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Research Article
Efficacy and Safety of Ceftriaxone *versus* Probiotics in Chinese Infants with Acute Gastroenteritis: A Preliminary Study

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Abstract

Background and Objective: To prevent the progression of gastroenteritis (GE) among infants and children aged less than 5 years, liquid probiotic is commonly proscribed. However, probiotics have some limited effects in reversing the GE and preventing its progression. The present study compared ceftriaxone *versus* probiotics in Chinese infants with acute GE. **Materials and Methods:** Infants with acute GE (persistent symptoms of GE for >2 weeks) were enrolled. Two hundred patients (100 infants in each group) were randomized to (1:1) either intravenous ceftriaxone (50 mg/kg daily) or probiotic for up to 5 days. The number of episodes of vomiting, diarrhea and stool consistency were assessed at baseline and during treatment period. The number of infants who re-visited hospital and fully recovered were assessed. **Results:** Both the study drugs were effective in reducing the episodes of vomiting and diarrhea when compared to their baseline indicates of vomiting and diarrhea. The mean number of vomiting and diarrhea episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone. A slightly greater number of infants treated with probiotics had to re-visit hospital when compared to ceftriaxone (12% vs. 8%). Of the total, 87% of infants were fully recovered after taking probiotic, whereas 94% of infants were fully recovered after taking ceftriaxone. Mean change in stool consistency throughout treatment duration was numerically favorable in infants treated with ceftriaxone as compared to probiotics. **Conclusion:** The infants treated with ceftriaxone had faster recovery from GE when compared with probiotics.

Key words: Ceftriaxone, diarrhea, gastroenteritis, infant, probiotics, rehydration, treatment satisfaction, vomiting

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Gastroenteritis (GE) among children especially in infants is one of the most common causes of concern worldwide, accounting for approximately 2 million of mortality for children ages less than 2 years. Although, with the rapidly evolving treatment modalities including vaccination, the morbidity and mortality due to GE has been reduced numerically[1,2]. However, it remains a common cause of hospitalization and increased frequency of hospital visits for consultation, which indirectly increases the financial and emotional burden on parents and their families[3].

Considering the treatment option for GE among children aged less than 5 years, it was advised that an appropriate level of rehydration be maintained for children who had GE to prevent hospitalization[4]. In general, Oral Rehydration Solution (ORS) has been advised to give to children at regular intervals to maintain hydration. However, ORS does not reduce the severity and duration of GE, it just only provides some level of symptomatic relief[1,2,5,6]. There are several drugs commonly used in GE to reduce the duration of GE, especially the episodes of diarrhea, vomiting and hydration, which are the most common causes of hospitalization and increased hospital visits and doctor consultations. However, the effects do not last for a long time and it was observed that anti-diarrhea treatment has no impact on the progression of GE from mild to moderate and from moderate to acute cases of GE. In addition, zinc was known to have a healing effect and is commonly used as adjuvant therapy or sometimes as standalone therapy in mild cases of GE[7]. It was reported that zinc has good healing potential can reduce episodes of diarrhea and vomiting and also helps in maintaining the rehydration. These effects help in reducing hospitalization. However, again zinc has limited effect in reducing the severity of GE and has minimal effect in preventing the serious complications of GE. Thus, there is a need for treatment option that numerically decreases the episodes of diarrhea and vomiting and also helps in maintaining the rehydration. In addition to these effects, the most sought effect is of new treatment is to prevent the hospitalization and reduce the severity of GE as much as possible. Antibiotics are a class of medications that kill the bacterial infection that leads to GE and thereafter reduce the episodes of diarrhea and vomiting and also help in maintaining rehydration[8]. Also, the eradication of potential bacterial infections can prevent hospitalization and reduce the severity of GE. To prevent the progression of GE among infants and children aged less than 5 years, liquid probiotic is commonly prescribed by doctors, which increase the growth of good bacteria that may overcome the detrimental effects of pathogenic organisms. However, several reports suggested that probiotics have some limited effects in reversing the GE and preventing its progression, therefore, it is important to add other medications along with the standard home remedies. Probiotics are the most common anti-bacterial agents that can help reduce episodes of diarrhea and vomiting and also help in maintaining rehydration[9-11]. However, its effects in several cases of GE are questionable. The same case with the use of probiotics as a treatment option in GE. The use of ceftriaxone in GE is not well established and has not been tested in acute cases although there are several advices that ceftriaxone can be a potential treatment option in acute cases of GE, due to its anti-microbial effects and sensitizations towards different types of microorganism. Since ceftriaxone is effective against gram-negative bacteria, we assume that it numerically reduces the episodes of diarrhea and vomiting and also helps in maintaining the rehydration. In clinical practice, probiotics were noted are the most common anti-bacterial agents widely used in the treatment of GE for children aged less than 5 years. Probiotics were selected as standard therapy in the present study to compare the effect of ceftriaxone in children aged 2 years or less.

