

Use of probiotics in the treatment of erythematotelangiectasic and papulopustular rosacea

Uso de probiótico no tratamento da rosácea eritêmatoelangiectásica e papulopustular

Uso de probióticos en el tratamiento de la rosácea eritematotelangiectásica y papulopustulosa

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Abstract

Background: The interaction between the gut and skin microbiota is linked to skin diseases. It is believed that through the use of oral probiotics it is possible to modulate the intestinal microbiota and regulate skin diseases. **Objective:** The study aims to analyze the efficacy of oral probiotics in the treatment of erythematotelangiectatic and papulopustular rosacea through the theory of the relationship between intestinal and skin microbiota. **Methods:** The study consisted of a randomized, controlled, double-blind, experimental clinical trial with comparative efficacy. The study sample (n=25) was divided into two groups: the experimental group received the oral probiotic plus a topical cream of Adapalene 1mg and the control group received the placebo and the same topical cream of Adapalene 1mg. To assess the effectiveness of the treatment, two questionnaires were proposed regarding the impact of rosacea on the patients' lives before and after one month of treatment. **Results:** In the experimental and control groups, the sum of the RosaQoI and DLQI questionnaire scores decreased compared to before the treatment was applied. There was no significant difference between the results before and after treatment with probiotics and placebo. **Conclusion:** Both groups showed slight clinical improvement, with no superiority of probiotics. However, more clinical trials are needed due to the limitations of the study, such as the small sample size and the interference of the winter climate in the southern region of the country, which may have interfered with the clinical and statistical analysis of this study.

Keywords: Rosacea; Probiotics; Microbiome; Skin.

Resumo

Fundamentos: A interação entre a microbiota intestinal e cutânea está ligada às doenças de pele. Acredita-se que através do uso de probiótico oral é possível modular a microbiota intestinal e regular doenças cutâneas. **Objetivo:** O estudo visa analisar a eficácia do uso de probióticos orais no tratamento da rosácea eritemato-telangiectásica e papulopustular através da teoria de relação entre a microbiota intestinal com a da pele. **Métodos:** O estudo consiste em um ensaio clínico randomizado controlado e duplo cego, de caráter experimental e eficácia comparativa. A amostra do

estudo (n=25) foi dividida em dois grupos: o grupo experimental recebeu o probiótico oral mais um creme tópico de Adapaleno 1mg e o grupo controle recebeu o placebo e o mesmo creme tópico de Adapaleno 1mg. Para a avaliação da eficácia do tratamento foram propostos dois questionários a respeito do impacto da rosácea na vida dos pacientes antes e após um mês de tratamento. Resultados: Nos grupos experimental e de controle a soma da pontuação do questionário RosaQol e DLQI diminuiu em comparação a antes da aplicação do tratamento. Não houve diferença significativa entre os resultados antes e depois do tratamento com probióticos e placebo. Conclusão: Ambos os grupos apresentaram ligeira melhora clínica, sem superioridade dos probióticos. No entanto, são necessários mais ensaios clínicos, devido a limitações do estudo, como tamanho amostral pequeno e interferência do clima de inverno na região sul do país, que podem ter interferido na análise clínica e estatística do presente estudo.

Palavras-chave: Rosácea; Probióticos; Microbioma; Pele.

Resumen

Antecedentes: La interacción entre la microbiota intestinal y la cutánea está relacionada con las enfermedades de la piel. Se cree que mediante el uso de probióticos orales es posible modular la microbiota intestinal y regular las enfermedades cutáneas. Objetivo: El estudio pretende analizar la eficacia de los probióticos orales en el tratamiento de la rosácea eritematotelangiectásica y papulopustulosa. Métodos: El estudio consistió en un ensayo clínico experimental, aleatorizado, controlado, doble ciego y de eficacia comparativa. La muestra del estudio (n=25) se dividió en dos grupos: el grupo experimental recibió el probiótico oral más una crema tópica de Adapalene 1mg y el grupo control recibió el placebo y la misma crema tópica de Adapalene 1mg. Para evaluar la eficacia del tratamiento, se propusieron dos cuestionarios sobre el impacto de la rosácea en la vida de los pacientes antes y después de un mes de tratamiento. Resultados: En los grupos experimental y de control, la suma de las puntuaciones de los cuestionarios RosaQol y DLQI disminuyó en comparación con antes de aplicar el tratamiento. No hubo diferencias significativas entre los resultados antes y después del tratamiento con probióticos y placebo. Conclusión: Ambos grupos mostraron una ligera mejoría clínica, sin superioridad de los probióticos. Sin embargo, se necesitan más ensayos clínicos debido a las limitaciones del estudio, como el pequeño tamaño de la muestra y la interferencia del clima invernal en la región sur del país, que puede haber interferido en el análisis clínico y estadístico de este estudio.

