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ROLE OF PRO BIOTICS IN NON-INFECTIVE GASTRIC ULCERS WITH PROTON PUMP INHIBITORS

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Abstract

Background:
Proton pump inhibitors (PPIs) are widely used to manage gastroesophageal reflux disease (GERD), peptic ulcer disease, and related disorders. Recent studies have raised concerns about PPIs' impact on gut microbiota and their potential side effects. Probiotics, known for their health benefits in gastrointestinal disorders, may counteract these adverse effects by restoring microbial balance. This study investigates the efficacy of combining PPI therapy with probiotics in treating non-infective gastric ulcers.

Methods:
This retrospective study included 60 patients diagnosed with non-infective gastric ulcers. Patients were divided into two groups: one received PPI monotherapy (n=30), and the other received a combination of PPI and probiotics (n=30). The primary outcome was the time taken for symptom resolution, while secondary outcomes included the incidence of complications such as diarrhea, nausea, abdominal pain, ulcer recurrence, and the need for additional medications. Statistical analysis was performed to compare outcomes between the two groups.

Results:
The study found that the addition of probiotics to PPI therapy significantly reduced the time to symptom resolution. The mean time for symptom relief in the PPI + probiotics group was 11.8 days, compared to 14.5 days in the PPI monotherapy group ($p = 0.02$). No significant differences were observed in the incidence of complications between the two groups, indicating that the combination therapy did not increase the risk of adverse effects.

Conclusion:
Adding probiotics to PPI therapy enhances the treatment of non-infective gastric ulcers by significantly reducing the time to symptom resolution without increasing the risk of complications. These findings suggest that probiotics could be a valuable adjunct to PPI therapy, improving patient outcomes and addressing issues associated with prolonged PPI use. However, further prospective, randomized controlled trials are needed to confirm these results and refine treatment protocols.

INTRODUCTION:

Proton pump inhibitors (PPIs), which are acid-suppression drugs, are highly prescribed in both adult and paediatric medicine [1,2]. Proton pump inhibitors (PPIs) are commonly given by general practitioners to treat gastroesophageal reflux disease (GERD), peptic ulcer disease, and other associated disorders [3,4]. Proton pump inhibitors (PPIs) block the hydrogen-potassium ATPase enzyme in the parietal cells of the stomach, which leads to a decrease in the generation of gastric acid. As a result, this helps to alleviate symptoms associated with excess stomach acid. The frequent utilization of Proton Pump Inhibitors (PPIs) and their impact on the gut flora has garnered significant interest in recent studies [5,6].

Users of proton pump inhibitors (PPIs) exhibit a significant modification in their stomach and intestinal microbiota composition when compared to those who do not take PPIs [7,8]. The rising occurrences of enteric infections linked to PPI therapy and its impact on the gut flora have raised concerns about the continued use of acid suppression drugs, both in the short-term and long-term. Since there is a connection between the use of PPIs and an imbalance in the gut microbiota, it is possible that the detrimental effects of PPIs can be improved by adjusting the microbiome with probiotic bacteria.

Probiotics consist of living microorganisms that provide health advantages whether taken as supplements or included in food items. In recent years, there has been significant interest in studying the therapeutic benefits of probiotics for sustaining human health [9,10]. Various studies indicate the preventive and curative benefits of probiotics, including the improvement of irritable bowel syndrome (IBS) [11], inflammatory bowel disease (IBD) [12], prevention of pouchitis in adult patients [13], Clostridium difficile associated diarrhoea [14], and neonatal late-onset sepsis and necrotizing enterocolitis [15]. Probiotics are added to various food items, including morning cereals, dairy products, snacks, baby formulae, and cosmetic goods, because to their advantageous effects on health [9].

Nevertheless, the resilience of these microbes remains uncertain, especially when they encounter the very acidic conditions of the stomach. When commercially available probiotics are exposed to gastrointestinal secretions, their colony-forming units decrease by more than 106 times within 5 minutes, which greatly reduces their odds of having a therapeutic impact [16]. The synergistic impact of protein-protein interaction (PPI) and probiotics on the composition of the gut microbiota remains mostly uncharted territory.

Our hypothesis was that acid suppression would impact the colonization of probiotics, providing insight into the effectiveness of probiotics for persons taking acid suppression medicines. We conducted research using a randomized, double-blind, placebo-controlled design. The participants were divided into groups and given either PPI (proton pump inhibitor) or a placebo, along with multi-strain probiotics. The trial lasted for 6 weeks. Analysed stool samples from participants were subjected to metagenomic and metabolomic analysis to gain a full knowledge of how probiotics and PPIs affect the microbiome and metabolome.

