

12-2017

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Does the use of prophylactic probiotics prevent antibiotic-associated diarrhea in adults using one or more antibiotics?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Suwanee, Georgia

December 15, 2017

Abstract

OBJECTIVE: The objective of this selective Evidence Based Medicine (EBM) review is to determine if the use of probiotics can prevent the incidence of antibiotic-associated diarrhea (AAD) in adults using one or more antibiotics.

STUDY DESIGN: Systematic review of three randomized, double-blind, placebo controlled trials in the English language published between 2013 and 2014.

DATA SOURCES: Data sources obtained for this review were articles published in peer-reviewed journals found using PubMed and Cochrane databases.

OUTCOME MEASURED: All three studies defined diarrhea as the passage of three or more loose stools in a 24-hour period. All the studies used the Bristol Stool Scale. Stool consistency and frequency was recorded by patients, relatives, or clinical staff.

RESULTS: Three double-blind, placebo-controlled trials were included and analyzed in this review. None of the three studies showed a statistical significance in AAD between their control groups and the groups receiving probiotics. The Chatterjee et al. study had a p-value of 0.19 and a Numbers Needed to Treat (NNT) of -20.83, the Wright et al. study had a p-value of 0.729 and a NNT of 28.57, and the Allen et al. study had a p-value of 0.72 and a NNT of 250.

CONCLUSION: The three double-blind, placebo-controlled trials analyzed in this review showed no benefit in the use of probiotics for the prevention of AAD when comparing the placebo groups and the probiotics groups.

KEYWORDS: probiotics, antibiotic-associated diarrhea.

INTRODUCTION

The widespread use of antibiotics, whether warranted or not comes with the risk of a patient developing antibiotic-associated diarrhea. Antibiotics can reduce native bacteria in the gastrointestinal tract, regardless if the antibiotic is a beta lactam that disrupts cell walls, a macrolide that prevents ribosomal build-up, or a quinolone that causes DNA break down. The reduction of this symbiotic bacteria causes harm to the host in more ways than one. The reduction causes malabsorption of nutrients, it can also allow opportunistic bacteria that is normally maintained in controlled levels to multiply without limits. Both of these processes can cause a patient to develop loose stools, or further complicate the disease process.

The term probiotics means for life¹ and it describes live organisms that are used to enhance or replenish the native gastrointestinal flora found in the small and large intestines of humans. Although there are many different types of probiotics, the three double-blind, placebo-controlled trials reviewed in this paper all used a strain of lactobacillus. Two of the three double-blind, placebo-controlled trials used lactobacillus as well as Bifidobacterium. Their selection was based on their local production capabilities. Two of the studies used a capsule to deliver the probiotic, the third study used a suspension.

In 1906, French Pediatrician, Henry Tissier, recognized that children with diarrhea had a low number of bacteria with a Y-shaped morphology.² He also found that this bifid bacterium were found in greater numbers in the stool of healthy children.² This and similar discoveries around the turn of the 20th century by other scientists who concluded similar results was the beginning of the prophylactic use of probiotics. It was not long before the scientific community realized that good health was associated with appropriate numbers of symbiotic bacteria in the

gastrointestinal tract. The probiotics help maintain the healthy balance of organisms found in our small and large intestine. When these ratios are altered, there is possibility for illness.

Diarrhea is defined as three or more loose or watery stools per day.^{3,4,5,6} Two of the three double-blind, placebo-controlled trials used the Bristol Stool Scale (BSS)⁷ to define bowel movements with stool type 6 and type 7 as diarrhea.^{3,5} The third study did not use the Bristol Stool Scale and defined diarrhea as the passage of at least three or more watery or loose stools per day for at least two days.⁴

One of the most researched pathogens causative of antibiotic-associated diarrhea is *Colostrum difficile*, or *C. difficile*. The bacterium *C. difficile* is a spore forming bacteria that is identified in 15-25% of cases of antibiotic-associated diarrhea (AAD).⁶ In addition to AAD, the bacterium *C. difficile* can cause serious complications including toxic megacolon and even death.⁶ Most of these deaths are seen amongst patients 65 years old and older.⁸ In 2011 alone 453,000 were diagnosed with a *C. difficile* infection and 29,300 died from complications.⁸

In the United States in 2009, 10.7 billion dollars were spent on antibiotic prescriptions.⁹ Of those antibiotics prescribed, 30% were prescribed for infections that are self-limiting or viral infections.¹⁰ Antibiotic-associated diarrhea can occur whether the antibiotic is warranted or not. When antibiotics are given for self-limited or viral infections, it increases the number of times that providers may need to provide treatment for AAD and its complications. These nosocomial complications are not covered by insurance companies and government programs. This puts an unnecessary and costly burden on providers in all healthcare settings, as well as potentially damage the delicate provider-patient relationship.

