

## THE CLINICAL EFFICACY OF MULTI- STRAIN PROBIOTICS (PROTEXIN) IN THE MANAGEMENT OF ACUTE GASTROENTERITIS IN CHILDREN TWO MONTHS TO TWO YEARS OLD

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**KEYWORDS**

Protexin, probiotics, acute gastroenteritis

**ABSTRACT**

Acute gastroenteritis is considered as one of the most common causes of morbidity and mortality worldwide. In the Philippines, the World Health Organization (WHO) noted that acute gastroenteritis is the most common cause of morbidity and it ranks among the top 20 causes of mortality. The standard treatment as provided by WHO is the use of oral rehydration solution, intravenous fluid if indicated, and zinc supplement. Recently, the use of probiotics has been introduced as an adjunct to the treatment of acute gastroenteritis; however, its role in the management of the disease has not yet been fully established.

**Objective:** This study aims to determine the clinical efficacy of multi-strain probiotics (Protexin) as adjunct treatment of acute gastroenteritis.

**Methodology:** This is a randomized, single-blinded, clinical trial of patients with acute gastroenteritis from age two months to two years old and who were assigned to either Standard Treatment only (Control Group) and Standard treatment plus Protexin (Protexin Group). Both study groups were treated in accordance to the WHO standard regimen of treatment for diarrheal diseases with the addition of a Protexin given to Group B. The frequency of purging, character or texture of stool, length of hospital stay, and adverse reaction to the drug were noted.

**Results:** A total of 51 patients were eligible for the study. No untoward event was noted from both groups and no adverse reaction was observed when Protexin was used during the study. The Protexin group had a significant decline in purging rate—as early as the second day—which is almost half the purging rate in the control group. Although both groups showed improvement in stool consistency, the experimental group showed significant improvement on the second hospital day. The experimental group had a significantly shorter course of hospitalization of at least one day. The analysis of variance showed a significant difference between the two study groups regarding purging rate, stool consistency, and duration of hospital stay.

**Conclusion:** Protexin is both efficacious and safe in patients 2 months to 2 years old with acute gastroenteritis. Thus Protexin is beneficial and provides an additional therapeutic modality in the treatment of acute gastroenteritis.

## INTRODUCTION

The problem of acute gastroenteritis (AGE) is considered as one of the most common causes of morbidity and mortality in the world. According to WHO, the mortality rate among 0-to-4-year olds and 0-to-15-year olds ranked third and fourth, respectively, in 2001.<sup>1</sup> In the Philippines, WHO noted that AGE is the most common cause of morbidity and ranks among the top 20 causes of mortality in 2002.<sup>2</sup> Local studies among infants by the Department of Health (DOH) revealed that diarrhea ranked second in morbidity and fourth in mortality.<sup>3</sup> With regard to developing countries such as ours, AGE is one of the most common causes of consult in the emergency room and one of the most common causes of admission among the pediatric age group.<sup>9</sup> Similarly, in this institution, AGE is the second most common cause of consult and admission—approximately 18.4% of the total consultations.<sup>4</sup>

The standard treatment according to the WHO guidelines is the use of oral rehydration solution (ORS), intravenous fluid if indicated, and zinc supplement. However, ORS and intravenous fluids may not be sufficient in averting the disease process.<sup>9,10</sup> Recent studies advocate the use of probiotics as adjunctive treatment or prevention of diarrheas.<sup>17</sup>

This study aims to determine the clinical efficacy of multi-strain probiotics (Protexin) in the treatment of acute gastroenteritis.

## MATERIALS AND METHODS

This study is a randomized, single-blinded, clinical trial involving admitted patients with AGE aged two months to two years old. Diarrhea in patients is defined as increased water in stool resulting to a liquid consistency and frequent purging occurring less than 2 weeks. The study was conducted in Baguio General Hospital and Medical Center from June 1 to 30, 2006. Informed consent was secured from the parents of potential subjects prior to enrollment in the study. The following were the inclusion criteria: a. patients aged two months

to two years old; b. admitted due to AGE with no signs, some signs or severe signs of dehydration; c. diarrhea of less than two weeks duration; and d. gastroenteritis is not due to other disease processes.