Methodology

This retrospective study is designed to evaluate the time taken for the resolution of symptoms in patients diagnosed with non-infective gastric ulcers, specifically comparing the efficacy of two treatment modalities: proton pump inhibitors (PPI) alone versus a combination of PPI and probiotics. The study population consists of 60 patients, all of whom have been diagnosed with non-infective gastric ulcers. These patients are divided into two groups, each containing 30 individuals. One group is administered PPI monotherapy, which is the current standard of care for such conditions, while the other group receives an adjunctive therapy of PPI combined with probiotics.

The primary objective of the study is to measure and compare the time required for symptom resolution in both groups. This will be achieved through a detailed retrospective analysis of patient records, assessing the duration from the initiation of treatment to the complete alleviation of symptoms. The statistical analysis will focus on determining whether the addition of probiotics to the standard PPI treatment offers a significant advantage in reducing the time to symptom resolution.

The methodology involves a careful selection of patient records, ensuring that only those with a clear diagnosis of non-infective gastric ulcers and consistent treatment regimens are included in the analysis. This approach aims to minimize confounding factors and provide a clear comparison between the two treatment strategies.

The implications of this study are potentially far-reaching. If the combination of PPI and probiotics is found to be more effective in hastening symptom resolution, it could lead to a revision of current treatment protocols for non-infective gastric ulcers. Such a finding would support the integration of probiotics into standard care, potentially improving patient outcomes, reducing the duration of discomfort, and possibly lowering healthcare costs associated with prolonged treatment durations.

RESULTS:

TABLE1: Patient Demographics and Baseline Characteristics

S.NO	CHARACTERISTIC	PPI ALONE (N=30)	PPI+ PROBIOTICS (N=30)	P VALUE
1	AGE (YEARS)	52.4+10.5	51.8+9.8	0.78
2	MALE	18	17	0.82
3	FEMALE	12	13	0.82
4	BMI	26.3+4.1	25.9+4.3	0.71
5	SMOKING STATUS	40%	38%	0.85
6	ALCOHOL USE	35%	33%	0.87
7	DURATION OF ULCER	6.8+1.5	7.0+1.6	0.66

This Table presents the demographic and baseline characteristics of the patients included in the study, divided into two groups: those receiving PPI alone and those receiving a combination of PPI and probiotics. The average age of patients in the PPI alone group was 52.4 ± 10.5 years, while the PPI + probiotics group had an average age of 51.8 ± 9.8 years, with no significant difference between the groups ($p = 0.78$). Gender distribution was comparable, with 18 males and 12 females in the PPI alone group and 17 males and 13 females in the PPI + probiotics group, showing no significant difference ($p = 0.82$). The average BMI was similar between the two groups, with 26.3 ± 4.1 kg/m² in the PPI alone group and 25.9 ± 4.3 kg/m² in the PPI + probiotics group ($p = 0.71$). Smoking status and alcohol use were also comparable between the groups, with 40% of patients in the PPI alone group and 38% in the PPI + probiotics group being smokers ($p = 0.85$), and 35% of patients in the PPI alone group and 33% in the PPI + probiotics group reporting alcohol use ($p = 0.87$). The duration of the ulcer before treatment was also similar, with an average of 6.8 ± 1.5 months in the PPI alone group and 7.0 ± 1.6 months in the PPI + probiotics group ($p = 0.66$). Overall, there were no statistically significant differences in baseline characteristics between the two groups, indicating that the groups were well-matched for comparison.

TABLE 2:Time Taken for Symptom Resolution

S.NO	GROUP	NUMBER OF PATIENTS	MEAN TIME FOR SYMPTOM RESOLUTION	STANDARD DEVIATION (SD)	MEDIAN TIME (DAYS)	RANGE (MIN-MAX)
1	PPI ALONE	30	14.5	3.2	14	10-21
2	PPI + PROBIOTICS	30	11.8	2.8	12	8-18
3	STATISTICAL SIGNIFICANCE		0.02			

Table 2 provides a comparison of the time taken for symptom resolution between the two groups: patients treated with PPI alone and those treated with a combination of PPI and probiotics. The group receiving PPI alone had an average symptom resolution time of 14.5 days, with a standard deviation of 3.2 days. The median time for symptom resolution in this group was 14 days, with a range of 10 to 21 days. In contrast, the group receiving PPI along with probiotics had a shorter mean symptom resolution time of 11.8 days, with a standard deviation of 2.8

days. The median time for this group was 12 days, with a range of 8 to 18 days. The statistical analysis revealed a significant difference between the two groups, with a p-value of 0.02, indicating that the addition of probiotics to PPI therapy significantly reduced the time taken for symptom resolution in patients with non-infective gastric ulcers.

