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Original Article

Paediatrics Section

Probiotics in the Prevention of Antibiotic Associated Diarrhoea in a Tertiary Teaching Hospital in Pokhara: A Prospective Study

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ABSTRACT

Introduction: Diarrhoea is an undesirable side effect when treating common infections in children with antibiotics. Though studies have shown the effectiveness of probiotics in preventing antibiotic associated diarrhoea, and there is no documented research in Nepal regarding this issue.

Aim: The objective of this study was to observe the efficacy of probiotics for the prevention of antibiotic associated diarrhoea when co-administered with an oral antibiotic in children with respiratory tract infections who attended the outpatient department in Manipal Teaching Hospital, Pokhara, Nepal.

Materials and Methods: A prospective interventional study was conducted from January 2016 to October 2016 in which 174 children attending the outpatient department in Manipal Teaching Hospital, Pokhara, Nepal and requiring antibiotics for respiratory tract infection were enrolled using convenient sampling method. Eighty-seven of the subjects received standard antibiotic treatment with amoxicillin and clavulanate (control group) and another 87 children received the same antibiotic which was prescribed along with probiotics (probiotic group).

Result: Out of the 174 eligible children enrolled in the study, diarrhoea occurred in 11/87 (12.6%) of the patients in the control group and in 1/87 (1.1%) patient in the probiotic group {relative risk, 12.45, 95% CI(1.57,98.67)}. The co-administration of probiotic with amoxicillin and clavulanate significantly decreased the incidence of diarrhoea in the probiotic group (p= 0.003).

Conclusion: Co-administration of probiotics in children receiving oral amoxicillin and clavulanic acid reduces the risk of diarrhoea.

Keywords: Amoxicillin, Children, Clavulanic acid, Respiratory tract infection

INTRODUCTION

Antibiotics are increasingly prescribed for various illnesses. Children are the main consumers of antibiotics with usage rates stated to be three times higher than that of the adult population [1,2]. It has been observed that the usage of broad spectrum antibiotics such as combination of amoxicillin and clavulanic acid is progressively rising, whereas, usage of older narrow spectrum penicillins are decreasing [1,3]. A common side effect of consumption of broad spectrum antibiotics is Antibiotic Associated Diarrhoea (AAD) [1,4]. AAD is defined as otherwise unexplained diarrhoea that occurs when antibiotics are administered [1,4]. It is reported that among the paediatric population receiving broad spectrum antibiotics, 8-62% have diarrhoea [5-10]. One of the measures to control AAD includes the use of probiotics. Probiotics are live, microbial agents which when administered to the host, confer health benefits. They restore resistance to colonization by pathogenic bacteria [11]. Although, several previous studies [1,5-7,10] have documented the efficacy of probiotics in preventing AAD, no such study has been conducted in Nepal. Therefore, this study was designed to assess the effectiveness of a commonly available probiotic (*Lactobacillus sporogenes*, *Streptococcus faecalis, Clostridium butyricum,* and *Bacillus mesentericus*) in preventing AAD when prescribed with amoxicillin and clavulanate in children with respiratory tract infections in Manipal Teaching Hospital, Pokhara, Nepal.

MATERIALS AND METHODS

A prospective interventional study was carried out to evaluate the efficacy of a commonly available probiotic (trade name Bifilac) in the prevention of AAD in children. The study was conducted between January 2016 to October 2016. Prior to being enrolled in the study, a written informed consent was obtained from atleast one parent. The consent form and study protocol were reviewed and approved by the ethical review committee of Manipal Teaching Hospital, Pokhara. A total of 174 children between the ages of six months to 16 years of age, attending the paediatric Outpatient Department (OPD) of Manipal Teaching Hospital, Pokhara were enrolled in this study using the convenient sampling method. For the calculation of the sample size, a pilot study was conducted. It showed that the diarrhoea proportion in the control group =0.12; proportion in the probiotic group=0; Power (%) =80. Alpha Error (%) =5; Side =2; therefore the required sample size for each arm =77.

Paediatric patients who required oral antibiotic for a respiratory tract infection, requiring antibiotics for atleast five days and among those, children whose guardians gave consent for participation in the study were included in the study. Whereas, exclusion criteria included those having diarrhoea in the preceding week, children having any chronic diseases, children receiving or received any antibiotic in the preceding one week, those having severe disease necessitating admission and children having any known hypersensitivity reaction to β-lactams.

