

**Original Article**

Evaluation of the effects of zinc supplementation on the symptoms and duration of the disease in acute viral gastroenteritis



Akut viral gastroenteritlerde oral çinko kullanımının hastalığın semptomları ve süresine etkisinin değerlendirilmesi

Cigdem El^a, Mehmet Emin Celikkaya^b

^aHatay Mustafa Kemal University, Tayfur Ata Sokmen Faculty of Medicine, Department of Pediatrics, Hatay, Turkey

^bHatay Mustafa Kemal University, Tayfur Ata Sokmen Faculty of Medicine, Department of Pediatric Surgery, Hatay, Turkey

ABSTRACT

Introduction: Acute viral gastroenteritis is the second most common cause of high morbidity and mortality in childhood. Viral gastroenteritis is the most common cause of severe diarrhea and associated hospitalizations especially in toddlers. It has been shown that the administration of 20 mg of zinc daily during acute diarrhea reduces the duration of watery diarrhea by 25% and it has been reported to have protective and therapeutic effects in the acute period. The aim of this study is to retrospectively determine the beneficial effects of oral zinc supplementation on the severity and duration of complaints of toddlers who were treated in our clinic with the diagnosis of acute viral gastroenteritis.

Methods: Toddlers who were hospitalized in the Department of Pediatrics for acute viral gastroenteritis between October 2016 and March 2018 were included in the study. The study was retrospective and the data of the patients were obtained from the patient files. The diagnosis of acute viral gastroenteritis was made by detecting the adenovirus-rotavirus antigen in the fresh stool specimens. The patients were divided into two groups. Group 1: patients who received zinc supplementation in addition to support treatment. Group 2: patients who received only supportive therapy.

Results: The mean number of vomiting was 3.60 / day and watery diarrhea was 5.20 / day in group-1 while number of vomiting was 6.1 / day and watery diarrhea was 8.9 / day in group-2 in the 36th hour during treatment. The tolerability of oral feeding at 36 th hour was 49.39% (41) in group-1 and 45.07% (32) in group-2. The mean number of vomiting and watery diarrhea in group-1 cases at 72th hours was 1.2 / day and 4.30 / day, while in group-2 cases, 3.90 / day and 7.20 / day.

Conclusions: Although the physiopathology of the effects of zinc on gastroenteritis is not yet fully understood, diarrhea is seen both as a cause and as a result of zinc deficiency. The fact that patients with gastroenteritis benefit from zinc support suggests that zinc enhances this effect by increasing intestinal immunity.

Keywords: Acute viral gastroenteritis, rotavirus, adenovirus

ÖZ

Giriş: Akut viral gastroenteritler çocukluk çağında yüksek morbidite ve mortalitenin en sık ikinci sebebidir. Özellikle oyun çağı ve okul çağı çocukluk döneminde tüm dünyada şiddetli ishallerin ve buna bağlı hastane yatışları ile bebek ölümlerinin en sık nedeni viral gastroenteritlerdir. Akut ishal sırasında günlük 20 mg çinko verilmesinin sulu dışkılama süresini %25 azalttığı gösterilmiştir ve akut dönemde koruyucu ve terapötik etkileri olduğu bildirilmiştir. Bu çalışmanın amacı, çocukluk çağında morbiditesi ve mortalitesi yüksek hastalıkların başında gelen akut viral gastroenterit tanısıyla kliniğimizde tedavi edilen 2-5 yaş arası oyun çağı çocuk hastaların yakınmalarının şiddeti ve süresi üzerinde oral çinko kullanımının etkisini retrospektif olarak belirlemektir.

Yöntem: Akut viral gastroenterit tanısıyla Ekim 2016 – Mart 2018 tarihleri arasında yatırılarak tedavi edilen 2-5 yaş arası oyun çağı dönemindeki çocuk hastalar çalışmaya alındı. Çalışma retrospektif olup hastaların verileri hasta dosyalarından elde edildi. Akut viral gastroenterit tanısı taze dışkı örneğinde adenovirüs-rotavirüs antijeni saptanması ile konuldu. Hastaların verileri Çinko tedavisi alanlar (Grup-1) ile çinko tedavisi almayanlar (Grup-2) arasında karşılaştırıldı.

