

Rectal Enema Multi Strain Probiotic Therapy Might Mitigate Pruritus, Dermatology Triage and Diamine Oxidase Levels Among Dogs with Food Allergy: Cohort Study

Rektal Enema Çoklu Suş Probiyotik Tedavisi Gıda Alerjisi Olan Köpeklerde Kaşıntı, Dermatoloji Triaajı ve Diamin Oksidaz Düzeylerini Azaltabilir: Kohort Çalışması

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ABSTRACT Objective: The incidence and spatial distribution of allergic diseases are significantly increasing in university practice along with field conditions. Increased plasma levels of histamine and diminished diamine oxidase (DAO) activity have been explored as biomarkers of deduced histamine catabolism. Given histamine participates in allergic inflammation, recent data presented the beneficial efficacy of probiotics for combatting. In the present study the aim was to determine the efficacy of rectal enema multi-strain probiotic chain treatment against food allergy (FA) and relevant clinical signs. **Material and Methods:** In a total of 8 dogs' diagnosis of FA was based on i) history, ii) clinical signs and iii) adopting a trial diet with low carbohydrate. Demographic data involved breed, triage level of pruritus (black color coded severe pruritus, whereas red and green denoted: moderate and minor itching behaviour). DAO levels were determined by use of dog specific test kits via ELISA. **Results:** At the end of a 10 days trial of rectal enema multi-strain probiotic treatment both pruritus scores and triage levels were diminished. Mean blood DAO levels (ng/mL) of circulating values were comperatively addicted to before and after treatment (5 vs. 12). Besides DAO levels were significantly increased at day 10 analytes, in contrast to day 0 initial values. Rectal enema multi-strain probiotic treatment was well tolerated without any adverse effects. **Conclusion:** It was strictly suggested that rectal enema multi-strain probiotic therapy could i) lower pruritus scores and alter triage colors, ii) increase DAO levels in dogs with FA.

ÖZET Amaç: Alerjik hastalıkların insidansı ve anlık dağılımı, üniversite pratiğinde saha koşullarıyla birlikte önemli ölçüde artmaktadır. Artan plazma histamin seviyeleri ve azalan diamin oksidaz (DAO) aktivitesi, histamin katabolizmasının bir biyobelirteci olarak keşfedilmiştir. Histamin, alerjik inflamasyona katıldığı göz önüne alındığında son veriler, probiyotiklerin mücadele için yararlı etkinliğini ortaya koymuştur. Bu çalışmanın amacı, rektal lavman yoluyla çoklu suş probiyotik zincir tedavisinin gıda alerjisine [food allergy (FA)] ve ilgili klinik belirtilere karşı etkinliğini belirlemektir. **Gereç ve Yöntemler:** Toplam 8 köpekte FA tanısı i) öykü, ii) klinik belirtiler, iii) düşük karbonhidratlı bir deneme diyetinin benimsenmesine dayandırıldı. Demografik veriler kaşıntının ırkını, triaj seviyesini (siyah renk kodlu şiddetli kaşıntıyı, kırmızı ve yeşil ise orta ve hafif kaşıntı davranışı) içeriyordu. DAO seviyeleri, ELISA yoluyla köpeğe özgü test kitleri kullanılarak belirlendi. **Bulgular:** On günlük rektal enema çoklu suş probiyotik tedavisi denemesinin sonunda, hem kaşıntı skorları hem de triaj seviyeleri azaldı. Ortalama kan DAO seviyeleri (ng/mL), öncesi ve sonrası gibi karşılaştırmalı olarak (5'e karşı 12) bağımlıydı. Ayrıca DAO seviyeleri, 0. gün başlangıç değerlerinin aksine 10. gün analitlerinde önemli ölçüde arttı. Rektal enema probiyotik tedavisi, herhangi bir yan etki olmaksızın iyi tolere edildi. **Sonuç:** Rektal enema çoklu probiyotik suş tedavisinin i) kaşıntı skorlarını azaltabileceği ve triaj renklerini değiştirebileceği, ii) FA'lı köpeklerde DAO seviyelerini artırabileceği kesinlikle önerildi.