The antibiotic we chose to use for this study was amoxicillin and clavulanate, a broad spectrum β-lactum which is frequently used in the paediatric population for respiratory tract infections. The participating children were alternatively allocated to two groups: 87 were given the antibiotic alone (the control group) and another group of 87 children received antibiotic plus a probiotic (the probiotic group). The probiotic used in this study was a combination of *Lactobacillus sporogenes* 50 Millions, *Streptococcus faecalis* T-110 30 Million,

Clostridium butyricum TO-A 2 Million, and *Bacillus mesentericus* TO-A 1 Million. The reason for choosing this particular probiotic was because this was the probiotic preparation which is available in our hospital pharmacy in a sachet form and is easily available in a form which is best suited for the paediatric population.

The probiotic was administered twice a day and the prescribed antibiotic was administered orally in an age appropriate manner. Parents were asked to record the stool frequency and consistency daily and report to the paediatric OPD five days after the initiation of therapy, or earlier if any complications occurred. In addition, they were also asked to record any other side effects or complaints they might have observed during the course of treatment. If the children weren't brought to the pediatric OPD after five days, they were contacted via telephone in order to monitor for AAD. AAD was defined as presence of atleast three loose/liquid stools per day starting from the day of initiation of antibiotics. In addition to this, patient's characteristics such as age, sex, principal diagnosis and duration of antibiotic therapy were also recorded. The data obtained was collected and analysed using SPSS version 19.0 and a p-value <0.05 was considered statistically significant. Chi-Square test was used for categorical data, independent sample t-test for continuous data and relative risk was calculated to assess risk.

RESULTS

[Table/Fig-1] summarizes the demographic and clinical characteristics of the participating children. It was seen that the differences of demographic and clinical characteristics of the two groups were not statistically significant.

[Table/Fig-2] shows the frequency and duration of diarrhoea in the control and probiotic groups. In the control group, out of the 11 patients who developed diarrhoea, one had to be discontinued with the antibiotic treatment after five days of therapy due to 10-12 diarrhoeal episodes per day. He was switched over to an alternative antibiotic and standard oral therapy was given to him for diarrhoea. In the probiotic group, only one patient developed diarrhoea; the antibiotic was withdrawn after three days, an alternative antibiotic was given and oral treatment for diarrhoea was initiated and the probiotic was continued. The diarrhoea improved within one day after discontinuing amoxicillin and clavulanate in both the cases.

In both the groups, none of the patients required hospitalization to manage the diarrhoea, nor was there any necessity of using intravenous rehydration therapy. Further more, no adverse effects due to probiotics were noted.

Variables	Control group N=87 number (%)	Probiotic group N=87 Number (%)	p-value
Gender			
Male	46 (52.9)	50 (57.5)	0.542
Female	41 (47.1)	37 (42.5)	
Age (years)	5.0±4.16	5.11±3.71	0.855
Diagnosis			
Pharyngitis	44 (50.6)	48 (55.2)	0.762
Tonsillitis	26 (29.9)	23 (26.4)	
Otitis Media	9 (10.3)	7 (8.0)	
Pneumonia	7 (8.0)	9 (10.3)	
Sinusitis	1 (1.1)	0	
Duration of antibiotics (days)	6.23±1.28	6.26±1.68	0.879
Diarrhoea			
Yes	11 (12.6)	1 (1.1)	0.003**
No	76 (87.4)	86 (98.8)	
Relative risk 95% Confidence Interval	12.45 (1.57,98.67)	1	

[Table/Fig-1]: Demographic and clinical characteristics of the study groups.
**Statistically significant

Characteristics	Control Group (N=87)	Probiotic Group (N=87)
Frequency of diarrhoea (mean and SD)	4.14±2.35	4.67
Duration of diarrhoea (mean and SD) {days}	3.45±0.93	3
Need for discontinuation of antibiotic	1	1
Need for hospitalization to manage diarrhoea	Nil	Nil
Need for I/V rehydration	Nil	Nil
Adverse effects occurring during study	Nil	Nil

[Table/Fig-2]: Characteristics associated with antibiotic-associated diarrhoea.

DISCUSSION

In the present study, a single antibiotic (amoxicillin and clavulanate) was used for the treatment of upper respiratory tract infections. In a study done by Surawicz CM et al., they had used both single and multiple antibiotics [12]. They stated that, certain antibiotics given in combination were the determinate factor for an increased risk of diarrhoea, especially combinations containing clindamycin, cephalosporins or trimethoprim-sulfamethoxazole [12]. However, their study was carried out in adult, in-patients. Several studies have shown that the risk of AAD increases with use of multiple antibiotics [4,12,13]. In the present study, since additional antibiotics were not given, this aspect could not be studied. Also, because of the frequent use of β-lactam antibiotics and high risk of AAD associated with this group of antibiotic, we chose to study the effect of probiotics on just one type of β-lactam for the prevention of AAD [4,13].