The possibility of loss of income and patients has incentivized the medical field to look for preventative measures to avoid antibiotic-associated diarrhea. One of those measures is the use of probiotics as prophylactics for the prevention of AAD. This market had 36.6 billion dollars in global sales in 2015,¹¹ and is expected to almost double in just 5 years.¹¹ Other measures used to prevent or treat AAD is increased hydration, broad-spectrum antibiotics, and anti-diarrheal medications.

It is known that antibiotics lower the number of native bacteria in the gastrointestinal tract.⁶ There has been limited older research that have provided a statistical significance in the use of probiotics for the prevention of AAD. However, it is also known that bacteria are ever evolving,⁶ and continuous research is needed to prove or disprove the current efficacy of probiotics. More research is needed to determine exactly what mechanisms probiotics use to help combat AAD. There also needs to be more research to differentiate if there is a higher rate of AAD with the usage of multiple antibiotics at the same time versus only one antibiotic. Lastly, it is not known if there are any long-term effects from short-term or chronic consumption of probiotics. The study done by Chatterjee et al. made mention of participants being withdrawn from the study if an adverse effect was noted but it did not state if the medication that caused the adverse effect was a probiotic or an antibiotic. The study by Allen et al. also withdrew patients based on adverse reactions, however the study states that the withdrawal was done to reduce the number of medications that the patients were taking rather than due to concerns of the safety of the probiotics. It is worth noting that the Allen et al. study had an exclusion criterion for potential participants that had previously had a reaction to probiotics, however it doesn't provide details of what those adverse reactions were.

In the current healthcare setting, the use of probiotics for the prevention and treatment of antibiotic-associated diarrhea is done with no clear preference in type or number of probiotic. It is based mainly on preference of the patient or the provider, and the local availability. The wide availability, perceived safety, and relative low cost has made the use of probiotics a popular choice as patients attempt to avoid the use of more medication to fix the initial complication of medication use.

OBJECTIVE

The objective of this selective Evidence Based Medicine (EBM) review is to determine if the use of probiotics can prevent the incidence of antibiotic-associated diarrhea in adults using one or more antibiotics.

METHOD

The studies discussed in this review are three double-blind, placebo-controlled randomized trials. Inclusion criteria used for study selection included that the participants were all over 18 years old, they received at least one type of antibiotic, and that the trials was done as double-blind, placebo-controlled. The only intervention required for study selection of the trials was the use of at least one of the popular and widely available types of probiotics, lactobacilli or bifidobacterial probiotic. The trials selected included a comparison of the probiotics to a visually matched placebo. The purpose of the trials was to compare whether the probiotics could prevent AAD. The inclusion criteria of the trials needed to include the description of diarrhea as at least three soft or watery stools per day. Studies were not excluded based on whether the Bristol Stool Scale was used, or the specific number of episodes of bowel movements per day. Also, this systematic review does not seek to ascertain if the use of probiotics reduced the number of days

with diarrhea or the amount of bowel movements per day. Lastly, no trial was excluded based on which antibiotic was used, and no differentiation was made between antibiotics and their individual incidence of AAD.

Research was done in both PubMed and Cochrane for the studies used. Keywords used for the articles were “probiotic” and “diarrhea.” The words “children”, “review”, “observational”, and “drink” were excluded to ensure that only pertinent trials were used. Also, to provide the most current data, only studies published in the last 5 years were used. Any study in a language other than English was excluded. To ensure the outmost rigor in the selection, only studies published in peer-review journals were utilized. The three studies were selected based on their relevance to the topic in question as well as the inclusion of patient oriented evidence that matters (POEMS). All the studies defined a statistically significant p-value of < 0.05. Specific inclusion and exclusion criteria, as well as demographic data are listed on table 1.