There is a direct comparative study evaluating the efficacy and safety of ceftriaxone *versus* probiotics in Chinese infants with acute gastroenteritis. Thus, the current study evaluates the efficacy and safety of ceftriaxone *versus* probiotics in Chinese infants with acute GE.

MATERIALS AND METHODS

Study area: From 20th March, 2021 to 1st January, 2022 study was performed at Beijing Chaoyang Hospital, Capital Medical University, Beijing, China.

Ethics approval and consent to participate: Written informed consent was obtained from parents/legal guardians on behalf of each subject. Institutional ethics committee approval was taken from the Beijing Chaoyang Hospital before commencing this study. The study received approval from the institutional ethics committee of the Beijing Chaoyang Hospital, the vide approval No. BCH1547 dated 15 March, 2021.

Inclusion criteria: In the present study, Chinese infants with acute GE were enrolled. The infants were eligible if they had persistent symptoms of GE for >2 weeks.

Exclusion criteria: As per the pediatric consultant, the infants with GE who were not suitable candidates to enroll in the preset study then were excluded.

Treatments: Subjects were randomized to receive (1:1) either ceftriaxone (50 mg/kg as intravenous daily, treatment group) or probiotic (standard group) for up to 5 days. Each enrolled infant was carefully monitored and followed up for 1 week. Probiotic supplements included *Streptococcus thermophilus* (60 mg), *Lactobacillus rhamnosus* (28 mg), *Lactobacillus acidophilus* (28 mg), *Bifidobacterium lactis* (20 mg), *Bifidobacterium infantis* (20 mg), fructooligosaccharides (20 mg). The dose of ceftriaxone or probiotic was adjusted accordingly if needed.

Endpoints: The baseline characteristics of each enrolled infant were assessed. The primary endpoint was the failure of treatment, which was defined as the occurrence of >2 episodes of vomiting within 24 hrs after administering the first dose of assigned treatment. The secondary endpoint of interest was the occurrence of diarrhea episodes-the number of episodes and diarrhea duration were assessed. The side effects of assigned treatment in each group were also observed. Side effects that occurred within 24 hrs of the first dose in both treatments were assessed. In addition, the need for hospitalization, duration of hospitalization, need for the second visit to the hospital within the treatment period, the satisfaction of parents after completion of treatment, the time of recovery from symptoms (vomiting and diarrhea) of GE and percentage of infants who recovered from diarrhea and stool consistency were assessed in either treatment group. Safety was monitored and reported.

Statistical analysis: Considering this was a preliminary study, the, sample size was not calculated, however, approximately 200 infants (100 infants per arm) were planned for this study. Applicable statistical tests were used to analyze data (quantitative data) based on type and distribution (normal and non-normal). In the case of non-normal data, the Whitney test was used whereas, for normal data, the unpaired t-test was used. In the case of categorical data, data were analyzed using the fisher exact or Chi-square test based on the size of the data. Analysis was done using Graph Pad (version 3.01) software, San Diego, California, USA.

RESULTS

Two hundred infants (100 infants per arm) were randomized and all patients completed the study. Demography data were similar across groups (Table 1). In both groups, the majority of infants enrolled were female infants. The majority of infants in treatment groups were aged 1.6 years. Overall, the infants' characteristic was found comparable between both the treatment groups. The median age was also found similar in both groups.