Keywords: Diamine oxidase; food allergy; dog

Anahtar Kelimeler: Diamin oksidaz; gıda alerjisi; köpek

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The big question always arise in our clinical practice, is whether histamine is a friend or a foe? or both. This biogenic amine is commonly distributed and participated in the vast majority of biological conditions.^{1,2} Both endogen or exogen histamin (probably food originated) could induce dramatic allergic phenomena. Histamine could participate as a vasodilator/hypotensive compound, capable of elevating vascular permeability.³⁻⁵ For a better understanding, the entire manuscript the present author conducted a search on a beneficial allergy vocabulary herein presented in Table 1. Taking into account the role of histamin in allergy the present author conducted a search involving dogs with food allergy (FA) and the purpose was to investigate the probable efficacy of rectal enema multi-strain probiotic therapy that could combat pruritus, dermatology triage and diamine oxidase (DAO) levels.

MATERIAL AND METHODS

RESEARCH PERIOD/INCLUSION CRITERIA

The present study was conducted at the University of Aydin Adnan Menderes, Faculty of Veterinary, Department of Internal Medicine in a total of 8 privately owned dogs with FA. First enrolment criteria were selection of dogs without any drug administration, that could potentiall interfere with DAO levels. Dogs with a comorbidity were excluded. Complete blood count and serum biochemistry along with endocrine assays were available on days 0 and 10 for entire cases. Diagnosis of FA was based on i) history, ii) clinical signs and iii) adopting a trial diet.⁶⁻⁸ Diet elimination-challenge trial was restricted to one specific commercially available low carbohydrate diet (Gastro digestive support, Virbac, France) for a minimum of 6 weeks. Beneficial vocabulary was taken into consideration in each session of clinical practice.

RECTAL ADMINISTRATION PROCEDURE

It was performed as shown Figure 1. Briefly a rectal catheter was used similarly to what has been described previously 15 cm apart from rectum, gently.^{9,10} The probiotic powder was mixed and poured on with lactated ringer solution which had similar pH to the colon of dogs.

TABLE 1: Beneficial allergy glossary was adopted from and other relevant literature showed.^{23,24}

Food intolerances	-Composed of i) allergic reactions and ii) non-immunological reactions to food components. -Pharmacological respond to histamine (i.e. vasodilation and induced dermatitis)-source European College of Veterinary Dermatology
Histamine	-Significant mediator of allergic clinical signs -Defects in its catabolism could participate with disease severity -Even if it is liberated from the granulocytes for processing allergiciatopic degranulation could not be broken down effectively, excess could accumulate with contribution to stimulated adverse effects of the amine
Allergy	Type I hypersensitivity reaction (composed of allergen-specific IgE occurrence, inflammatory mediator release)
Microorganisms capable of degrading histamine (diamine oxidase producers) ²²	- <i>Lactobacillus curvatus</i> , <i>Lactobacillus sakei</i> , <i>Lactobacillus sp.</i> , <i>Weissella hellenica</i> , <i>Leuconostoc mesenteroides</i> , <i>Leuconostoc sp.</i> , <i>Escherichia faecium sp.group</i> , <i>Sarcina lutea</i>
<i>Bifidobacterium infantis</i> and <i>Bifidobacterium longum</i>	-Anti-allergic and histamin suppressor ¹⁵
Diamine oxidase (DAO)	-Enzyme capable of catabolizing histamin in gut lumen -Could decrease in relationship with intestinal dysfunctions (i.e., inflammatory bowel disease/irritable bowel syndrome), by several drugs etc.) in that histamine concentrations could exceed the capacity of DAO for decomposing

IgE: Immunoglobulin E.

METHODOLOGY AND INTERPRETATION OF SELECTED BIOMARKER

DAO Analysis

DAO ELISA kits: Canine Diamine Oxidase ELISA Kit purchased by RDA Group, İstanbul (from My Biosource.com) commercially available. As denoted with the available web site (<https://www.mybiosource.com/dao-canine-elisa-kits/diaminee-oxidase/739902>), this assay proved existed high sensitivity/specificity for the detection of DAO. Sera samples included from dogs with a diagnosis of FA. Quantitative Competitive Assay via ELISA Device existed at the facility of RDA Group, İstanbul. Sensitivity was 1.0 ng/mL, with a detection range of 0.312-20 ng/mL. Storage facilities composed 2-8°C, which were then sent to immediately RDA Group, İstanbul.