Previous studies showed 25-50% reduction in AAD with probiotic therapy compared to placebo [14]. In our study 12.6% (11) of the children on amoxicillin and clavulanate had diarrhoea; AAD was reduced to 1.1% (1) in our study when probiotics were co-administered with the antibiotic. This single case of diarrhoea inspite of giving probiotics in our study shows that though probiotics reduces diarrhoea, they may not be 100% effective. In a study done by Vanderhoof JA et al., 26% (25) of antibiotic and placebo treated children experienced diarrhoea, whereas with the co-administration of probiotic, the diarrhoea was reduced to 8%(7) [15]. Jirapinyo P et al., in Thailand conducted a double blind placebo controlled study in which probiotics were provided to children with severe bacterial infections and receiving treatment with broad spectrum antibiotics. The study results demonstrated that the study group receiving probiotics had fewer episodes of diarrhoea (37.5%) than the control group (80%) [16]. In both above mentioned studies, it is observed that the incidence of diarrhoea was higher in the control groups in comparison to our study where it was 11(12.6%). The possible reason for this could be that AAD should be evaluated up to eight weeks after the treatment since diarrhoea may occur up to two months after end of such treatment [17]. In our study, some cases of AAD may have been missed due to the following reason as AAD was only evaluated for the duration in which patient received antibiotics. We chose to analyse diarrhoeal episodes only occurring during the period of antibiotic treatment because diarrhoea which occurs later might occur due to causes other than antimicrobial agents. Nepal is a country with hygiene issues with diarrhoea being a common problem. So, the more later we follow up the patient, the more unlikely that diarrhoea occurred due to antibiotics.

In addition, both the above mentioned studies showed that probiotics indeed reduced the episodes of diarrhoea. This is similar to what we found in our study i.e., in our study the risk of AAD was 12.45 times higher in children in the control group. However, in a study done by Casem RA in the Philippines, did not show a statistically significant difference in AAD with or without probiotics (p= 0.322) [18]. This difference could be attributed to the different doses and duration and type of antibiotics used. Some conditions require higher empirical doses for a longer duration and this fact could account for the inconsistency of results; and as already stated earlier, some antibiotics have greater propensity for causing diarrhea [17].

The mean frequency of diarrhoea per day in the control group was 4.14±2.35 and as only one patient in the probiotic group had diarrhoea, the mean frequency in his case was 4.67 diarrhoeal episodes per day. We were not able to perform any statistical analysis due to this single number in our study. Similar observations were made in a study by McFarland LV et al., where the diarrhoeal episodes were found to be 5.21±1.2 in the placebo group and 4.9±2.2 episodes per day in the treatment group [13]. These figures are similar to the ones seen in our study, but there were some pertinent differences in our studies; McFarland's study was done in an adult population and the probiotic studied was different from the one used in our study.

The mean duration of diarrhoea in our study was 3.45±0.93 days in the control population. The single case having AAD with probiotics suffered for 3 days. Again due the limited size of our results, statistical analysis wasn't performed. Casem RAO in her study found the duration of AAD in the control group to be 3.06±0.68 days and in the probiotic group to be 2.45±0.69; she concluded that there was a significant reduction in the duration of diarrhoea among patients receiving probiotics as co-treatment (p=0.032) [18]. By contrast, Ruszczynski M et al., study did not show any statistical significance in the duration of AAD between the placebo and probiotic groups (p=0.6) [5]. Similar to other studies, we observed in our study that no child needed hospitalization due to AAD and the diarrhoea improved within a day of discontinuation of the antibiotic in those receiving it [8,19,20]. However, it cannot be denied that AAD may be a cause of compliance failure because many parents may discontinue the use of antibiotic prescribed due to their discontent over loose stools. The most effective way to prevent AAD is still strict, critical and judicious use of antibiotics. However, keeping in mind that probiotics are relatively cheap and there were no adverse effects observed during its use, probiotics was seen to be useful as a co-therapy to prevent AAD when given with amoxicillin and clavulanate.

LIMITATION

Major limitation in this study were a small number of subjects and lack of proof that the diarrhoea which occurred with the ingestion of antibiotics, was indeed AAD. As we cannot rule out the possibility of concurrent viral/bacterial gastroenteritis in our study, the AAD should be considered to be of possible, rather than of obvious antibiotic origin.

CONCLUSION

In conclusion, it is seen that diarrhoea with amoxicillin and clavulanate was not uncommon in our pediatric OPD. Results from this study support the use of probiotics in prevention of AAD. Furthermore, no side effects were seen from the use of probiotics. Therefore, we concluded that probiotics may be a safe and effective way of preventing diarrhoea in patients receiving amoxicillin and clavulanate in whom diarrhoea would be disadvantageous. However, larger, multi-centric studies using different types of antibiotics could help corroborate our findings before a definite conclusion can be made.

DISCLAIMER

This project was not funded/supported by any organization or drug company.

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