Palabras clave: Rosácea; Probióticos; Microbioma; Piel.

1. Introduction

Rosacea is a chronic inflammatory disease that affects the skin causing erythema, flushing, telangiectasias, papules and pustules, mainly on the central face, followed by cheeks, chin and forehead. They can also cause a burning sensation and pain in the eyes (Vemuri et al., 2015). The exact prevalence and incidence of rosacea remains unknown due to a variety of cultural, social, and methodological biases in epidemiological studies. Furthermore, in relation to the etiology of rosacea, there is a composition of multivariate processes that include deregulated inflammatory processes with perivascular or pilosebaceous infiltrate, vascular and lymphatic events, glandular hyperplasia and fibrosis. At the same time, this heterogeneous histological picture suggests an unclear pathophysiological event of the onset of rosacea (Buddenkotte & Steinhoff, 2018). Although several hypotheses have been proposed, the exact pathogenesis of rosacea remains unclear.

The epidermis of subjects affected by rosacea expresses a greater quantity of toll-like receptors 2 (TLR2) - involved in the recognition of PAMPs (pathogen-associated molecular patterns) - than healthy individuals, indicating a possible explanation for these increased inflammatory responses to external stimuli. Furthermore, increased expression of TLR2 can lead to abnormal production of cathelicidin antimicrobial peptides and increased expression and activity of the serine protease kallikrein (KLK5), common features of the disease. This finding suggests a role for the microbiome and TLR2 in controlling epidermal inflammation, considering that under normal conditions the collection of microbes that populate the skin activates TLRs, but does not promote inflammation (Yamasaki & Gallo, 2011).

Currently available treatment options include topical brimonidine or intense pulsed light (IPL) for persistent background erythema; topical metronidazole, azelaic acid, ivermectin or oral doxycycline, and isotretinoin for rosacea papulopustules; and cyclosporine eye drops for ocular rosacea (Schechter et al., 2009). Nevertheless, new etiological discoveries such as the role of cathelicidin antimicrobial peptides in aberrant innate immune responses, the role of mast cells as key mediators of cathelicidin-initiated inflammation in rosacea, characterization of inflammatory infiltrate and

cytokine/chemokine profiles, including activation of the Th1/Th17 pathway, and elucidation of mediators and receptors involved in neurovascular and neuroimmune aspects of rosacea will possibly contribute to new therapies.

The gut-skin association likely involves a complex, multifactorial interaction between the nervous, immune, and endocrine systems, as well as environmental factors such as diet and medications. If the composition of the microbiome changes for any reason, the reactivity of the immune system can subsequently change and eventually lead to inflammatory skin diseases. Due to the discovery of this association between intestinal and skin microbiota, the use of probiotics for the treatment of skin diseases has been studied, through balancing the protective barrier of the intestine and, consequently, the skin microbiome. Probiotics are believed to provide therapeutic benefits through several mechanisms. To begin with, they are believed to prevent pathogenic bacteria from colonizing the gastrointestinal tract, which would otherwise lead to disease. In addition, they are believed to improve the barrier function of the colonic mucosa. Furthermore, probiotics can help modulate the immune system, which can help move away from pro-inflammatory immune reactivity (Butel, 2014). And finally, they can synthesize and secrete metabolites that may have nutritional benefits and anti-inflammatory effects (Simpson et al., 2005).

Thus, based on the strong association between the integrity of the intestinal microbiota and the health of human skin and the effectiveness of probiotics in balancing the intestinal protective barrier, the present study aims to evaluate the impact of using oral probiotics made from *Lactobacillus acidophilus* and *Bifidobacterium lactis* in the treatment of erythematotelangiectatic and papulopustular rosacea, in addition to analyzing the performance of the treatment in improving the quality of life of patients with rosacea.

2. Methodology

This research is an experimental, randomized, controlled, double-blind clinical study (Merchán-Haman & Tauil, 2021). The clinical trial is considered the gold standard in clinical research, as it involves the random allocation of participants to different treatment groups, which minimizes bias and gives the results greater validity (Sharma et al., 2020). In the double-blind design, neither the participants nor the researchers know who is receiving the active treatment or the placebo, which avoids unconscious influences on the results, ensuring greater objectivity (Amatuzziet al., 2003). An experimental study involves the manipulation of independent variables to assess their effect on a dependent variable. This approach allows the effects to be analyzed by comparing the results obtained in an experimental group and those observed in a control group. The clear definition of specifications by the researcher aims to guarantee comparisons, contributing to the validity of the results achieved (Lima, 2011). Comparative effectiveness consists of direct evaluation of various interventions, which can help determine the real effectiveness of a given procedure or intervention in specific groups. Carrying out these studies is essential to base clinical decisions based on solid and relevant evidence, promoting a more informed and effective clinical practice (International Ethical Guidelines for Health-Related Research Involving Human Beings Prepared by the Council of International Organizations for Medical Sciences (CIOMS) In Collaboration with the World Health Organization (WHO), n.d.).