During performing the study ethical guidelines were followed up, and written owner consent was available for animals enrolled. Taken into consideration in which Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) were taken into consideration throughout all work with humanity. There was no pain or discomfort reported or detected in any animal, as this study did not involve any drug administration. Aydın Adnan Menderes University, Local Ethics Committee (HADYEK) report with no: 64583101/ 2019/022 (date: February 26, 2019) was deemed available for performing the study.

RESULTS

Figure 1, Figure 2, Figure 3, Figure 4 showed all necessary findings throughout the manuscript. Demographic data involving breed and triage level of pruritus were all deemed available in Figure 2. Colors were identified and adopted from field triage (Animal Triage Procedures Wyoming Department of Health and Veterinary Disaster Triage: Making the Tough Decisions” by Wayne E. Wingfield). Black color-coded severe pruritus, whereas red and green were as follows: moderate and minor itching behaviour.

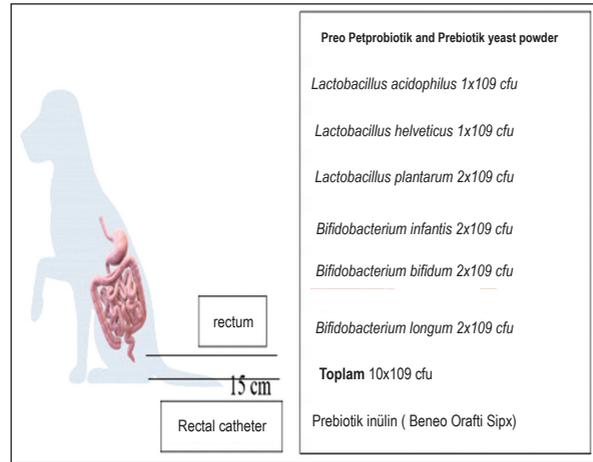


FIGURE 1: Schematic representation of rectally administered multichain probiotic powder Preo Pet (Prebio) ven 15 cm forwarded from rectum.

Case		Triage Level of pruritus	
No	Breed		
I	Doberman	Red	Green
II	Pomeranian	Green	Green
III	King Charles Cavalier	Black	Green
IV	Crossbred	Red	Green
V	Crossbred	Red	Green
VI	Maltese terrier	Black	Red
VII	Kangal	Black	Red
VIII	Boxer	Black	Green

FIGURE 2: Triage level of pruritus at the beginning (day 0 and at the end of trial).

TOLERANCE OF RECTAL ENEMA PROBIOTIC THERAPY

There was no side effects noticed or existed during the rectal enema of probiotic administration (Figure 3). All participant dogs accepted well. The present author was the head of the clinical practice at all