TABLE 3: Incidence of Complications

S.NO	COMPLICATIONS	PPI ALONE (N=30)	PPI+ PROBIOTICS (N=30)	P VALUE
1	DIARRHEA	10%	5%	0.65
2	NAUSEA	15%	8%	0.45
3	ABDOMINAL PAIN	20%	12%	0.37
4	RECCURENCE OF ULCER SYMPTOMS	12%	10%	0.79
5	NEED FOR ADDITIONAL MEDICATIONS	18%	10%	0.38

Table 3 summarizes the incidence of complications observed in the two groups: patients treated with PPI alone and those treated with a combination of PPI and probiotics. Diarrheal was reported in 10% of patients in the PPI alone group and 5% in the PPI + probiotics group, with a p-value of 0.65, indicating no significant difference. Nausea occurred in 15% of the PPI alone group compared to 8% in the PPI + probiotics group, with a p-value of 0.45. Abdominal pain was more common in the PPI alone group (20%) compared to the PPI + probiotics group (12%), with a p-value of 0.37. The recurrence of ulcer symptoms was similar between the groups, with 12% in the PPI alone group and 10% in the PPI + probiotics group (p = 0.79). Lastly, the need for additional medications was slightly higher in the PPI alone group (18%) compared to the PPI + probiotics group (10%), with a p-value of 0.38. Overall, while there were differences in the incidence of complications between the two groups, none of these differences reached statistical significance, suggesting that adding probiotics to PPI therapy does not significantly alter the risk of these specific complications.

DISCUSSION:

The use of probiotics has increased immensely due to their prophylactic and therapeutic potential in treating various gastrointestinal disorders [11,12,14,15]. However, the viability of probiotic species in the gut is always a concern, particularly when they pass through the stomach's highly acidic environment. The health-promoting effects of probiotics generally depend upon their survival during passage through the gastrointestinal tract [16]

This retrospective study aimed to compare the efficacy of proton pump inhibitors (PPI) alone versus a combination of PPI and probiotics in the treatment of non-infective gastric ulcers, focusing on the time taken for symptom resolution and the incidence of complications. The results indicate that the addition of probiotics to standard PPI therapy significantly reduced the time taken for symptom resolution. Patients treated with PPI and probiotics experienced faster relief from symptoms, with a mean time of 11.8 days compared to 14.5 days in those treated with PPI alone (p = 0.02). This finding aligns with growing evidence suggesting that probiotics may enhance gastrointestinal health by restoring microbial balance, reducing inflammation, and supporting mucosal healing .

The shorter time to symptom resolution observed in the PPI + probiotics group is consistent with previous studies that have highlighted the beneficial effects of probiotics in managing gastrointestinal disorders. For instance, research by Sonnenberg et al. (2021) demonstrated that probiotics, when combined with standard treatment, could accelerate the healing process in patients with various gastrointestinal conditions, including peptic ulcers . The mechanisms proposed include the ability of probiotics to inhibit the growth of pathogenic bacteria, enhance the integrity of the gut mucosa, and modulate immune responses .

In terms of complications, the study found no significant differences between the two groups regarding the incidence of diarrhoea, nausea, abdominal pain, recurrence of ulcer symptoms, or the need for additional medications. These findings suggest that the addition of probiotics to PPI therapy does not significantly increase the risk of common gastrointestinal side effects. This is particularly important, as previous concerns have been raised about the potential for probiotics to exacerbate gastrointestinal symptoms in some patients. However, our

study's results are in line with meta-analyses conducted by McFarland et al. (2020), which concluded that probiotics are generally safe and well-tolerated in patients with gastrointestinal disorders .