A summary of number and duration of vomiting and diarrhea incidences was presented in Table 2. Both the study drugs were effective in reducing the episodes of vomiting when compared to their baseline indicates of vomiting. However, improvement was numerically greater in infants treated with ceftriaxone as compared to probiotics. The mean number of vomiting episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone. With regards to diarrhea, both the study drugs were effective in reducing the episodes of diarrhea when compared to their baseline indicates of diarrhea. However, improvement was numerically greater in infants treated with ceftriaxone as compared to probiotics. The mean number of diarrhea episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone.

Both the study drugs were effective in reducing the duration of vomiting when compared to their baseline duration of vomiting. However, improvement was numerically greater in infants treated with ceftriaxone as compared to probiotics. The mean duration of vomiting episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone. With regards to diarrhea, both the study drugs were effective in reducing the duration of diarrhea when compared to their baseline duration of diarrhea. However, improvement was numerically greater in infants treated with ceftriaxone as compared to probiotics. The mean duration of diarrhea episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone.

Table 1: Patient characteristics before treatment

Parameters	Probiotic (n = 100)	Ceftriaxone (n = 100)	p-value	Degree of freedom	95% Confidence Interval (using the approximation of Katz)
Median age (years)	1.8	1.9	>0.05 (Mann-Whitney test)	N/A	N/A
Gender					
Female sex (%)	58 (58)	52 (52)	0.4773 (χ^2-test)	1	0.8513 to 1.500
Male sex (%)	42 (42)	48 (48)			
Weight (kg) median value	10.4	11.2	>0.05 (Mann-Whitney test)	N/A	N/A

Variables presented as median or frequencies (%), N/A: Not applicable and a p-value less than 0.05 was considered significant

Table 2: Number and duration of vomiting and diarrhea incidences

Parameter	Probiotic (n = 100)	Ceftriaxone (n = 100)	p-value
#Vomiting incidences	4.2 (2.3)	3.2 (1.3)	>0.05
Duration of vomiting	2.6 (2.1)	1.8 (2.1)	>0.05
#Diarrhea incidences	5.4 (2.8)	4.2 (2.4)	>0.05
Duration of diarrhea	3.6 (2.3)	2.8 (2.5)	>0.05

#Mean (standard deviation) value, Unpaired t-test was used for statistical analysis and a p-value less than 0.05 was considered significant

Table 3: Number of subjects who re-visited the hospital after treatment

Parameter	Probiotic (n = 100)	Ceftriaxone (n = 100)	p-value	Relative risk	95% Confidence interval (using the approximation of Katz)
Yes (%)	12 (12)	8 (8)	0.4804 (Fisher's exact test)	1.227	0.8327 to 1.809
No (%)	88 (88)	92 (92)			

Variables presented as frequencies (%) and a p-value less than 0.05 was considered significant

Table 4: Number of subjects with satisfaction level

Parameter	Probiotic (n = 100)	Ceftriaxone (n = 100)	p-value	Degree of freedom
Low satisfaction level	07 (7)	04 (4)	<0.0001 (Chi-squared test for independence)	2
Intermediary satisfaction level	43 (43)	16 (16)		
High satisfaction level	50 (50)	80 (80)		

Variables presented as frequencies (%) and a p-value less than 0.05 was considered significant

Table 5: Number of subjects with recovery status of diarrhea after treatment

Parameter	Probiotic (n = 100)	Ceftriaxone (n = 100)	p-value	Relative risk	95% Confidence interval (using the approximation of Katz)
Yes recovered	87 (87)	94 (94)	0.1464 (Fisher's exact test)	0.7025	0.4995 to 0.9880
Not recovered	13 (6)	6 (6)			

Variables presented frequencies (%) and a p-value less than 0.05 was considered significant

A summary of subjects who re-visited the hospital after treatment was presented in Table 3. The majority of infants treated with probiotics had to re-visit hospital when compared to ceftriaxone (12% vs. 8%). As 92% of infants had not re-visited to hospital after taking ceftriaxone, whereas 88% of infants had not re-visited to hospital after taking probiotic. Overall, ceftriaxone treatment offers greater advantages in infants with GE when compared to probiotics. This indicated that ceftriaxone treatment offers numerically greater clinical benefits in infants with GE as compared to probiotics.