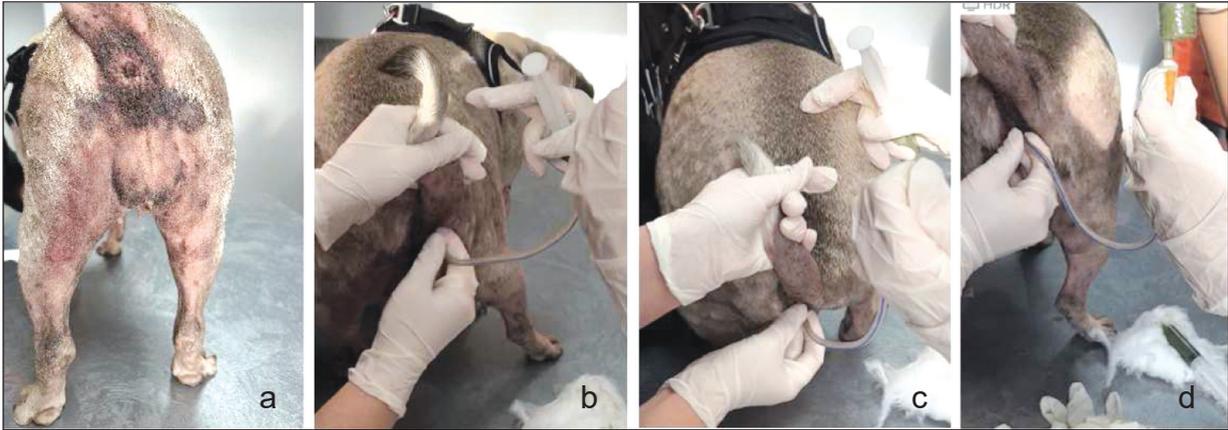


FIGURE 3: This case was initially diagnosed with a) perianal pruritus and presumptive diagnosis of food allergy (perianal hyperpigmentation was severe), b-d) Several different stages of rectal catheter administration carefully performed by referring veterinary surgeon.

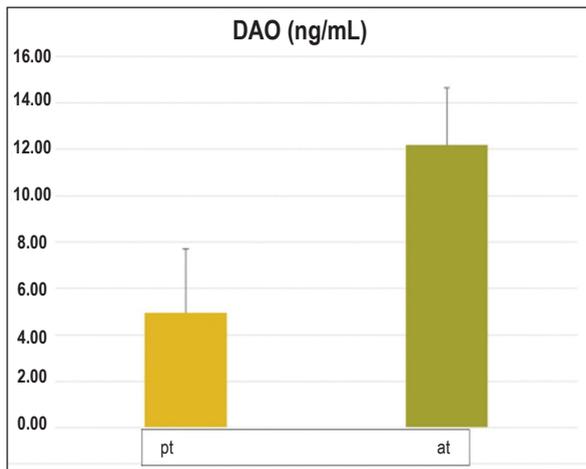


FIGURE 4: Mean (ng/mL) circulating DAO levels.
DAO: Diamine oxidase; pt: Prior to treatment at: after treatment.

times. Only experienced staff was accompanied for supportive help.

DAO Levels

Mean DAO levels of circulating values were shown in Figure 4. Mean values were comparatively additive to before and after as follows: 5 vs. 12.

DISCUSSION

Although it is known that leaky gut-related increases in intestinal permeability and deterioration of the intestinal microbiota plays a role in dermatological disease, there are still unknowns regarding term of both diagnosis and treatment. This was a motivating factor for performing this study.

In a prior study investigating the interaction among atopic dermatitis and intestinal microbiota in dogs, *Lactobacillus plantarum* and *Lactobacillus paracasei* probiotic enema was used against itching combatting.⁹ In that study, in a total of 12 dogs with atopic dermatitis probiotic enema was applied 10-15 cm forward from the rectum via foley/rectal catheter. Pruritus was significantly diminished between days 0 and 10. Successfully applied *L. plantarum* and *L. paracasei* strains were denoted as antipruritic lactic acid bacteria, which were all suggested both for clinical recovery and relief of itching in dogs with atopic dermatitis.⁹ Another study investigated rectal enema probiotic combinations in dogs with atopic dermatitis and determined circulating serum zonulin levels.¹¹ In that open-label, self-controlled case series composed of 6 privately owned dogs with atopic dermatitis rectal enema probiotic protocol was applied once daily for 10 days. Median CADESI-04 ($p=0.028$) and VAS pruritus scores ($p=0.028$) along with circulating zonulin ($p=0.026$) levels were all entirely diminished on day 10 in contrast to on day 0 day values. The selected *Lactobacillus* probiotic strains presented a positive influence on skin inflammation and diminished pruritus.¹¹ In the present study similar to what has been reported above there was a positive respond on combatting skin inflammation in which pruritus triage was diminished and altered in 7 out of 8 cases, denoting green ($n=6$) and red ($n=2$) triage colors among cases enrolled herein.