Table 1 – Demographics and Characteristics of included studies

| Study | Type | # pts | Age | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|---------------------------|------|-------|---------|---|--|-----|--|
| Allen, et al. (2013) | RCT | 2941 | 71-83.5 | >65 years old, admitted to hospital, use of parenteral antibiotics within the last 7 days or about to start | Already had diarrhea, immunocompromised, required intensive care, had a prosthetic heart valve, suffered from Colostrum difficile in the past 3 months | 23 | Two strains of lactobacilli and two strains of bifidobacterial or placebo were taken daily for 21 days |
| Chatterjee, et al. (2013) | RCT | 396 | 18-70 | 18 to 70 years old with prescription of a systemic oral antibiotic for seven days | Had a course of systemic antibiotics in the last one month prior to screening, underlying | 53 | L. acidophilus and Bifidobacterium or placebo |

| | | | | | | | |
|-----------------------|-----|----|--------|---|---|---|--|
| | | | | | Gastrointestinal disease such as ulcerative colitis, crohn's disease, malabsorption, GI bleeding, etc. | | were taken for 14 days |
| Wright, et al. (2015) | RCT | 87 | 66-101 | >65 years old admitted the geriatric ward | Recent bowel surgery, artificial heart valve, rheumatic heart disease, infective endocarditis, intolerance or allergy to cow milk protein or citrus, artificial feeding, critical care, immunosuppression | 1 | Yakult or placebo twice daily during admission |

OUTCOMES MEASURED

All the studies analyzed defined diarrhea as the passage of three or more loose or watery stools in a 24-hour period. Both the Chatterjee et al. study and the Wright et al. study required the diarrhea to be present for at least 2 consecutive days. Allen et al. did not specify a required length of time for diarrhea to be present. The study by Chatterjee et al. is the only study to not use the Bristol Stool Scale for accurate definition of stool samples. The study used the subjective terms 'watery' and 'loose' instead of an objective way of measurement. Both the Allen et al. study and the Wright et al. study used the Bristol Stool Scale type 6 or type 7 in their definition of diarrhea. The Allen et al. study also allowed participants of the study to describe diarrhea without the use of the Bristol Stool Scale. This was after the participants were discharged from inpatient care. Allen et al. used research nurses while the participants were admitted in the hospitals and phone interviews to assess the participants once they were discharged. Chatterjee et al. gave patients a diary for the patients to record their bowel movements. The diary was

reviewed at day 7 and at day 14. Wright et al. used the treatment teams to record the participant's bowel movements.

RESULTS

The Allen et al. study began with 2981 participants, of those participants 2941 completed the trial and were analyzed. There were many different reasons why 40 participants were excluded from the analysis. Reasons included participants being too unwell, being lost to follow up, participants declining, participants having diarrhea at recruitment, or being withdrawn by a relative. 1470 participants were placed in the probiotic group and 1471 participants were placed in the control group. The probiotic group was given a capsule containing the different probiotics once a day with food for 21 days. The control group was given a visually matched placebo once a day with food for 21 days. Both groups received the prescribed antibiotics daily based on the prescription criteria specific for each antibiotic. The study used research nurses to document the stool from each participant while the participants were in the hospital. After discharge, telephone interviews were used to document the findings from each participant. 159 participants developed AAD in the probiotic group, that is 10.8% of participants in that group. In the placebo group, 10.4% of participants or 153 out of 1471 participants developed AAD. The p-value of the Allen et al. study was 0.72. With the use of dichotomous data, a RBI of 0.038 and an ABI of 0.004 were calculated. This data was then used to calculate the NNT which was 250. These results are recorded in table 4.

Table 4: Allen et al. - Probiotics vs placebo for prevention of AAD

| Study | P-value | RBI | ABI | NNT |
|--------------|---------|-------|-------|-----|
| Allen et al. | 0.72 | 0.038 | 0.004 | 250 |

P value considered significant if < 0.05

The Chatterjee et al. study started with 396 participants and 343 participants completed the study. 44 participants were lost to follow up and 13 were withdrawn because they deviated from the protocols. After withdrawals, 176 participants were in the probiotic group, and 167 participants were in the placebo group. The probiotic group was given 2 capsules twice daily for 14 days. The control group was given identical looking placebo capsules twice a day for 14 days. Both groups received the prescribed antibiotics daily based on the prescription criteria specific for each antibiotic. Both groups received a diary used to record the number of stools per day, the consistency, and color of stool, in addition to any other symptoms. The diary was reviewed at day 7 and at day 14. 19 participants developed AAD in the probiotic group, that is 10.8% of participants in that group. In the placebo group, 15.56% of participants or 26 out of 167 participants developed AAD. Even though the probiotic group had a smaller incidence of AAD, it is not statistically significant. The *p*-value for the Chatterjee study is 0.191. With the use of dichotomous data, a RBI of -0.308 and an ABI of -0.048 were calculated. This data enabled us to calculate the NNT of -20.83. These results are recorded in table 2.

