Review / *Derleme*

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A Revision of Probiotic Safety in Children

Çocuklarda Probiyotik Güvenliğinin Gözden Geçirilmesi

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Abstract

Probiotics have been used as health-promoting components for a significant period of time. Their benefits have also been scientifically proven in certain indications such as acute gastroenteritis, antibiotic-associated diarrhea, prevention of nosocomial infections, infantile colic. Probiotic consumption has increased tremendously over the past 20 years. In recent publications, scientists have begun to voice their concerns regarding safety. The main side effects of probiotics are systemic infections, gastrointestinal side effects, antibiotic resistance gene transfer, harmful metabolic effects and immune system stimulation. Children in the pediatric age group, particularly premature infants with short bowel syndrome, immunocompromised individuals, children with congenital heart disease, and those with genetic syndromes, are at a higher risk of experiencing adverse effects related to probiotics. In this review, we addressed the potential safety gaps of probiotics in children and discussed the measures that can be taken to mitigate these vulnerabilities.

Keywords: Probiotics, safety, advers reaction, children

Öz

Probiyotikler çok uzun süredir sağlığı geliştirici unsurlar olarak kullanılmaktadır. Bu ürünlerin akut gastroenterit, antibiyotik ilişkili diyare, hastane enfeksiyonlarının önlenmesi, infantil kolik gibi belirli endikasyonlarda faydaları bilimsel olarak da kanıtlanmıştır. Probiyotik tüketimi son 20 yılda muazzam şekilde artmıştır. Son zamanlarda yapılan yayınlarda bilim insanları güvenlik hakkındaki endişelerini dile getirmeye başlamışlardır. Probiyotiklerin başlıca yan etkileri, sistemik enfeksiyonlar, gastrointestinal yan etkiler, antibiyotik direnç geni transferi, zararlı metabolik etkiler ve bağışıklık sistemi stimülasyonudur. Çocuk yaş grubunda prematüre bebekler kısa bağırsak sendromlu, immün sistemi baskılı, konjenital kalp hastası, genetik sendromu olan çocuklar probiyotiklere bağlı istenmeyen etkiler açısından özellikle risk altındadır. Bu derlemede, çocuklarda probiyotiklerin olası güvenlik açıklarını ve bunların önüne geçebilmek amacıyla alınabilecek önlemleri tartıştık.

Anahtar Kelimeler: Probiyotik, güvenlik, istenmeyen etki, çocuk

Introduction

The term probiotic derives from the Latin words "pro" and "bios" and means "for the living". World Health Organization (WHO) defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (1). Although this definition is generally accepted, it was revised in 2014 in order to avoid misuse as "live strains of meticulously selected microorganisms that provide a health benefit to the host when administered in adequate amounts" (2).

In fact, the introduction of probiotics into our lives dates back to as early as the 3rd millennium BCE. In the last 30 years, the protective and therapeutic potential of probiotics in many health fields has been the subject of many studies. Therefore, the use of probiotics has garnered attention both from a scientific and commercial standpoint (3). The lack of a widely used guide on the use, regulations, and maximum safe doses of probiotics until now raises questions about safety in mind. Therefore, a more detailed evaluation of the safety of probiotics and probiotics has become mandatory.

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In 1994, probiotics were classified as food supplements by the U.S. Food and Drug Administration (FDA), therefore they were allowed to be marketed and sold over-the-counter, and these products were not strictly controlled like pharmaceutical drugs (4). Concerns about the safety of probiotics were raised for the first time at the workshop held in Helsinki in 1996, and some recommendations were made in terms of safety (5).

In 2001, Marteau wrote the first review to systematically classify probiotic-related safety issues in an oderly manner, followed by a guideline published by WHO in 2002 that brought this topic to attention for the first time. (6). According to this guideline, probiotics are theoretically associated with four specific types of adverse effects in individuals with underlying conditions. These are systemic infections, harmful metabolic activities, immune stimulation in vulnerable individuals and gene transfer (6,7). In order to prevent these undesirable effects, the WHO has recommended a series of controls for probiotics before production, including monitoring for toxin production, hemolytic potential, antibiotic resistance, and metabolic activities. They also suggest measuring their potential for causing infection in immunocompromised animals and improving post-marketing surveillance for better monitoring of side effects.

