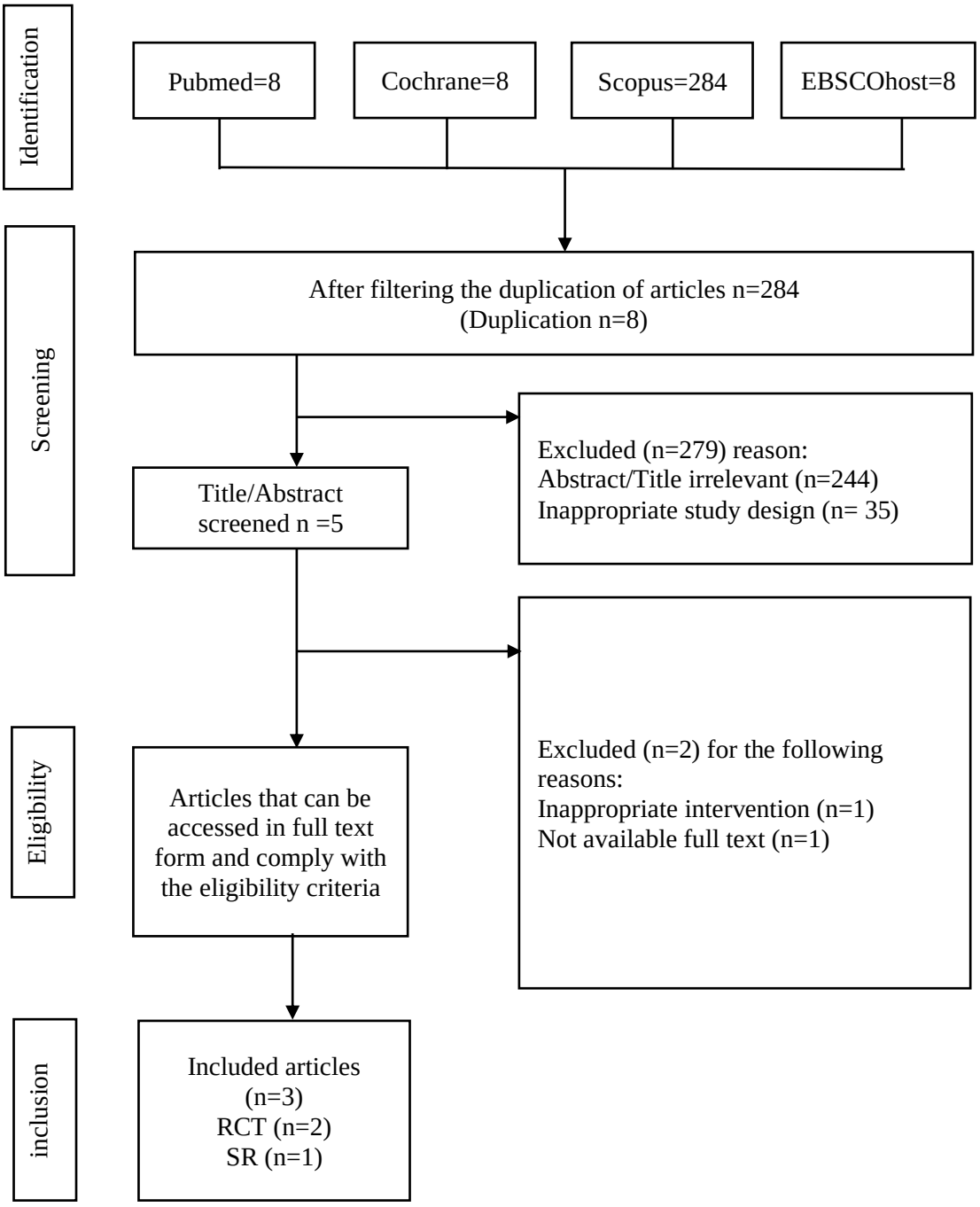

Figure 1. Prisma's flow chart

Table 1. Resources and search strategy

Database	Search Strategy		Hits
Medpub	(((Probiotic[Title/Abstract]) OR (Probiotics[Title/Abstract])) AND ((((Wound Healing[Title/Abstract]) OR (Wound Healings[Title/Abstract])) OR (Healing, Wound[Title/Abstract])) OR (Healings, Wound[Title/Abstract]))) AND (((((((Surgical Wound[Title/Abstract]) OR (Surgical Wounds[Title/Abstract])) OR (Wound, Surgical[Title/Abstract])) OR (Wounds, Surgical[Title/Abstract])) OR (Surgical Incision[Title/Abstract])) OR (Incision, Surgical[Title/Abstract])) OR (Incisions, Surgical[Title/Abstract])) OR (Surgical Incisions[Title/Abstract]))		8
Cochrane Library	ID	Search Hits	8
	#1	probiotic OR probiotics	7982
	#2	MeSH descriptor: [Probiotics] explode all trees	3004
	#3	wound healing OR Healing, Wound OR Healings, Wound OR Wound Healings	15326
	#4	MeSH descriptor: [Wound Healing] Explode all trees	7605
	#5	Surgical wound OR Wounds, Surgical OR Surgical Wounds OR Surgical Incision OR Incision, Surgical OR Wound, Surgical OR Incisions, Surgical OR Surgical Incisions	22394
	#6	MeSH descriptor: [Surgical Wound] explode all trees	496
	#7	#1 OR #2	8980
	#8	#3 OR #4	16854
	#9	#5 OR #6	22394
	#10	#7 AND #8 AND #9	8
	#11	#10 in Trials	8
Scopus	(probiotic OR probiotics) AND (wound AND healing OR healing AND wound OR healing AND process) (surgical AND wound OR surgical AND site OR surgical AND incision OR wound AND surgical)		284
EBSCOhost	AB probiotic AND AB (wound healing or healing process) AND AB (surgical wound or surgical site)		8

Table 2. Study characteristic

Article	Study Design	Population	Intervention	Outcome
Wälivaara D.-Å., et al. (2019)[9]	*Randomized controlled trial*	Subject is: 64 patients over 18 years of age with impacted or partially impacted mandibular third molars with a history of pericoronitis	Patients divided into 2 groups received either L. reuteri probiotics or placebo lozenges for 2 weeks	Distribution of clinical cure scores after 1 and 2 weeks after third molar surgery.
Togo C, et al. (2022)[10]	*Systematic Review*	Subject is: 348 patients aged 11 months to 85 years with probiotic therapy on surgical wound healing	One arcticle evaluated probiotic: patients were divided into 2 groups receiving probiotics and a placebo	Laboratory taken at baseline, 60th day, 120th day
Mohseni S, et al. (2017)[11]	*Randomized controlled trial*	Subject is: 60 patients aged 40-85 years with grade 3 diabetic foot ulcers	Patients were divided into 2 groups that received probiotic capsules consisting of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum,* and *Bifidobacterium bifidum* (2×10^9 CFU/g respectively) for 12 weeks	Rate CRP, IL-6, TNF-α

Table 3. Validity criteria

	Number of patients	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Wälivaara D.-Å., et al. (2019)[9]	+	+	+	+	+	+	+	Moderate	1B