Patients with rosacea of the erythematotelangiectatic and papulopustular subtypes participated in this study, diagnosed by the Dermatology department, linked to a hospital in the northern region of Rio Grande do Sul, from June to September 2021. Patients were recruited through invitation, with an estimated number of 25 people. Patients of both sexes, over 18 years of age and residents of the city of Passo Fundo-RS (Brazil) and neighboring cities participated in this study. Individuals who were already using any other skin treatment, pregnant and breastfeeding women, as well as those with hypersensitivity to any substance present in probiotics were excluded.

The patients were submitted to a questionnaire prepared by the authors themselves, which had statements such as sex,

age, phototype, level of education, family history of rosacea, duration of rosacea, subtype of rosacea and previous treatments for rosacea.

Participants were randomly divided into two groups: the experimental group received treatment with the probiotic under study and topical adapalene cream and the control group received placebo tablets and the same topical adapalene cream, obtained through the researchers' own funding. The treatment under study, proposed to the experimental group, consists of the FQM Melora probiotic Probiac, two tablets once a day for one month, composed of a combination of *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subspecies *bulgaricus* and *Bifidobacterium bifidum*. The control group used placebo tablets of oral probiotics. Both groups used the topical cream Adapalene 1mg to be applied every other day to the face.

In the first interview (D0), two questionnaires were applied: the Dermatology Life Quality Index (DLQI), used to measure the quality of life of people with skin diseases in the past week, comprises four possible answers, with each corresponds to a score - really a lot (3 points), a lot (2 points), a little (1 point) and not at all (0 points). The interpretation of the final sum of scores corresponds to the categories: no effect on the patient's life (0-1 points), little effect on the patient's life (2-5 points), moderate effect on the patient's life (6-10 points), large effect on patients' lives (11-20 points) and extremely large effect on patient's lives (21-30 points).

The other questionnaire applied was the RosaQol, developed in the United States, translated, culturally adapted and validated into Brazilian Portuguese by Tannus et al. (2018), contains questions related to the discomfort of patients with rosacea⁷. The 21 items in this questionnaire are grouped according to the similarity of their concepts, creating domains that denote a specific aspect of quality of life (social, physical, functional or psychological). For example, items 13, 15 and 21 correspond to the "Functional capacity" domain, which address the aspects of "mobility" and "self-care", items 1, 3, 4, 5, 7, 8, 10, 11, 12, 14 and 20 correspond to the "emotional component" related to depression, anxiety and well-being, and items 2, 6, 9, 16, 17, 18 and 19 correspond to the "symptoms" domain translated into the clinical aspect of pathology. The RosaQol score was calculated by averaging the responses to the 21 items, grouped by domains. Responses to the items were "always", "often", "sometimes", "rarely" and "never", recorded on a scale from 1 (never) to 5 (always). Thus, the higher the total RosaQol score, the worse the patient's quality of life.

Descriptive statistics were performed and the t test was applied to compare two means (different variances). To this end, a significance level of 5% was adopted ($p\text{-value} = < 0.05$). All analysis were performed using version 4.0.0 of the R software. The study complies with Resolution 466/2012 of the National Health Council, the clinical trial was approved by the Research Ethics Committee of the University of Passo Fundo, in 2021, under opinion 4,780,755. All participants were instructed and signed the Informed Consent Form confirming their agreement to participate in the research.

This study is based on the precepts of bioethics, such as autonomy, beneficence, justice, equity and human dignity. It therefore complies with Resolution 466/2012 and the principles of the Research Ethics Committee 510/2016 of the National Health Council, dated April 7, 2016, regarding the inclusion of individuals in research. This study was evaluated by the Research Ethics Committee (CEP) of Faculdade ATITUS Educação, located in Passo Fundo RS, with registration number 4.780.755 and holds the Certificate of Presentation for Ethical Assessment (CAAE) protocol number 44923321.0.0000.5319 as required by the Brazilian Ministry of Health, CNS/CONEP. In order to obtain the consent of the participants as research volunteers, all those involved signed an Informed Consent Form (ICF), agreeing to their voluntary participation in the study and guaranteeing the right to revoke consent at any stage, without suffering any penalties or losses, in accordance with the principles of respect for human dignity, freedom and autonomy.