Lactic acid producing bacteria (LAB; *Lactobacillus* spp., *Bifidobacterium* spp., *Enterococcus* spp., *Streptococcus* spp., *Staphylococcus* spp., *Lactococcus, Enterococcus*), *Bacillus* and *Saccharomyces* type fungi are microorganisms used as probiotics. Many types of probiotics, including *Lactobacilli*, *Bifidobacterium*, lactococci and some yeasts, have been classified as generally recognized as safe (GRAS) by WHO. Although other spore-forming forms such as *Bacillus*, *streptococci*, enterococci are not included in this classification, they are used as probiotics (8). The European Food Safety Authority (EFSA), the institution responsible for food safety in European Union countries, is also responsible for probiotics. Similarly, EFSA has created a qualified presumption of safety (QPS) list and included *lactobacilli* and *bifidobacteria*, but not *enterococci* (9). However, EFSA refrained from making definite judgments about the microorganisms included or not included in this list, did not give a safety guarantee regarding the microorganisms on the list, or stated that it did not mean that the organisms not on the list were dangerous (10).

Some expert organizations, such as the European Product Safety Forum (PROSAFE), have also provided recommendations regarding the implementation of probiotic. According to PROSAFE, the addition of non-naturally occurring strains carrying known virulence genes to human and animal foods should be avoided. Additionally, it has been emphasized that the assessment of the pathogenic potential of the produced strains and the conduct of double-blind human studies are important tools in terms of ensuring reliability (11). In 2017, European Society for the Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) highlighted the inadequacies in the quality of commercial probiotic products, and recommended that more stringent quality control measures be taken in products prescribed for the pediatric age group in order to prevent this. Furthermore, it is recommended that undesirable effects be followed up and recorded by health authorities (12). In 2018, independent experts convened under the leadership of the European Pediatric Association (EPA) and discussed the indications and special circumstances for the use of probiotics. In conclusion, it was stated that probiotics were generally safe, but it was emphasized that caution should be exercised when prescribing them in special patient groups (13).

In a review of 384 clinical studies on probiotics, prebiotics and synbiotics by Bafeta et al. in 2018, it was noted that there was a significant lack of reporting adverse effects in the existing studies (14). Despite the presence of case reports documenting adverse effects following the use of probiotics, especially in populations with underlying diseases, there is still a lack of robust reporting on adverse effects in clinical studies. Additionally, the absence of an effective post-marketing surveillance system contributes to the incomplete availability of precise numerical data in this regard.

In this review, we examined the adverse effects and possible mechanisms under four headings.

Infections

The most significant known side effect of probiotics with a good safety profile is infections. The first case report of pediatric patients developing fungemia associated with probiotic use was published in 1995 (15). In 1998, Salminen et al. extensively addressed the potential of probiotics to cause systemic infections (5). Subsequently, the number of case reports documenting infections following probiotic use has started to increase, particularly in immunocompromised patients.

Bacterial translocation is defined as the passage of bacteria from the gastrointestinal tract into the sterile spaces of the body. Especially in individuals with impaired intestinal barrier, immunosuppression, and intestinal prematurity, live organisms within the intestine may infiltrate into the non-intestinal regions and cause systemic infections. It has been suggested that the ability to adhere to the intestinal mucosa and mucolytic activity of probiotic strains facilitate translocation. Clinical infection occurs as a result of the microorganism entering the blood stream as a result of translocation (3,16-18).

Bacteremia, sepsis, endocarditis, fungemia and local infections are main probiotic-related infections (19). Premature infants and critically ill patients are prone to bacteremia and fungemia due to intestinal dysbiosis, weak immunity, presence of invasive procedures and devices, and use of broad-spec-

trum antibiotics (16). In a review published in 2014 in which infants taking probiotics to prevent necrotizing enterocolitis (NEC) were evaluated, no cases of bacteremia were reported, and the risk of bacteremia associated with probiotic use was stated to be negligible (20). In a randomized controlled study published in 2016, in which approximately 1200 premature babies were enrolled and Bifidobacterium breve was used as probiotic to prevent the development of NEC and sepsis in preterm infants, the participating physicians reported no harm associated with the use of probiotics (21).