The following were the exclusion criteria: a. intractable vomiting (vomiting less than five successive times); b. any intake of antibiotics before or during the illness; c. diagnosed case of chronic inflammatory disease, short GUT syndrome, ulcerative colitis, or Crohn's disease; e. presence of co-morbid conditions such as shock, sepsis, oral intake not tolerated; and f. bloody diarrhea.

The enrolled patients were then randomized to either Standard Treatment (control group) or Standard treatment plus Protexin (Protexin group). The Control Group involved patients hydrated in accordance to the standards of treatment as provided by WHO including zinc supplement. The Protexin Group was given the standard treatment as provided by WHO with the addition of Protexin. The list of the control and case groups was kept by the assigned research assistant.

The ingredients present in Protexin are fructooligosaccharide (FOS), traces of soya and probiotic cultures at 1 billion CFU per sachet. The probiotic cultures present are: *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium infantis* (child specific), *Lactobacillus bulgaricus*, and *Bifidobacterium longum*. The recommended dose is one sachet, once a day for three-to-five days, given with or after food intake. It can be added to food, water, milk or juice.<sup>8</sup>

The Protexin was provided by Alphamed Pharma Inc. for the duration of the study. The Protexin is packaged in a single pouch sachet with a dose of one sachet mixed with food or milk and taken once a day for 5 days for the experimental group. The initial dose was given within six hours from the time of admission. A

research assistant was responsible in administering Protexin to the case group.

The following parameters were noted:

- a. length of hospital stay;
- b. frequency of bowel movement;
- c. consistency of stool per bout of purging;
- d. laboratory results (complete blood count or CBC, stool examination, stool culture); and
- e. adverse reaction as a result of treatment.

Criteria for discharge:

1. Good oral intake i.e. no vomiting, with restoration of appetite as compared to the premorbid state;
2. Progressive weight gain or return to pre-morbid weight;
3. Decreased frequency of purging;
4. Resolution of the signs and symptoms of dehydration;

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For any adverse event or adverse reaction contracted by the any of the participants in the study, the following measures were performed:

- a. Patient will be excluded immediately from the study;
- b. Evaluation and adequate management will be given as warranted by the condition. If needed, referral to other department/s is to be done;
- c. Investigation is to be pursued in order to prove that the adverse event and the use of the probiotics had caused the aforementioned condition.

Statistical measurements employed are Mean difference and ANOVA (analysis of covariance).

## RESULTS

A total of 78 patients were included in the study, 39 patients were enrolled in each of the respective groups. In the Control Group, however, 12 patients were later excluded due to conditions warranting antibiotic use such as intestinal amebiasis (6), urinary tract infection (4) and intestinal parasitism (2). Similarly in the Protexin Group, 24 patients were later eligible in the study and the rest were excluded due to urinary tract infection (7), intestinal amebiasis (5), voluntary withdrawal of parents (2), and intestinal parasitism (1). No untoward event or adverse reaction was noted regarding the use of Protexin.

**Table 1. Frequency of Purging**

| Day | Frequency of Purging |      |                 |      |
|-----|----------------------|------|-----------------|------|
|     | Control (n=27)       |      | Protexin (n=24) |      |
|     | Frequency            | Mean | Frequency       | Mean |
| 1   | 131                  | 4.85 | 118             | 4.91 |
| 2   | 125                  | 4.63 | 63              | 2.65 |
| 3   | 74                   | 2.74 | 18              | 0.75 |
| 4   | 40                   | 1.48 | 6               | 0.25 |
| 5   | 20                   | 0.74 | 2               | 0.08 |

**Table 2. Analysis of Variance Frequency of Purging (Control and Protexin group)**

| Hospital Day | F      | Significance (p < 0.05) |
|--------------|--------|-------------------------|
| Day 1        | .008   | .928                    |
| Day 2        | 6.133  | .017                    |
| Day 3        | 18.042 | .000                    |
| Day 4        | 3.850  | .055                    |
| Day 5        | 1.758  | .191                    |

Tables 1 and 2 show the frequency and significant differences of purging between the two groups. On the first day of the study, both groups had almost similar frequency of purging. On the second to the fifth day, most of the

patients in Group B had a decreased rate of purging compared to Group A.