A summary of subjects with satisfaction levels after treatment was presented in Table 4. When compared to the high satisfaction level category between both the treatment groups, it was observed that the ceftriaxone treatment offers higher satisfaction as compared to probiotics. This indicates that ceftriaxone treatment offers greater clinical benefits in infants with GE as compared to probiotics. When compared to the low to intermediary satisfaction level category between both the treatment groups, it was observed that the ceftriaxone treatment offers higher satisfaction as compared to probiotics. This indicated that ceftriaxone treatment offers greater clinical benefits in infants with GE as compared to probiotics. Compared to ceftriaxone, the level of satisfaction was numerically higher in infants treated with probiotics.

A summary of subjects with recovery status of diarrhea after treatment was presented in Table 5. Numerically a greater number of infants treated with probiotics were not fully recovered when compared to ceftriaxone (13% vs. 6%). Of the total, 87% of infants were fully recovered after taking probiotic, whereas 94% of infants were fully recovered after taking ceftriaxone. Overall, ceftriaxone treatment offers greater advantages in infants with GE when compared to probiotics. This indicates that ceftriaxone treatment offers numerically greater clinical benefits in infants with GE as compared to probiotics.

A summary of the time of recovery from symptoms (vomiting and diarrhea) of GE was presented in Fig. 1. The infants treated with ceftriaxone had faster recovery from GE when compared with probiotics. This indicated the onset of action was rapid with ceftriaxone as compared to probiotics. This indicated that ceftriaxone treatment offers numerically greater clinical benefits in infants with GE as compared to probiotics.

A summary of the change in stool consistency throughout the treatment duration was presented in Fig. 2. Both the study drugs were effective in improving the consistency of stool when compared to their baseline consistency. However, improvement in the consistency of stool was numerically greater in infants treated with ceftriaxone as compared to probiotics. Mean change in stool consistency throughout treatment duration was numerically favorable in infants treated with ceftriaxone as compared to probiotics.

The frequent side effects noted across the treatment group were gastrointestinal (GI) related, although the incidence of GI-related events more in ceftriaxone compared to probiotics, however, there were no GI-related events that led to discontinuation of ceftriaxone and none of them were serious. All GI events that occurred in this study were of milder

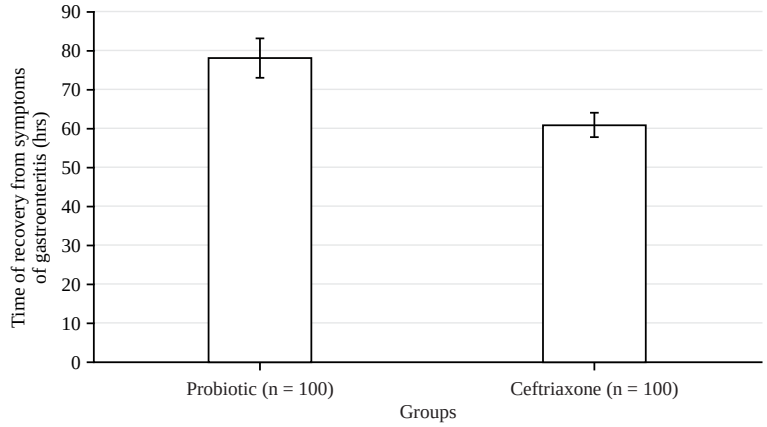

Fig. 1: Time of recovery from symptoms (vomiting and diarrhea) of gastroenteritis

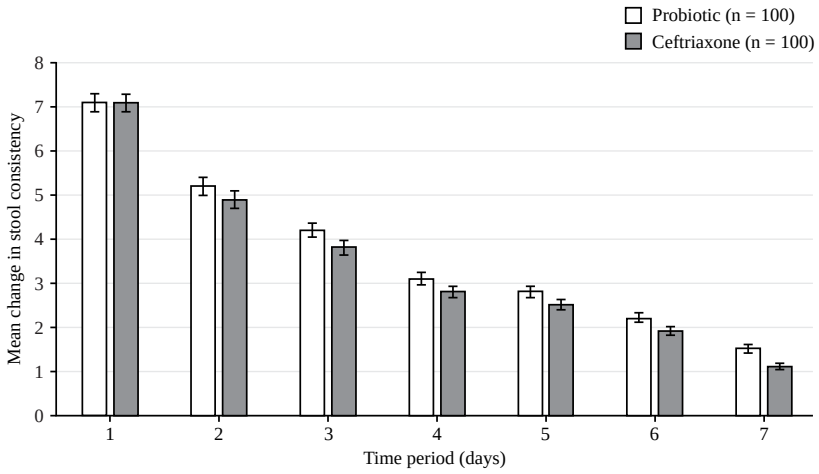

Fig. 2: Change in stool consistency throughout treatment duration
On x-axis stool consistency higher the number higher is stool consistency