In a review which screened 49 cases of probiotic-related invasive infection in pediatric patients published in 2021, sepsis was reported as the most common infection, and the most frequently identified causative agents were *Lactobacillus* spp. (35%), *Saccharomyces* spp. (29%), *Bifidobacterium* spp. (31%), *Bacillus clausii* (4%), and *Escherichia coli* (2%) (22). In this review, it was reported that 80% of the cases consisted of children under the age of two, and three deceased cases were lost to follow-up. Except for one case, all of the cases had underlying conditions that facilitated the development of invasive infection, and all three deceased. Cases had serious comorbidities. Especially prematurity and intravenous catheter use are the most frequently reported predisposing factors; short bowel syndrome, enteral/parenteral nutrition, conditions with inflammation in the intestines, abdominal surgery, respiratory support, congenital heart disease and genetic syndromes are other risk factors. Although the survival rate was high in most of the cases, the patients had to be treated with intravenous and broad-spectrum antibiotics (22).

In 2021, prolonged *Bacillus clausii* bacteremia was detected in a 17-month-old child. What makes this case report interesting is that the child had no underlying health problems, only a recent history of diarrhea. Based on this, it was suggested that as a result of impaired intestinal permeability, spores of *Bacillus clausii* intermittently became vegetative and crossed the intestinal barrier, which had already been impaired due to diarrhea, and entered the bloodstream (23).

Except for the last mentioned case, the other hosts had comorbidities. Based on this data, we can infer that the immune system of the host is important in terms of susceptibility to infection rather than the probiotic strain itself. The risk of infection associated with the use of probiotics should be kept in mind, especially in special patient groups whose immune system is suppressed.

Metabolic Activities

Lactobacillus and *Bifidobacterium* are the most commonly used bacteria in probiotic products and produce lactic acid (19). When we look back in history, products such as yogurt, sour cabbage and pickles, which are rich in bacteria that produce lactic acid, have been used for years and no health problems have been experienced. There are several forms of lactic acid, one of which is D-lactate. D-lactic acidosis is a problem that also affects neurocognitive development and causes encephalopathy particularly in children with short bowel syndrome. A high amount of D-lactate occurs due to a short intestinal transit time and undigested carbohydrates are fermented by bacteria (24). The lactic acid produced is not actually a significant threat to human health, except for individuals with short bowel syndrome. Data on the relationship between probiotics and D-lactic acidosis are uncertain and controversial. The Food and Agriculture Organization of the United Nations (FAO)/WHO Nutrition Commission (Codex Alimentarus) allowed only L-lactate-producing probiotics to be added in infant formula (25). Although there are case reports on probiotic-related lactic acidosis in the literature, there is no clear recommendation on this issue (26,27). However, caution is advised, particularly in patients with short bowel syndrome, regarding this aspect (3).

In 2018, Rao et al. described a new clinical condition in patients with short bowel syndrome, which is characterized by postprandial cognitive impairment, flatulence, and abdominal bloating; thought to develop due to excessive bacterial growth in the small intestine and possibly probiotic-induced D-lactic acidosis (28). Other symptoms accompanying this clinical picture are fatigue, restlessness, disorientation and weakness. The resolution of this situation with discontinuation of probiotics and antibiotic treatment in 85% of the patients strengthened the idea that it occurs as a result of bacterial overgrowth in the small intestine, fermentation of carbohydrates by probiotic bacteria, and D-lactic acidosis (19,28).

Certain lactic acid producing Bacilli are capable of producing biogenic amines such as histamine, tyramine, putrescine. These substances can trigger headaches by altering the blood flow reaching the central nervous system in susceptible individuals (3). Some probiotics used in dairy products may cause allergic reactions and hypotension as a result of histamine release (16).

Certain probiotics are known to contain bile acid hydrolase enzymes, which have been shown to lower cholesterol levels. However, it has been reported that the dysregulated expression of this enzyme may cause a tendency to gallstone formation and obesity by disrupting lipid metabolism (16). In 2012, Million et al. demonstrated that some *lactobacillus* species affect weight gain in humans and animals, both in randomized controlled trials and in humans (29). However, it has been stated that this effect depends on the host, strain and many other variables.