Togo C, et al. (2022)[10]	+	+	+	+	+	+	-	Moderate	1A-
Mohseni S, et al. (2017)[11]	+	+	+	+	+	+	+	Moderate	1B

* Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779
**Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.
+ clearly mentioned in the article; - not done; ? Not stated clearly
- Systematic review and meta-analysis with troublesome heterogeneity

Table 4. Relevance criteria

Authors	Population similarity	The similarity of determining factors	Outcome similarity
Wälivaara D.-Å., et al. (2019)[9]	+	+	+
Togo C, et al. (2022)[10]	+	+	+
Mohseni S, et al. (2017)[11]	+	+	+

In the RCT study by Wälivaara et al.[10], patients who underwent third molar tooth extraction surgery were given oral lozenge supplementation with three lozenges per day containing two strains, namely *L. reuteri* (DSM 17938 and ATCC PTA 5289, ProDentis®, BioGaia AB, Stockholm, Sweden), or placebo for 2 weeks. The active lozenges contained at least 2×108 live bacteria of the combined strains per lozenge. At the end of the 2-week follow-up, there was no difference between the groups. However, when analyzing the subset of 25 patients who attended the follow-up at 1 week separately, the distribution of healing scores showed a positive impact for the probiotic intervention group. In another study by Mohseni et al.[11], conducted on diabetic foot ulcer patients, supplementation with probiotic capsules containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus Fermentum*, and *Bifidobacterium bifidum* (each 2×109 CFU/g) or placebo was given. The results showed a reduction in the length, width, and depth of the ulcers. Additionally, the study had a low loss to follow-up rate of 1.6%. Therefore, the results of this study are statistically significant with a high level of confidence.[12] The study by Mohseni et al.[11] explains that cells from the ulcer layer examined after 10 days of *Lactobacillus plantarum* treatment showed a decrease in the number of wound bacteria, apoptotic and necrotic cells, modified interleukin (IL)-8 production, and induced wound healing. The anti-infective mechanism of probiotics in patients with diabetic ulcers may be attributed to their increased ability to combat pathogenic microorganisms or modulate the host immune response, as well as their production of various antimicrobial substances such as organic acids, hydrogen peroxide, low molecular weight antimicrobial agents, diacetyl, bacteriocins, and their anti-inflammatory properties. Additionally, the study by Wälivaara et al.[10] explains that the administration of probiotics in third molar surgery showed no significant difference in clinical wound healing scores between the groups and that there were no major complications or secondary infections in both groups. This lack of impact is likely due to the use of antibiotics after the procedure.