Table 6: Number of side effects

Parameter	Probiotic (%) (n = 100)	Ceftriaxone (%) (n = 100)
GI related	2.5	7.2
Sleepiness	2.5	5.6
No adverse effects	95	59

severity and did not require rescue treatment to manage the GI events (Table 6).

Overall, both the study drugs had acceptance safety profiles and the risk-benefit ratio was favorable.

DISCUSSION

In China, there is no head-to-head study comparing the efficacy and safety of ceftriaxone *versus* probiotics in Chinese infants with acute gastroenteritis. Thus, the present study evaluated the efficacy and safety of ceftriaxone *versus* probiotics in Chinese infants with acute GE. To current knowledge, this is the first clinical study carried out to evaluate the efficacy and safety of ceftriaxone *versus* probiotics in Chinese infants with acute GE.

In the present study, both the study drugs were effective in reducing the episodes of vomiting when compared to their baseline indications of vomiting. However, improvement was numerically greater in infants treated with ceftriaxone as compared to probiotics. The mean number of vomiting

episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone. With regards to diarrhea, both the study drugs were effective in reducing the episodes of diarrhea when compared to their baseline indicates of diarrhea. However, improvement was numerically greater in infants treated with ceftriaxone as compared to probiotics. The mean number of diarrhea episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone. The results of the episodes of vomiting and diarrhea that are controlled by probiotics in the current study are consistent with those of a randomized trial, and analysis of 2 randomized placebo-controlled trials[12-14]. Considering the treatment option for GE among children aged less than 5 years, it was advised that an appropriate level of rehydration be maintained for children who had GE to prevent hospitalization. To prevent the progression of GE among infants and children aged less than 5 years, liquid probiotic is commonly prescribed by doctors, which increase the growth of good bacteria that may overcome the detrimental effects of pathogenic organisms. However, several reports suggested that probiotics have some limited effects in reversing the GE and preventing its progression[15], therefore, it is important to add other medications along with the standard home remedies.

The majority of infants treated with probiotics had to re-visit hospital when compared to ceftriaxone (21% vs . 8%). A total of 92% of infants had not re-visited to the hospital after taking ceftriaxone, whereas 79% of infants had not re-visited to the hospital after taking probiotics. Overall, ceftriaxone treatment offers greater advantages in infants with GE when compared to probiotics. This indicated that ceftriaxone treatment offers greater clinical benefits in infants with GE as compared to probiotics. There are several drugs commonly used in GE to reduce the duration of GE, especially the episodes of diarrhea, vomiting and hydration, which are the most common causes of hospitalization and increased hospital visits and doctor consultations. However, the effects do not last for a long time and it was observed that anti-diarrhea treatment has no impact on the progression of GE from mild to moderate and from moderate to acute cases of GE. In addition, zinc was known to have a healing effect and is commonly used as adjuvant therapy or sometimes as standalone therapy in mild cases of GE. It was reported that zinc has good healing potential and able to reduce episodes of diarrhea and vomiting and also helps in maintaining hydration. These effects help in reducing hospitalization. However, again zinc has limited effect in reducing the severity of GE and has minimal effect in preventing the serious complications of GE. Thus, there is a need for a treatment option that numerically decreases the episodes of diarrhea and vomiting and also helps in maintaining the rehydration. In addition to these effects, the most sought effect of new treatment is to prevent hospitalization and reduce the severity of GE as much as possible.

Antibiotics are a class of medications that kill the bacterial infection that leads to GE and thereafter reduce the episodes of diarrhea and vomiting and also help in maintaining rehydration. Also, the eradication of potential bacterial infections can prevent hospitalization and reduce the severity of GE. Among several antibiotics, the probiotic is the most common anti-bacterial agent that can help reduce the episodes of diarrhea and vomiting and also helps in maintaining rehydration.