Bulgular: Çinko tedavisi verilen grup-1'deki olguların 36.saatteki ortalama kusma ve dışkılama sayısı 3,6/gün ve 5,2/gün iken çinko almayan grup-2 olgularınki 6,10/gün ve 8,90/gün idi.36. Saatte oral beslenmeyi tolere etme grup-1 de % 49.39 (41) iken grup-2 de % 45.07 (32) idi.72.saatte grup-1 olguların ortalama kusma ve dışkılama sayısı 1,20/gün ve 4,30/gün iken grup-2 olgularda 3,90/gün ve 7.20/gün idi.

Sonuç: Çinkonun gastroenteritler üzerindeki etkilerinin fizyopatolojisi henüz tam olarak anlaşılammış olmakla birlikte ishaller, hem çinko eksikliğinin bir nedeni, hem de bir sonucu olarak görülmektedir. Gastroenteritli olguların çinko desteğinden fayda görmesi, çinkonun intestinal immunitiyi artırarak bu etkiyi sağladığını düşündürmektedir.

Anahtar kelimeler: Akut viral gastroenterit, rotavirüs, adenovirus

Received	Accepted	Published Online	Corresponding Author	E-mail
October 17, 2018	December 13, 2018	March 18, 2019	Cigdem El, MD	cigdem.el@hotmail.com
Correspondence	Cigdem El, MD.Hatay Mustafa Kemal University, Tayfur Ata Sokmen Faculty of Medicine, Department of Pediatrics, Postal code: 31060 Hatay, Turkey			

Introduction

Acute diarrhea is more than three a day in the form of watery diarrhea is less than two weeks and the most common cause of acute viral gastroenteritis. Acute viral gastroenteritis is the second most common cause of high morbidity and mortality in childhood. Viral gastroenteritis is the most common cause of severe diarrhea and associated hospitalizations especially in toddlers [1-3]. Acute diarrhea is more common with viral causes, whereas chronic or persistent diarrhea and dysentery are more common with non-viral agents. More than 500,000 children under 5 years of age worldwide lose their lives due to acute viral gastroenteritis [2, 4]. It causes bloodless and mucusless diarrhea, accompanied by vomiting and fever, especially in the spring and last spring. It can cause severe dehydration, electrolyte imbalance, metabolic acidosis and even convulsions due to severe vomiting and watery diarrhea [1, 2, 3, 5]. Therefore, the delays in diagnosis and treatment cause morbidity, mortality and serious economic losses [5, 6]. The first goal in the management of acute gastroenteritis is to replace the loss of fluid-electrolyte which is caused by dehydration and that may caused mortality. The course of acute viral gastroenteritis has been reported to be more severe in early childhood in the literature. Studies have shown that zinc supplementation, an essential nutrient, has positive effects on diarrhea severity and duration [2, 4, 6-8]. It has been shown that the administration of 20 mg of zinc daily during acute diarrhea reduces the duration of watery diarrhea by 25% and it has been reported to have protective and therapeutic effects in the acute period. Recommended to use for an average of 2 weeks [4, 7, 8]. The aim of this study is to retrospectively determine the beneficial effects of oral zinc supplementation on the severity and duration of complaints of toddlers who were treated in our clinic with the diagnosis of acute viral gastroenteritis.

Methods

With the decision dated 11/10/2018 and numbered 56893, Mustafa Kemal University ethics committee approval was received. 154 patients between 2 and 5 years old were hospitalized in the Department of Pediatrics for acute viral gastroenteritis between October 2016 and March 2018 were included in the study.