3. Results

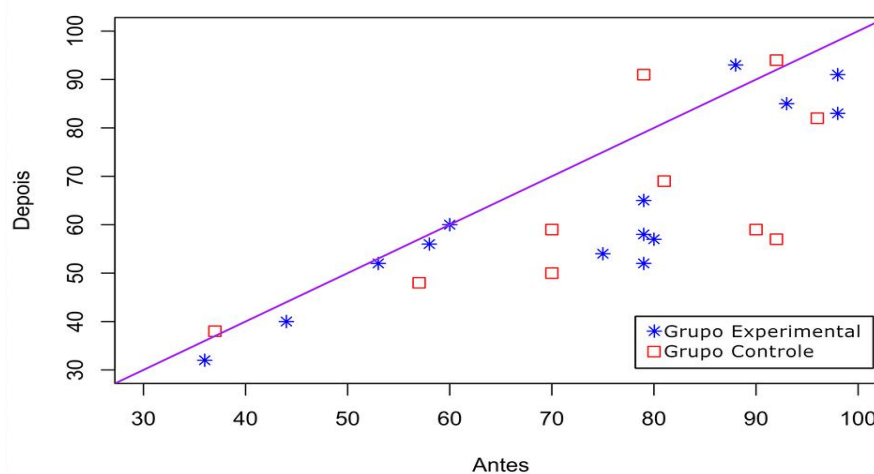
3.1 Description of the study population

The study population consisted of 25 (n=25) patients, 68% (n=17) aged 20-40 years, 28% (n=7) aged 41-60 years and 4% (n=1) older than 60 years. Among them, 84% women (n=21) and 16% men (n=4). Regarding groups, 56% of patients used probiotics (n=14) and 44% took placebo tablets (n=11). When analyzing skin phototype, information was collected from 23 of the 25 patients. Of these, 26.1% (n=6) of the interviewees classified as phototype I, 47.8% (n=11) phototype II, 26.1% (n=6) phototype III. Phototypes IV, V and VI had no representatives in the sample. The responses regarding family history of rosacea, 52% (n=13) were positive for family history and 48% (n=12) were negative. Regarding the duration of rosacea, 45.83% (n=11) had rosacea for 1-10 years and 54.17% (n=13) for more than 10 years. Regarding the rosacea subtype, 66.67% (n=16) had erythematotelangiectatic rosacea and 33.33% (n=8) papulopustular rosacea. The answers referring to previous treatments, 44% (n=11) did not use previous treatments, 20% (n=5) used intense pulsed light, 16% (n=4) topical metronidazole, 12% (n=3) azelaic acid and 8% (n=2), other types of treatment.

3.2 RosaQol questionnaire

In the experimental group, of 14 patients, only 1 (7.14%) worsened and 1 (7.14%) remained stable. In the control group, of 11 patients, 3 (27.27%) showed worsening. Quantitatively, considerable improvement was observed in both the control group (improvement of 72.7%) and the experimental group (improvement of 85.7%) as shown in Figure 1.

Figure 1 - RosaQol Questionnaire: Experimental vs Control.



Source: Author herself (2021).

In the experimental group, the sum of the RosaQol questionnaire score decreased by an average of 10.15 (± 9.98) from before to after the application of the treatment, while in the control group, it decreased by an average of 15.46 (± 18.6). In this comparison, no statistical significance was obtained between the difference averages before and after application of the treatment in both the experimental group and the control group (p-value = 0.4063). Thereby, the null hypothesis of equality of averages in the experimental and control groups was not rejected, which shows an equivalence of clinical results of treatment with oral probiotic and placebo. The Table 1 presents the average and standard deviation of RosaQol questionnaire scores before and after treatment for both study groups.

Table 1 - RosaQol questionnaire.

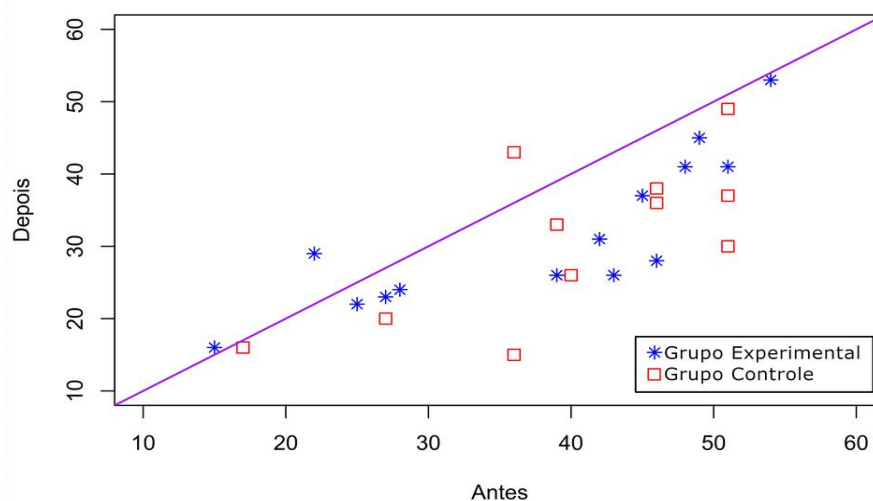
		Mean	Standard deviation	p-value
Experimental group	Before RosaQol	72,86	19,69	0,4063
	After RosaQol	62,71	18,61	
Control group	Before RosaQol	76,55	17,6	
	After RosaQol	61,09	21,52	