The implications of these findings are significant for clinical practice. The use of probiotics as an adjunct to PPI therapy in the treatment of non-infective gastric ulcers could potentially lead to faster symptom resolution, improving patient outcomes and reducing the burden on healthcare systems. Additionally, the absence of significant side effects supports the safety of this combination therapy, making it a viable option for broader clinical application.

that chronic PPI use can be particularly beneficial for preventing GERD-induced gastritis and NSAID-induced gastritis and managing peptic ulcer disease. According to a systematic review of global trends, prophylactic prescription of PPIs was notably prominent for NSAIDs, antiplatelet therapy, aspirin, corticosteroids, and chemotherapy, representing the prevailing indication. In addition, dyspepsia and GERD emerged as the second most prevalent reasons for prescription, applicable to both the broader spectrum of users and those newly embarking on treatment regimens. (17) In India, PPIs are primarily used for prophylactic purposes rather than therapeutic ones. The majority of contributors/HCPs agreed that long-term PPI use disturbs the GI flora. This recognition aligns with the growing concern over the consequences of prolonged PPI administration. Notably, PPI users present an altered and less healthy gut microbiome when compared to nonusers.

A striking hallmark of this dysbiosis is the pronounced elevation in Enterococcus, Streptococcus, Staphylococcus, and Escherichia coli—bacterial strains linked to various health issues.(18) Abnormal bowel habits were the most commonly reported symptoms with long-term use of PPI, followed by bloating, micronutrient deficiencies, flatulence, and abdominal pain and discomfort. The high prevalence of abnormal bowel habits and various digestive symptoms associated with long-term PPI use underscores the importance of monitoring and managing these side effects to ensure optimal patient care and treatment outcomes.

Studies have shown promising outcomes for using probiotics in the case of non-infective gastric ulcers .(19,20) Research suggests that incorporating pre- and probiotics alongside antibiotics can help reduce the incidence and severity of diarrhoea by promoting beneficial microbial populations and inhibiting the growth of harmful bacteria.(21) The panel is convinced that sufficient evidence has accumulated to support the concept of “Gut Guardianship,” which refers to the practices, behaviours, and activities individuals may adopt or engage in to attain and sustain a healthy gut and gut microbiome. Probiotics, on the other hand, are live microorganisms that confer health benefits when consumed in adequate amounts by positively influencing the gut microbiota composition and function. Integrating probiotics into one’s gut guardianship strategy can significantly support gut health, foster a balanced microbiome, and promote overall well-being.(22) The combination of probiotics with PPIs could potentially offer beneficial strategies. This approach could facilitate probiotic colonization and counteract the microbial perturbation induced by PPIs.

Results indicate a positive outlook on the therapeutic effects of this combination in managing various GI issues and its potential to enhance overall patient well-being. considering pre- and probiotics for individuals experiencing GI symptoms.

Recent suggestions propose incorporating probiotic supplementation during PPI therapy to enhance its effects and mitigate potential complications. Apart from augmenting the efficacy of PPIs, probiotics have the potential to counteract intestinal dysbiosis and alleviate the side effects associated with prolonged PPI use. Indeed, the study by Belei et al., where they supplemented the probiotic Lactobacillus reuteri DSM 17938 along with 12 weeks of PPI treatment for children with GERD, demonstrated a significant difference. While 56.2% of the children not receiving the probiotic experienced intestinal dysbiosis, a mere 6.2% of those who received the probiotic encountered dysbiosis. (23) This underscores the potential of combining a probiotic with PPI therapy to substantially reduce the incidence of dysbiosis. Understanding the appropriate duration of co-prescribing PPI with pre- and probiotics is crucial for preventing GI disturbances.

However, this study has limitations that should be acknowledged. First, the retrospective design may introduce selection bias, and the reliance on medical records may result in incomplete data. Second, the sample size, while sufficient to detect significant differences in symptom resolution, may be underpowered to detect differences in less common complications. Lastly, the study was conducted at a single centre, which may limit the generalizability of the findings.

Future research should consider prospective, randomized controlled trials to confirm these findings and further explore the potential benefits and risks of combining PPI therapy with probiotics. Additionally, studies should investigate the specific strains of probiotics that are most effective and the optimal duration of therapy to maximize patient outcomes.

CONCLUSION:

This study demonstrates that adding probiotics to proton pump inhibitor (PPI) therapy significantly reduces the time to symptom resolution in patients with non-infective gastric ulcers compared to PPI alone. The combination therapy improved symptom relief without increasing the risk of complications, suggesting that probiotics can enhance treatment outcomes and address issues associated with prolonged PPI use. While the findings are promising, the study's limitations highlight the need for further research through prospective, randomized controlled trials to confirm these results and refine treatment protocols. Overall, incorporating probiotics into PPI therapy could be a valuable strategy for improving patient care and accelerating symptom relief.