The study was retrospective and the data of the patients were obtained from the patient files. The diagnosis of acute viral gastroenteritis was made by detecting the adenovirus-rotavirus antigen in the fresh stool specimens. The virus was detected in the fresh stool sample by a qualitative immunochromatographic assay (Rota / Adenovirus Rapid Test Card, GenxBio, India). The patients were divided into two groups:

Group 1: patients who received zinc supplementation in addition to support treatment.

Group 2: patients who received only supportive therapy.

A daily dose of 20 mg as a zinc supplement was added orally (Zinobest suspension, Drogosan, Ankara, Turkey) during hospitalization period. Age, sex, application season, clinical findings, number of vomiting and watery diarrhea, daily progression of clinical and laboratory findings, time to start oral feeding, transition to complete oral feeding and time to terminate intravenous therapy and duration of hospital stay in patients were evaluated. The data of the patients were compared between Group-1 and Group-2. The data of all patients was obtained from the hospital information system. Gastroenteritis cases that with blood-mucus stools and by microbial agents other than viruses were excluded from the study. And also, infants under 2 years of age and school-age children over 5 years old, patients with immunodeficiency or any chronic disease and malnutrition were excluded from the study.

Patients with incomplete information were contacted with the communication numbers in the hospital information system. Patients who could not complete their information were excluded from the study.

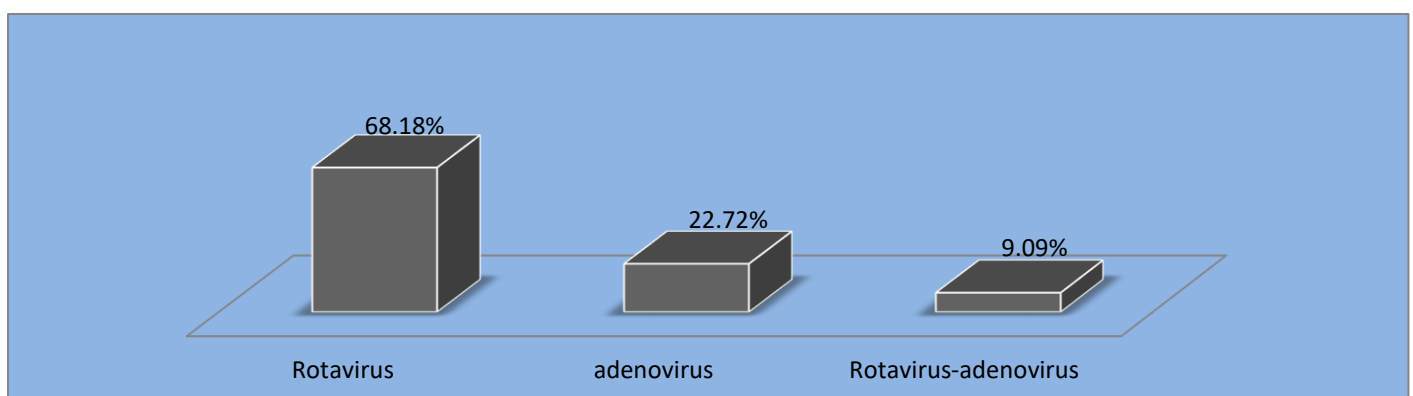
Statistical analysis

The data was entered in the SPSS 20.00 program. The relationship status was checked with the Mann-Whitney U test and the significance state was determined according to $p < 0.05$. Mean and standard deviation of the data was checked.

RESULTS

154 patients (36.84%) of 462 toddlers with acute gastroenteritis were due to with viral agents. The median age of the patients was 4.1 years. It is determined that 68.18% (n: 105) of the viral cases were rotavirus, 22.72% (n: 35) of adenovirus and 9.09% (n: 14) of coexisting rotavirus-adenovirus (Table-1).

Table 1. Adenovirus and rotavirus ratio in toddlers



In our study, the highest rate of rotavirus positivity was detected in the months of December and February, while the most common positivity of adenovirus had seen in November, December and January. All patients had fever, nausea, vomiting, oral intake deteriorate, severe watery diarrhea and dehydration. Severe dehydration and electrolyte imbalance (metabolic acidosis, oliguria-anuria, increased urine density) were present in 33.11% (n: 51) of the patients and hyponatremic and hypoglycemic convulsion in 12.98% (n: 2).