**Table 4. Analysis of Variance Texture/Character of Stool (Control and Protexin group)**

| Hospital Days | F     | Significance (P ≤ 0.005) |
|---------------|-------|--------------------------|
| Day 1         | .887  | .351                     |
| Day 2         | 9.983 | .003                     |
| Day 3         | 3.573 | .068                     |
| Day 4         | .600  | .495                     |
| Day 5         | .     | .                        |

Gradual improvement of stool character was seen in both groups. The Protexin Group had a more rapid improvement of stool consistency compared to Control, which was significantly noted on the second hospital day.

Majority of patients in both groups were discharged after three hospital days. However, in a Control Group, four patients stayed for five hospital days and 11 patients for four hospital days, while in the Control Group, two patients for five hospital days and three patients for four hospital days.

## DISCUSSION

The study supports the use of Protexin for acute gastroenteritis because of its positive effects, namely a decrease in the rate of purging by Day 2 and shortening of hospital stay. This is consistent with many previous studies using probiotics.

The study done by Sudarmo et. al.<sup>11</sup> of the Child Health Department, Airlangga University Soetomo Hospital, showed a significant improvement in the remission rate, stool texture and stool frequency in patients taking probiotics, which was also observed in this study.

A local study using Ohhira OMX Capsules, in the treatment of acute non-bloody diarrhea in infants 3-24 months of age showed that the use of probiotics significantly shortened the duration of diarrhea. No adverse effects were noted similar to what was observed in this study.

Several studies propose that the beneficial effects of probiotics seem to be strain-specific and that probiotics may be viewed as antibiotics, with many choices of strains useful in different situations.<sup>13</sup> Another study using *Lactobacillus paracasei* Strain ST11 had no effect on rotavirus but improved the outcome of nonrotavirus diarrhea in Children.<sup>14</sup>

With the premise that probiotics are strain-specific, the use of multi-bacillary probiotics in this study has the hypothetical advantage for broad spectrum coverage of the possible enteropathogens affecting the gastrointestinal tract. Furthermore, the advantage of multiple mechanism of action is also achieved.

The proposed modes of action of Protexin include restoring microflora balance, enhancing immunity, competitive exclusion against undesirable bacteria, stimulation of peristalsis (reduced constipation, improved digestion), supply of digestive enzymes (breakdown food particles and lactose), reduce absorption of cholesterol by Lactic Acid Bacteria (LAB), and reduce inflammation (associated with arthritis).

The aforementioned modes of action are achieved by the following mechanisms:<sup>6,7</sup> first, by competitive exclusion—by competition for adhesion sites and competition for substrates; second, immunity through increased macrophage activity (cell-mediated response) and to stimulate antibody production (humoral/specific); third, the production of bacteriocins; fourth, through the gut by reduction of gut pH, thereby, optimizing growth of LAB's and discouraging coliforms e.g. *E. coli*; and last, improvement in digestion through the production of enzyme and vitamins.

According to its product monograph Protexin is safe, non-toxic, non-irritant, and well-tolerated. It is generally regarded as not hazardous even if taken 100 times more than the recommended dose. The most probable adverse reaction is mucosal conjunctival irritation secondary to the direct contact with the product.<sup>8</sup>

The safety profile of probiotics was shown in a study which looked the long-term

consumption of infant formulas containing live probiotic bacteria in a prospective, double-blind, randomized, placebo-controlled study of healthy infants aged three-to-24 months. It concluded that long-term consumption of formulas supplemented with *B. lactis* and *S. thermophilus* were well tolerated and safe.

However, Saavedra commented on his article about probiotics<sup>20</sup> that safety and specification of a particular probiotic agent and methods of delivery to a particular population for a particular purpose should be carefully documented before making broad recommendations.

## CONCLUSIONS

In conclusion, the use of multi-strain probiotics (Protexin) is effective, beneficial, and safe as an adjunct treatment of AGE in children aged two months to two years of age. It further reduces the purging rate and improves stool consistency as early as the second day and has reduced average hospital stay of at least one day, thereby, reducing time, morbidity and expenses due to prolonged hospital stay. Furthermore, the analysis of variance showed significant difference between the two groups with regards to purging rate, stool consistency and duration of hospital stay. Hence, the efficacy and safety of multi-strain probiotics (Protexin) is beneficial and may provide an additional therapeutic modality in the treatment of AGE in the future.

## RECOMMENDATIONS

A large-population, multi-center, randomized, placebo-controlled trial should be conducted to obtain statistically significant evidence. Participants may also be stratified according to the etiologic agent of their diarrhea.

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