Source: Author herself (2021).

3.2.1 RosaQol Questionnaire – "Emotional Component" Domain

In the domain related to patients' emoticons shown in Figure 2, of 14 patients in the experimental group, 2 (14.29%) showed worsening after applying the treatment. In the control group, of 11 patients, 1 (9.09%) worsened. A similar worsening is observed here between both groups.

Figure 2 - RosaQol Questionnaire - "Emotional Component" Domain: Experimental vs Control.



Source: Author herself (2021).

In the experimental group, the sum of the score for the “emotional component” domain of the RosaQol questionnaire decreased by an average of 6.57 (± 6.9) from before to after the application of the treatment, while in the control group, it decreased by an average of 8.82 (± 8.49). In this comparison, no statistical significance was obtained between the difference averages before and after application of the treatment in both the experimental group and the control group (p-value = 0.4852).

The Table 2 presents the mean and standard deviation of the scores for the “Emotional Component” domain of the RosaQol questionnaire before and after treatment for both study groups.

Table 2 - “Emotional Component” domain of the RosaQol questionnaire.

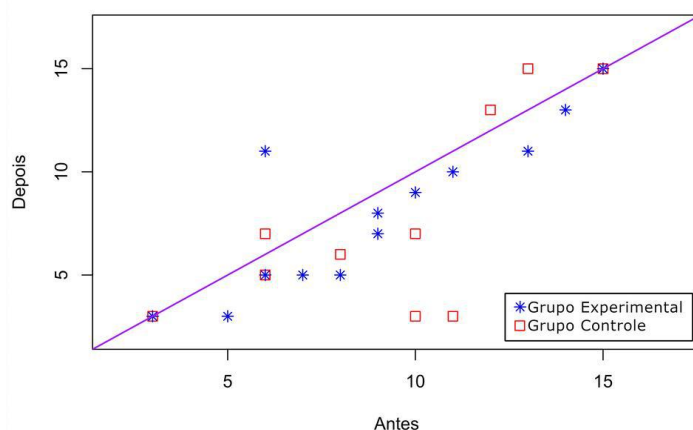
		Mean	Standard deviation	p-value
Experimental group	Emotional component before	38,14	12,33	
	Emotional component after	31,57	10,35	
Control group	Emotional component before	40,0	10,8	
	Emotional component after	31,18	11,0	0,4852

Source: Author herself (2021).

3.2.2 RosaQol questionnaire - "Functional capacity" domain.

In the “functional capacity” domain shown in Figure 3, of 14 patients in the experimental group, 1 (7.14%) patient showed worsening and 3 (21.43%) remained stable after application of the treatment. In the placebo group, of 11 patients, 3 (27.27%) showed worsening, and 2 (18.18%) remained stable. In this way, we obtained a clinical improvement of 71.4% in the experimental group and 54.5% in the control group.

Figure 3 - RosaQol Questionnaire - "Functional Capacity" Domain: Experimental vs. Control.



Source: Author herself (2021).

In the experimental group, the sum of the score in the “functional capacity” domain of the RosaQol questionnaire decreased by an average of 0.8 (± 1.85) from before to after the application of the treatment, while in the control group it decreased by an average of 1.64 (± 3.23). In this comparison, no statistical significance was obtained between the mean differences before and after application of the treatment in both the experimental group and the control group (p-value = 0.4503).

The Table 3 presents the mean and standard deviation of the scores in the “Functional capacity” domain of the RosaQol questionnaire before and after treatment for both study groups.

Table 3 - Functional Capacity - RosaQol Questionnaire.