The study by Togo et al.[9] explains that the health-enhancing properties of probiotics depend on the strains provided. The type and characteristics of the strains are crucial because probiotics can regulate cytokine production and activate antimicrobial immune responses. For example, some probiotics can induce interleukin (IL)-12, which enhances interferon (IFN)-γ secretion and activates natural killer (NK) cells. However, probiotics also stimulate increased production of IL-10, which induces antibody production and reduces inflammatory responses, thus balancing and contributing to healing processes. *Lactobacillus* strains are capable of inducing the production of pro-inflammatory cytokines such as IL-12 and IFN-γ, as well as anti-inflammatory cytokines like IL-10, while Bifidobacterium strains generally exhibit better induction of IL-10 compared to Lactobacillus strains. However, an in vitro study found little evidence for strain-specific effects of six probiotics on NK cell activity and NK or T cell activation. Cytokine production is differently influenced by probiotic strains from different species. Therefore, the biological significance of these strain-specific effects in vivo still needs to be clarified. In this study, wound assessment was conducted using clinical scores, and probiotic treatment did not show significant effects. Skin grafting is the preferred treatment for deep skin burns, where necrotic tissue and inflammation are removed, and physiological wound closure is expedited. The reduced need for grafting in patients treated with probiotics may be attributed to a lower incidence of infection, which is the second most common cause of graft failure. There is a possibility that therapeutic microorganisms can enhance systemic immune function that supports the healing process. Furthermore, oral probiotic administration also enhances the deposition of collagen, which is essential for wound healing.

The differences in the results obtained in the three articles of this study can be attributed to several factors, such as the types of strains used, the dosage of probiotics, the duration of administration, and the types of wounds experienced, as described in the studies included in Togo et al.[10] research. The study by Wälivaara et al.[10] explains that the clinical healing was assessed

2 weeks after the surgery, which was different from the initially planned assessment at one week after the procedure. Additionally, only 25 patients were available for follow-up in the first week, which supports the idea that probiotic administration can enhance healing. Mohseni et al.[11], who administered probiotics for 12 weeks, observed a significant reduction in the size of diabetic foot ulcers.

In the three studies, no serious side effects were reported during the interventions. The strengths of these studies include one study showing good validity and two articles reporting significant results, although the research by Wälivaara et al.[10] had a low level of confidence. The limitations of these studies are the relatively small sample sizes, variations in the types of strains used, and varying dosages of probiotics, which could potentially affect the effects on surgical wound healing.

In the clinical scenario, a 41-year-old female patient presents with an open surgical wound complaint following the repair of an incisional hernia. The age and diagnosis characteristics in the three studies are similar to those of the patient in the clinical scenario. The supplementation of probiotics for patients with surgical wounds cannot be recommended at this time due to the variations in probiotic strains, dosage, and duration of administration, as well as the low level of confidence in the research results.

Conclusion

The effectiveness of probiotic supplementation in accelerating wound healing in patients with surgical wounds has not shown consistent results. Based on the reviewed journal articles, it cannot be concluded that probiotic supplementation may improve surgical wound healing. This could be influenced by different strains, dosages, and locations of the surgical wounds, resulting in the administered probiotics not being strong enough to provide a significant effect in accelerating wound healing. Therefore, further research is needed to investigate the supplementation of probiotics in the wound healing of patients with surgical wounds, considering adequate strain types, dosage, duration of administration, as well as evaluating any potential side effects and safety.

Conflict of Interest

The authors declare that there is no conflict of interest.

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