In the present study, when compared to the high satisfaction level category between both the treatment groups, it was observed that the ceftriaxone treatment offers higher satisfaction as compared to probiotics. This indicates that ceftriaxone treatment offers greater clinical benefits in infants with GE as compared to probiotics. When compared to the low to intermediary satisfaction level category between both the treatment groups, it was observed that the ceftriaxone treatment offers higher satisfaction as compared to probiotics. This indicated that ceftriaxone treatment offers greater clinical benefits in infants with GE as compared to probiotics. Compared to ceftriaxone, the level of satisfaction was numerically lower in infants treated with probiotics.

In our study, numerically a greater number of infants treated with probiotics were not fully recovered when compared to ceftriaxone (18% vs. 6%). Of the total, 82% of infants were fully recovered after taking probiotics, whereas 94% of infants were fully recovered after taking ceftriaxone. Overall, ceftriaxone treatment offers greater advantages in infants with GE when compared to probiotics. This indicates that ceftriaxone treatment offers greater clinical benefits in infants with GE as compared to probiotics. The use of ceftriaxone in GE is not well established and has not been tested in acute cases although there are several advices that ceftriaxone can be a potential treatment option in acute cases of GE, due to its anti-microbial effects and sensitizations towards different types of microorganism. Since ceftriaxone is effective against gram-negative bacteria, it numerically reduces the episodes of diarrhea and vomiting and also helps in maintaining the rehydration. In clinical practice, mostly probiotics are the most common anti-bacterial agents widely used in the treatment of GE for children aged less than 5 years. Therefore, selected probiotics as standard therapy in the present study to compare the effect of ceftriaxone in children aged 2 years or less.

In the present study, the infants treated with ceftriaxone had faster recovery from GE when compared with probiotics. This indicated the onset of action was rapid with ceftriaxone as compared to probiotics. This indicated that ceftriaxone treatment offers greater clinical benefits in infants with GE as compared to probiotics. In addition, both the study drugs were effective in improving the consistency of stool when compared to their baseline consistency. However, improvement in the consistency of stool was numerically greater in infants treated with ceftriaxone as compared to probiotics. Mean change in stool consistency throughout treatment duration was numerically favorable in infants treated with ceftriaxone as compared to probiotics.

The frequent side effects noted across the treatment group were GI-related, although the incidence of GI-related events more in ceftriaxone compared to probiotics, however, there were no GI-related events that led to discontinuation of ceftriaxone and none of them were serious. All GI events that occurred in this study were of milder severity and did not require rescue treatment to manage the GI events.

Overall, current study results demonstrated that ceftriaxone and probiotics were found effective in the management of GE among infants. However, on compassion, the improvement in primary and secondary endpoints was noted meaningfully larger in infants who were treated with ceftriaxone compared to probiotics. Overall, ceftriaxone was a better alternative in the management of GE among infants. Overall, both the study drugs had acceptance safety profiles and the risk-benefit ratio was favorable. In the other limitations of the study, for example, the study made no distinction between different types of diarrheas, whether inflammatory or non-inflammatory, viral or bacterial and blindly prescribed ceftriaxone to all. Supportive treatment and rehydration and not prescribing antibiotics in most cases of diarrheal patients is now accepted as a scientific fact. It is impossible to act against these rules. Routine prescribing of antibiotics in diarrheal patients may prolong the period of diarrhea and may lead to complications.

CONCLUSION

The mean duration of diarrhea and vomiting episodes was numerically higher in infants treated with probiotics as compared to ceftriaxone. Ceftriaxone is more effective in the management of acute gastroenteritis among infants than probiotics. This study has revealed that ceftriaxone could be a better alternative as compared to probiotics in the management of acute gastroenteritis among infants. Overall, both the study drugs had acceptance safety profiles and the risk-benefit ratio was favorable.

SIGNIFICANCE STATEMENT

This preliminary study compared that ceftriaxone versus probiotics in Chinese infants with acute GE. Results has revealed that ceftriaxone could be a better alternative as compared to probiotics in the management of acute gastroenteritis among infants. The findings will help pediatricians to uncover critical areas of the management of acute gastroenteritis among infants that many clinicians have not evaluated.

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