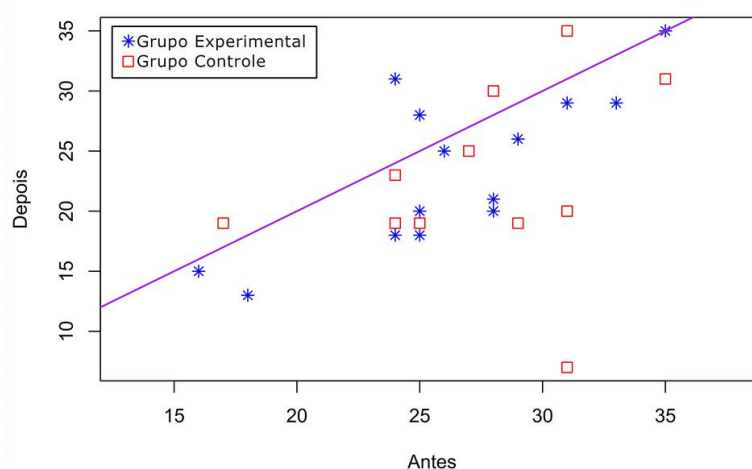
		Mean	Standard Deviation	p-value
Experimental group	Functional capacity before	8,5	3,82	0,4503
	Functional capacity after	7,7	3,91	
Control group	Functional capacity before	9,09	3,62	
	Functional capacity after	7,45	4,68	

Source: Author herself (2021).

3.2.3 RosaQol questionnaire - "Symptoms" domain

In the domain related to the patients' clinical symptoms shown in Figure 4, of 14 patients in the experimental group, 2 (14.29%) showed worsening and 1 (7.14%) remained stable after application of the treatment. In the control group, of 11 patients, 3 (27.27%) showed worsening. Therefore, we obtained clinical improvement of 78.6% in the experimental group and 72.7% in the control group. Again, very similar results between the two groups.

Figure 4 - RosaQol Questionnaire - "Symptoms" Domain: Experimental vs. Control.



Source: Author herself (2021).

In the experimental group, the sum of the score in the “symptoms” domain of the RosaQol questionnaire decreased by an average of 2.78 (± 4.19) from before to after the application of the treatment, while in the control group, it decreased by an average of 5 (± 7.92). Both groups had an improvement in scores, however, the improvement in the probiotic group was lower than that in the placebo group (p-value = 0.4152).

The Table 4 resents the mean and standard deviation of the scores for the “Symptoms” domain of the RosaQol questionnaire before and after treatment for both study groups.

Table 4 - Symptoms - RosaQol Questionnaire.

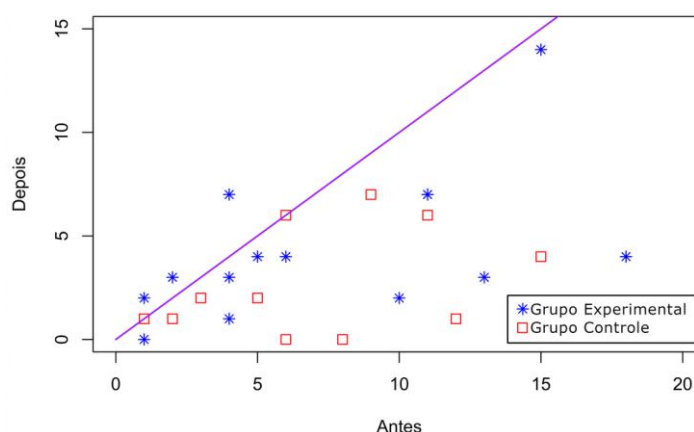
		Mean	Standard Deviation	p-value
Experimental group	Symptoms before	26,21	5,16	0,4152
	Symptoms after	23,43	6,51	
Control group	Symptoms before	27,45	4,87	
	Symptoms after	22,45	7,66	

Source: Author herself (2021).

3.3 Dermatology life quality index questionnaire (DLQI)

Of 14 patients in the experimental group, three (21.43%) worsened after applying the treatment. In the control group, of 11 patients, two (18.18%) remained stable and none worsened, as shown in Figure 5. In the analysis of this questionnaire, the result caused by the medicine is inferior to the placebo. It is not significant, but observational.

Figure 5 - DLQI Questionnaire: Experimental vs Control.



Source: Author herself (2021).

In the experimental group, the sum of the DLQI questionnaire decreased by an average of 3.14 (± 4.66) from before to after treatment, while in the patients in the control group, it decreased by an average of 4.37 (± 4.15) (p-value = 0.4963). The table 5 shows the mean and standard deviation of the DLQI questionnaire scores before and after treatment for both study groups.

Table 5 - Dermatology Life Quality Index (DLQI).