Table 2: Chatterjee et al. study – Probiotics vs placebo for prevention of AAD

| Study | P-value | RBI | ABI | NNT |
|-------------------|----------------|------------|------------|------------|
| Chatterjee et al. | 0.191 | -0.308 | -0.048 | -20.83 |

P value considered significant if < 0.05

The Wright et al. study started with 87 participants and 86 participants completed the study. 1 participant was withdrawn from the study because the participant's family had administered probiotics to the participant after the study had commenced, however the patient

was included in the statistical analyzes. 41 participants were placed in the probiotic group, and 46 participants were placed in the placebo group. The participants in the probiotic group received 65 milliliters bottles twice a day during the length of their admissions into the hospital (average length of admission was 24 days). The control group was given a visually matched placebo for the duration of their hospital stay (average consumption was 22 days). Both groups received the prescribed antibiotics daily based on the prescription criteria specific for each antibiotic. The treatment team used the Bristol Stool Scale to record the findings for both the placebo and the probiotic group. 5 participants in the probiotic group developed AAD. In the control group, 4 participants developed AAD. That is a 12% and 9% development of AAD, respectively. The p-value for this study was 0.729. With the use of dichotomous data, a RBI of 0.402 and an ABI of 0.035 were calculated. This data was used to calculate the NNT of 28.57. These results are recorded in table 3.

Table 3: Wright et al. - Probiotics vs placebo for prevention of AAD

| Study | P-value | RBI | ABI | NNT |
|---------------|----------------|------------|------------|------------|
| Wright et al. | 0.729 | 0.402 | 0.035 | 28.57 |

P value considered significant if < 0.05

DISCUSSION

The purpose of this systematic analysis of the studies was to determine if the use of popular and readily available probiotics is a safe alternative for the prevention of antibiotic-associated diarrhea in adults that use one or more antibiotics to treat bacterial infections. AAD is a very common side effect of the wide-spread use of antibiotics. While analyzing these studies it was calculated that among all participants, 11.41% developed antibiotic-associated diarrhea.

That 11.41% of participants is regardless of what antibiotic was used, which type of probiotic was used, or whether the participant received probiotics versus a visually-matched placebo. This high incidence rate is the reason why many people look for safer ways to preventing the development of diarrhea.

Only one study specifically mentioned the potential side effects of probiotic use. Chatterje et al. had participants document any adverse effects during their time in the trial. 2% of the participants in the probiotic group mention adverse effects. There was no mention of adverse effects reported in the control group. The adverse effects reported by participants were epigastric discomfort, abdominal pain, belching, and dyspepsia. Probiotics are mainly labeled as dietary supplements, which means that they are not extensively regulated by government agencies,¹² this makes the reporting of side effect very minimal.

The three studies concluded that the use of probiotics does not work as a prophylactic for the prevention of antibiotic-associated diarrhea. Of these studies, the study by Allen et al. showed a NNT of 250, meaning one out of every 250 patients would benefit from the use of probiotics to prevent antibiotic-associated diarrhea. The third study, by Chatterjee et al. had almost a 5% reduction of antibiotic-associated diarrhea in the probiotic group when compared to the control group. However, this reduction was not statistically significant.

CONCLUSIONS

After the analyzation of the three placebo-controlled double-blind trials, the use of probiotics for the prevention of antibiotic-associated diarrhea has not shown a statistically significant difference when compared to control groups. The Allen et al. study, being the largest

and with an NNT of 250 shows that there is no clinical or economic advantage for the use or recommendation of probiotics.

Further analysis may be necessary to evaluate whether different antibiotic regimens would benefit from probiotic use. Other areas open for analysis would be whether one type of probiotic is superior to another or whether a higher dosage of probiotic would prove more beneficial. An example of a possible future trial would be a study of specifically the use of lactobacillus in the prevention of antibiotic-associated diarrhea in patients taking a beta lactam. The studies analyzed in this paper all choose the probiotics based on their local availability. There is great momentum within the probiotic industry. The probiotic market is a multibillion-dollar global industry. Probiotics are easily accessible, and with the perception of a side-effect free profile, it is unlikely that their use will be slowed down. This momentum could be used to the advantage of scientists to run more specific trials to further expand our knowledge of their efficacy. However as per this review, the use of probiotics does not currently show enough statistical significance to be used in the prevention or treatment of antibiotic-associated diarrhea.

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