In our study, 53.24% (n: 82) of the cases were female and 46.75% (n: 72) of the cases were male. In our study, although the rate of rotavirus infection was found to be higher in girls than in boys, no statistically significant difference was observed ($p > 0.05$).

The number of vomiting at the time of diagnosis was 7.3 / day and the number of diarrhea was 11.6 / day. All patients were treated with support fluid treatment. The mean number of vomiting was 3.6 / day and watery diarrhea was 5.2 / day in group-1 while number of vomiting was 6.1 / day and watery diarrhea was 8.9 / day in group-2 in the 36th hour during treatment. The tolerability of oral feeding at 36 th hour was 49.39% (n: 41) in group-1 and 45.07% (n: 32) in group-2.

The mean number of vomiting and watery diarrhea in group-1 cases at 72th hours was 1.2 / day and 4.3 / day, while in group-2 cases, 3.9 / day and 7.2 / day. Starting of oral feeding at 72th hours and stopping rate of intravenous fluid requirement support were 83.1% (n: 69) in group-1 and 59.15% (n: 42) in group-2. The median hospitalization time was 5.3 days in group 1 while 8.1 days in group-2. These data showed that zinc supplementation had beneficial effects on vomiting, diarrhea, nutritional tolerability and hospitalization duration and this was statistically significant ($p < 0.05$) (Table-2).

Table 2. Comparison of clinical findings and hospitalization time between group 1 and group 2

	Group 1 (n=83)	Group 2(n=71)	P
The average number of vomiting at 36th hours /day	3.60	6.10	0.045
The average number of watery diarrhea at 36th hours/day	5.20	8.90	0.036
Tolerability of oral feeding at 36th hours	41	32	0.123
The average number of vomiting at 72th hours /day	1.20	3.90	0.028
The average number of watery diarrhea at 72th hours/day	4.30	7.20	0.043
Tolerability of oral feeding at 72th hours	69	42	0.038
The average hospitalization time/day	5.30	8.10	0.024

*Mann-Whitney U test (between groups)

In our study, 62.98% (n: 97) of patients were given antibiotic treatment in family medicine and pediatric emergency applications, but no clinical improvement was found.

Discussion

Acute viral gastroenteritis cases are the leading pathologies that cause morbidity especially in childhood [1, 4]. Viruses are the most common cause of acute gastroenteritis in toddlers. It is one of the main infectious causes of morbidity and mortality in early childhood. Nausea, vomiting, oral malnutrition, as well as abundant watery diarrhea, electrolyte disorders and dehydration lead to significant hospitalization [4, 5-7]. In the literature reported that, two million children under five years of age are admitted to the hospital with the diagnosis of acute viral gastroenteritis and nearly one in four cases have died [7-9]. Rotaviruses and adenoviruses are the most important causes of viral gastroenteritis in both infants and toddlers. In studies performed in various parts of the world, the prevalence of rotavirus was found to be between 5 - 71% and the prevalence of adenovirus was 1.5 - 23.60%, and the coexisting of rotavirus and adenovirus were 1.07 - 10.60% [4, 5, 10]. More than one pathogenic agent can be detected in acute gastroenteritis. Although bacteria and viruses can cause disease together, the most common is the coexisting of different viruses [3-5, 11]. In our study, 36.84% (n: 154) of children with acute gastroenteritis were found to be related to viral agents accordance with the literature. Viral gastroenteritis can be seen in every month of the year, especially in autumn, winter and spring months [1, 4, 5]. In our study, the highest rate of rotavirus positivity was determined in the months of December and February, and adenovirus positivity was most frequently observed in November, December and January.