In a study conducted in 2008 to evaluate the effect of probiotics on pancreatitis involving 291 patients, it was observed that among patients who experienced a severe pancreatitis attack and were given probiotics, the mortality rate due to

intestinal ischemia was higher compared to those who were not given probiotics. This situation suggested that this might be due to the increased oxygen demand in the intestinal mucosa due to the use of probiotics and the inability of the patient, who was already in critical condition, to meet this need (30). However, in a retrospective study conducted in 2012 with 99 patients with severe acute pancreatitis, it was stated that probiotics had no positive or negative effect on this patient group.

Gene Transfer

Another worrying issue about probiotics is the transfer of antibiotic resistance genes from probiotics to commensal bacteria in the intestinal flora. Mutations or the acquisition of mobile genetic elements carrying resistance genes are responsible for the spread of antimicrobial resistance. Resistance genes can be horizontally transferred from bacteria carrying these resistance genes to other bacteria. This process is known as horizontal gene transfer (HGT) and plays a key role in the development of resistant yeast and bacteria (32).

The human gastrointestinal tract is an ideal environment for HGT due to its bacterial density. Theoretically, certain genetic material of probiotics could be transferred to the established gut microbiota via HGT. In this context, concerns have arisen regarding the transferability of resistance genes by probiotics.

Lactobacillus, *Lactococcus*, *Bifidobacterium* species used as probiotics are generally not pathogenic, but they are intrinsically resistant to many antibiotics (8). In some *Lactobacillus* species, genes showing resistance to many antibiotics such as tetracycline, macrolide, chloramphenicol, and streptomycin have been identified and these studies have shown that aforementioned genes may be transferred transferred theoretically (33). However, most of resistance genes are localized in the chromosome and cannot be easily transferred to other species (8). There is currently no additional evidence presented regarding the transfer of resistance genes in the subsequent period (3).

Enterococci are also classified as lactic acid-producing bacteria and are used in the food industry during the fermentation process and in probiotic products. Enterococci are naturally found in the human intestinal flora, but they can sometimes be significant infectious agents. Resistance to vancomycin in enterococci may be intrinsic or acquired. There are numerous genes responsible for vancomycin resistance, among which *Van*A and *Van*B are localized in plasmids and can be transferred between bacteria through horizontal gene transfer (HGT). Vancomycin-resistant enterococci have the potential to pose a serious threat when the person is hospitalized or the immune system is suppressed (34). Therefore, if probiotics containing enterococci are to be used in the medicine, livestock or food industry; they should be tested for virulence factors and antibiotic susceptibility. EFSA recommends that all bacterial strains used as feed additives to be tested to determine their susceptibility to major antibiotics, and not to be used as a feed additive if there is an acquired resistance gene with risk of being transferred (35).

The uncontrolled simultaneous use of probiotic strains with antibiotics, especially in the livestock sector, can lead to the suppression of the intestinal microbiota due to antibiotics. This can result in the selective proliferation of resistant yeasts and bacteria, facilitating the transfer of resistance genes (32). In conclusion, it is important to screen probiotics used in both humans and animals for transferable resistance genes in terms of HGT potential. This will help in assessing the potential risks associated with the transfer of resistance genes.

Stimulation of the Immune System

The topic of stimulating the human immune system with probiotics is still controversial. Bacteria used as probiotics can stimulate the immune response through substances such as peptidoglycans, lipopolysaccharides and lipoteichoic acids found in the cell wall (36). Previous studies have demonstrated the effects of probiotics on cytokine secretion and dendritic cell function (37). The degree of this modulation varies considerably depending on the underlying immune status of the person, the strain or the dose administered (8). However, this risk is purely theoretical and has not been reported in any human population (16).

Conclusion

Although probiotics are used in many areas, we rarely encounter undesirable effects. Although adverse effects are seen especially in the population with underlying diseases, these effects generally have a good prognosis. As healthcare professionals, we believe it is important to exercise caution, particularly in high-risk patients, and closely monitor for any potential adverse effects.

Regulating probiotics as "medicine" instead of "dietary supplements" during the production phase, inspecting them more strictly by regulatory authorities before production, and including probiotics in the adverse effect reporting system and reporting them in the post-marketing process are important in terms of collecting more objective data. As larger and more systematic studies are conducted in this field, more definitive conclusions can be reached, which will guide healthcare professionals in providing appropriate recommendations.

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