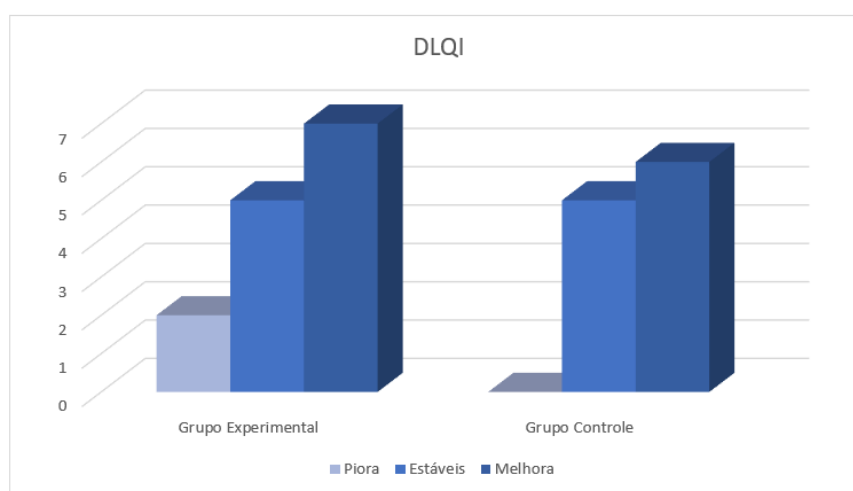
		Mean	Standard Deviation	p-value
Experimental group	DLQI before	7,5	5,46	0,4963
	DQLI after	4,36	3,52	
Control group	DLQI before	7,1	4,39	
	DLQI after	2,73	2,57	

Source: Author herself (2021).

3.3.1 DLQI categories

In the DLQI questionnaire, of the 14 patients in the experimental group, two had a category worsening, five remained stable and seven had an improvement, and of these seven, two had a considerable category improvement (> 2). In the 11 patients in the control group, none of the patients had a category worsening, five remained stable and six had an improvement, and of these six, four had a considerable category improvement (> 2). The Figure 6 shows the DLQI category changes for patients in the experimental group and those in the control group.

Figure 6 - Change of Category - DLQI Questionnaire.



Source: Author herself (2021).

4. Discussion

Patients with rosacea have an epidermis that expresses greater amounts of TLR2 than healthy individuals, which indicates a possible explanation for the increased inflammatory response to external stimuli, as they cause the abnormal production of cathelicidin antimicrobial peptides and increased expression and activity of the serine protease kallikrein (KLK5). This finding suggests a role for the skin microbiome and TLRs 2 in controlling epidermal inflammation, considering that under normal conditions the collection of microbes that populate the skin activates TLRs, but does not promote inflammation (Yamasaki & Gallo, 2011).

According to studies conducted by Parodi et al. (2018), patients with rosacea have a significantly higher prevalence of small intestinal bacterial overgrowth (SIBO) than healthy individuals and its eradication leads to a significant regression of skin lesions. Thus, clinical evidence suggests a close relationship between changes in the skin microbiome and the intestinal microbiome, indicating the potential pathogenetic role of SIBO in the development of rosacea (Parodi et al., 2008). However, the mechanistic basis behind these observations has not yet been confirmed. The gut-skin association likely involves a complex, multifactorial interaction between the nervous, immune, and endocrine systems, as well as environmental factors such as diet and medications.

Regarding probiotics, their applicability in the treatment of dermatological diseases, especially rosacea, has not yet been widely studied. Two meta-analyses failed to demonstrate any clinically significant changes in the severity of atopic dermatitis (AD) in children treated with probiotic supplementation (Lee et al., 2008). However, Lee et al. (2008) found a significant risk reduction (up to 61%) of pediatric AD in those who were treated with prenatal and/or postnatal probiotics. There are even fewer studies available on treating adults with AD with probiotics, but these studies have shown that there may

be a clinical benefit in adults (Niccoli et al, 2014 and Moroi et al., 2010). Probiotics are postulated to help atopic dermatitis by improving the diversity of intestinal flora, increasing skin and mucosal barrier function, and producing a primarily Th1 response.

A prospective, randomized and open study, developed by Jung et al. (2013), comparing the safety, efficacy and tolerability of an acne treatment, showed that probiotics not only reduce adverse events associated with chronic antibiotic use, but they can also play a synergistic role with antibiotics in the treatment of acne through of its anti-inflammatory effects and immunomodulatory properties while improving the patient's quality of life (Jung, Tse, Guiha & Rao, 2013). Therefore, since rosacea, similar to acne, is a skin pathology derived from unregulated inflammatory processes with perivascular or pilosebaceous infiltrate associated with innate immunological changes, oral probiotics are expected to have a therapeutic effect on rosacea. However, the data found in the present study diverge from this theory. When evaluating the data obtained from the RosaQol questionnaire, of the total number of patients in the experimental group, 7.14% worsened and 7.14% remained stable. In the control group, 27.27% showed worsening. Quantitatively, considerable improvement was observed in both the control group (improvement of 72.7%) and the experimental group (improvement of 85.7%). Still in relation to RosaQol, in the experimental group, the sum of the RosaQol questionnaire score decreased by an average of 10.15 (± 9.98) from before to after the application of the treatment, while in the control group, it decreased by an average of 15.46 (± 18.6). In this comparison, there was no statistical relevance in the difference between the means before and after the application of the treatment in both the experimental group and the control group (p-value = 0.4063), corroborating the equivalence of clinical results of treatment with the oral probiotic and placebo.