Contemporary hygiene research denoted that the microbial habitat and vulnerability to microbial products in infancy alter immunity and magnify the tolerance exitance against pervasive allergens.¹² Investigations also presented that oral probiotic supplementation conquers allergic responses.^{13,14} In a prior trial Lac-B, preferred for treatment of gastrointestinal issues, presented symptomatic relief of allergy among rats.¹⁵ Anti-allergic efficacy of Lac-B was proven in the latter study, in which freeze-dried *Bifidobacterium infantis* and *Bifidobacterium longum* could be responsible for his effect.¹⁵ To the present author's knowledge the results from that study should be taken into consideration effectively. The influence of Lac-B on allergic symptoms might be dedicated to suppression of *H1R* and *HDC* gene expressions, resulting with diminished histamine ingredient in the nasal mucosa, which could indicate vanquished histamine signalization.¹⁵ In the present study, in parallel line with the latter data, *B. infantis* (2×10^9 CFU), *Bifidobacterium bifidum* (2×10^9 CFU) and *B. longum* (2×10^9 CFU) probiotic chains composed in what [Preo Petprobiotik & Prebiotik (Preo Pet-Preobio/Turkey)] have been used rectally among dogs with FA could have hastened clinical recovery. Given *B. longum* BB536 deduced clinical signs of several allergic disorders with a high potential of anti-allergic efficacy both in animals and clinical trials.¹⁶⁻¹⁸ It should not be unwise to draw preliminary claim that this efficacy of *B. longum* along with other bifidobacterium species might have helped anti-allergic efficacy observed herein. Furthermore clinical recovery was also evidenced by the healing of intestinal mucosa, as evidenced by increased DAO levels. As was shown in Figure 4. mean DAO levels (ng/mL) were elevated, 5 vs. 12 ng/mL, before and after, respectively in the present study. DAO is an enzyme capable of catabolizing histamine in the gut lumen, and might be decreased in relationship with intestinal dysfunctions, elevated levels obtained in this study in dogs with FA, might reflect the efficacy of probiotic enema treatment modality (Table 1).

In a very interesting article 341 drugs, frequently preferred in intensive care units, were analyzed for

possible interaction (activation/inhibition) with DAO. By use of both canine and human DAO in vitro screening tests, 61 agents were capable of inhibiting DAO activity to several degrees. Out of those, 44 were capable of inhibiting DAO of both human and dog origins, whereas 4 inhibited the canine DAO and 13 the human DAO solely. Interestingly taking into account cephalosporines, cefotiam/cefuroxime were responsible for significant inhibition of human DAO activity, whereas cefotaxime, inhibited neither human nor canine DAO.¹⁹ This valuable information was specifically discussed herein in an attempt to stimulate colleagues not to use drugs capable of interacting with DAO in canine medicine. As aforementioned above in the present study none of the dogs involved were administered any drugs previously.

DAO activity and histamine release were the subject of an old study to those of dogs experimentally induced acute mesenteric artery occlusion. In that study, the authors suggested the protective role of intestinal DAO against intestinal ischemia.²⁰ In a prior study, aimed at determining the existence of biogenic amines (i.e. histamine and tyramine) via selected 15 probiotic strains to those of 6 lactic acid bacteria. *Lactobacillus casei* (TISTR 389) and *Lactobacillus delbrueckii* subsp. *bulgaricus* (TISTR 895) were detected to produce biogenic amines, whereas *Lactobacillus acidophilus*, *Lactobacillus lactis* subsp. *lactis*, *Lactococcus lactis* subsp. *lactis*, and *Lactobacillus plantarum* did not.²¹ In the present study *Lactobacillus acidophilus* 1×10^9 CFU, *Lactobacillus helveticus* 1×10^9 CFU and *Lactobacillus plantarum* 2×10^9 CFU were all *Lactobacillus* strains involved in which none of the strains were biogenic amine producers. Thus during the treatment modality of veterinary surgeons, especially in field conditions without laboratory work or evidence, biogenic amine producer probiotic strains should not be preferred.

CONCLUSION

In conclusion, it should not be unwise to draw a preliminary suggestion that intestinal permeability targeted and leaky gut repairing protocols should involve rectal enema probiotic treatment modality

with experienced skills and veterinary surgeons against FA among dogs.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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