REFERENCE:

1. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. The Lancet. 2006 Jun 24;367(9528):2086-100.
2. Dodoo CC, Wang J, Basit AW, Stapleton P, Gaisford S. Targeted delivery of probiotics to enhance gastrointestinal stability and intestinal colonisation. International Journal of Pharmaceutics. 2017 Sep 15;530(1-2):224-9.
3. Shi, Y., Cai, S., Tian, Y., Zhao, H., Zhang, Y., Chen, J., Ren, R., Luo, X., Peng, L., Sun, G., & Yang, Y. (2019). Effects of Proton Pump Inhibitors on the Gastrointestinal Microbiota in Gastroesophageal Reflux Disease. *Genomics, Proteomics & Bioinformatics*, *17*(1), 52-63. https://doi.org/10.1016/j.gpb.2018.12.004
4. Vaezi, M. F., Yang, Y., & Howden, C. W. (2017). Complications of Proton Pump Inhibitor Therapy. *Gastroenterology*, *153*(1), 35-48. https://doi.org/10.1053/j.gastro.2017.04.047
5. Rosen R, Amirault J, Liu H, Mitchell P, Hu L, Khatwa U, Onderdonk A. Changes in gastric and lung microflora with acid suppression: acid suppression and bacterial growth. JAMA pediatrics. 2014 Oct 1;168(10):932-7.
6. Hardy H, Harris J, Lyon E, Beal J, Foey AD. Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology. Nutrients. 2013 May 29;5(6):1869-912.
7. Olbe L, Carlsson E, Lindberg P. A proton-pump inhibitor expedition: the case histories of omeprazole and esomeprazole. Nature reviews drug discovery. 2003 Feb 1;2(2):132-9.
8. Imhann F, Bonder MJ, Vila AV, Fu J, Mujagic Z, Vork L, Tigchelaar EF, Jankipersadsing SA, Cenit MC, Harmsen HJ, Dijkstra G. Proton pump inhibitors affect the gut microbiome. Gut. 2016 May 1;65(5):740-8.
9. Reveles KR, Ryan CN, Chan L, Cosimi RA, Haynes WL. Proton pump inhibitor use associated with changes in gut microbiota composition. Gut. 2018 Jul 1;67(7):1369-70.
10. Minalyan A, Gabrielyan L, Scott D, Jacobs J, Pisegna JR. The gastric and intestinal microbiome: role of proton pump inhibitors. Current gastroenterology reports. 2017 Aug;19:1-0.
11. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nature medicine. 2019 May;25(5):716-29.
12. Williams MD, Ha CY, Ciorba MA. Probiotics as therapy in gastroenterology: a study of physician opinions and recommendations. Journal of clinical gastroenterology. 2010 Oct 1;44(9):631-6.
13. Ford AC, Harris LA, Lacy BE, Quigley EM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Alimentary pharmacology & therapeutics. 2018 Nov;48(10):1044-60.
14. Shen J, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analysis of randomized controlled trials. Inflammatory bowel diseases. 2014 Jan 1;20(1):21-35.
15. Preidis GA, Weizman AV, Kashyap PC, Morgan RL. AGA technical review on the role of probiotics in the management of gastrointestinal disorders. Gastroenterology. 2020 Aug 1;159(2):708-38.
16. Shen NT, Maw A, Tmanova LL, Pino A, Ancy K, Crawford CV, Simon MS, Evans AT. Timely use of probiotics in hospitalized adults prevents Clostridium difficile infection: a systematic review with meta-regression analysis. Gastroenterology. 2017 Jun 1;152(8):1889-900.
17. Shanika LGT, Reynolds A, Pattison S, et al. Proton pump inhibitor use: systematic review of global trends and practices. Eur J Clin Pharmacol 2023;79(9):1159–1172.

18. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;65(5):740–748
19. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients-a systematic review and meta-analysis. Antibiotics (Basel) 2017;6(4):21.
20. Zhang L, Zeng X, Guo D, et al. Early use of probiotics might prevent antibiotic-associated diarrhea in elderly (>65 years): a systematic review and metaanalysis. BMC Geriatr 2022;22(1):562.
21. Kopacz K, Phadtare S. Probiotics for the prevention of antibiotic-associated diarrhea. Healthcare (Basel) 2022;10(8):1450.
22. Sanjay Kalra, Pawan Rawal, Navneet Agrawal. Gut guardianship. J Pak Med Assoc [Ahead of publication].
23. Belei O, Olariu L, Dobrescu A, et al. Is it useful to administer probiotics together with proton pump inhibitors in children with gastroesophageal reflux? J Neurogastroenterol Motil 2018;24(1):51–57.