Furthermore, the "brain-gut-skin axis" documented in research by the authors by Arck et al. (2010) and Bowe et al. (2011) elucidated the action of neurotransmitters, hormones and other bioactive chemicals, such as short-chain fatty acids derived from the intestine, on receptors within the skin, causing changes in the skin flora. Furthermore, the "brain-intestine-skin axis" documented in research by the authors by Arck et al. (2010) and Bowe et al. (2011) has elucidated the action of neurotransmitters, hormones and other bioactive chemicals, such as gut-derived short-chain fatty acids, on receptors within the skin, causing changes in the skin flora (Arck et al., 2010 and Bowe & Logan, 2011). Through this mechanism, psychosocial stress may be implicated in the exacerbation or onset of various skin diseases, since the intestinal microflora produces neurotransmitters in response to stress and other external stimuli that can modulate skin function through neural pathways. With this in mind, this study assessed the impact of probiotics on the stigmata of depression, anxiety and well-being of the patients in the sample using the "emotional component" domain of the RosaQol questionnaire. However, despite the clinical improvement of the vast majority of patients, the experimental group saw an average decrease of 6.57 (6.9) in the sum of the scores for the "emotional capacity" domain from before to after the treatment, while the control group saw an average decrease of 8.82 (8.49), revealing a small and very similar improvement between both groups. Thus, in this comparison, there was no statistical significance between the mean differences before and after the treatment in either the experimental or control group (p-value = 0.4852).

Another case-control study carried out by Incel Uysal et al. (2019) on the increased risk of generalized anxiety disorder in patients with rosacea, evaluating approximately 400 individuals using a seven-item Generalized Anxiety Disorder scale, showed that effective treatment of rosacea symptoms leads to a significant improvement in psychosocial symptoms and health-related quality of life (Incel Uysal et al., 2019). The Dermatology Life Quality Index (DLQI) was used to evaluate the performance of oral probiotics on the quality of life of the patients in this study. The data found revealed that in the experimental group, the sum of the DLQI questionnaire decreased by an average of 3.14 (± 4.66) from before to after treatment, while in the control group, it decreased by an average of 4.37 (± 4.15) (p-value = 0.4963). Thus, both groups had an

improvement in quality of life, but without statistical significance to prove the effectiveness of the treatment, since the difference in scores before and after treatment is small and the results are very similar between the groups in the experiment.

One aspect to be considered in this research is the emotional characteristic of rosacea and the consequent fluctuation in the severity of the lesions depending on the patient's emotional state. In case of emotional stress, the neuroimmunocutaneous system (NICS) is responsible for releasing cytokines, mediators and neurotransmitters that are activated for this complex interaction (Arck et al., 2006). Therefore, it is necessary to consider that each patient in the study differs in terms of their emotional states, personal and social contexts and subjective perceptions of rosacea, which may interfere with the results obtained.

One of the limitations of the present study was that it was carried out during the winter period in the southern region of Brazil, characterized by low temperatures in relation to other regions of the country, which culminated in a relative clinical worsening of the sensitive skin of patients with rosacea and which interfered with the outcome of the treatment. Furthermore, the sample number of the research was not satisfactory to demonstrate statistical significance of the experiment, as the number of participants was small.

5. Conclusion

From this study, there was an observational improvement in rosacea manifestations in the general population sample, however, there was no clinical superiority of treatment with the probiotic in relation to placebo. Therefore, more studies need to be carried out with larger population samples, covering other regions of the country and with greater similarity of phenotypes between the study groups before concluding the effect of probiotics in the treatment of rosacea.

For future research and articles on the use of probiotics in the treatment of erythematotelangiectatic and papulopustular rosacea, a more comprehensive approach exploring different probiotic strains, specific dosages and treatment duration is suggested. In addition, comparative investigations between isolated probiotics and combined formulations could provide valuable insights into the relative efficacy of these therapeutic approaches. Randomized controlled trials with well-defined control groups and long-term follow-up are essential to adequately assess clinical outcomes such as reduction in skin inflammation, improvement in quality of life and tolerability of treatment. The inclusion of objective outcomes, such as standardized clinical scores and histopathological evaluations of the skin, can enrich the analysis of the results and contribute to a better understanding of the role of probiotics in the management of erythematotelangiectatic and papulopustular rosacea.

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