Rotavirus and adenovirus, which are highly contagious pathogens, are highly resistant to external environment and can maintain their vitality for months. The frequency of adenovirus and rotavirus infections is high in this period due to taking to mouths everything they can reach as a means of communication with their environment in toddlers and unfortunately many times this situation do not be seriously perceived by families [3-5]. However, after 12-72 hours of incubation, viral gastroenteritis causes clinically fever, nausea, vomiting, and bloodless and mucusless diarrhea. In a short period of time, oral ingestion disorder can lead to severe dehydration, electrolyte imbalance, convulsions and even hypovolemic shock [1, 5, 12]. All of our patients had fever, nausea, vomiting, oral intake, severe watery diarrhea and dehydration.

Severe dehydration and electrolyte imbalance were present in 33.11% (n: 51) of the patients. Hyponatremic and hypoglycemic convulsion was observed in 1.29% (n: 2) of the patients. This data suggests that viral gastroenteritis may rapidly deteriorate the clinic situation in accordance with the literature. The definitive diagnosis of viral gastroenteritis can be determined with detection of virus in the feces by electron microscopy, production of virus in feces culture and detection of virus antigen in feces (enzyme immunoassay method / latex agglutination test). Detection of rotavirus antigen in stool by latex agglutination method is commonly used basic diagnostic tests [4, 5]. we used the latex agglutination test as a diagnostic test in our study. In the literature, it is reported that the distribution of viral gastroenteritis agents among sex is not different [1, 4]. In our study, 53.24% (n: 82) of the cases were female and 46.75% (n: 72) were male. Although the rate of rotavirus infection was found to be modest higher in females than males in our study, there was no statistically significant difference ($p > 0.05$).

The tendency for all infections, especially acute gastroenteritis, is increasing in children with zinc deficiency at the same time, zinc deficiency is a serious cause of toddlers complications due to gastroenteritis [13]. Zinc deficiency is more common in the regions with low socioeconomic status. It has been reported in the literature that the addition of 20 mg of zinc per day during the treatment of acute gastroenteritis provides a significant improvement in disease duration and severity [8]. However, in the case of viral gastroenteritis, zinc support is still not accepted as a routine practice [7, 8, 14]. Although the physiopathology of the effects of zinc on gastroenteritis is not yet fully understood, diarrhea is seen both as a cause and as a result of zinc deficiency [14, 15]. The fact that patients with gastroenteritis benefit from zinc support suggests that zinc enhances this effect by increasing intestinal immunity [14, 15]. WHO recommends the using of zinc supplementation in the management of acute diarrhea [4, 9, 15, 16]. In our study, a significant improvement was observed in diarrhea, vomiting, nutritional tolerability and hospital stay in group-1 patients compared to group 2 in accordance with the literature. These findings suggest that zinc supplementation is beneficial since early period (Table-2).

Because most of the acute gastroenteritis is viral, antibiotic use is not routinely recommended in the treatment of these cases. Therefore, determination of the agent is very important in the cases with gastroenteritis in treatment and follow-up since the will also prevent the use of unnecessary antibiotics [3, 5, 11]. As a matter of fact, it is learned that 62.98% (n: 97) of all patients taked antibiotic treatment in family medicine and pediatric emergency services, but no clinical improvement.

Limitations

In this study, the absence of the placebo group and the absence of patient controls data after discharge is the limitation of this paper.

Conclusion

Our study suggest that viral agents are the most common cause of acute gastroenteritis in toddlers group in accordance with the literature. Adequate nutrition is the most important indicator of well-being in children. However rapidly deteriorate of nutrition in cases with acute viral gastroenteritis may mislead the physician and this situation can lead to be unnecessary empirically antibiotic treatment. For this reason, viral agents should be determined in pediatric age groups with acute viral gastroenteritis.

Consequently, if it is kept in mind the viruses as a important agent of severe acute gastroenteritis which may commonly seen in the cold seasons thus can be prevented many costly, unnecessary investigations and antibiotic usage in acute gastroenteritis.

Conflict of interest: None.

Financial support: None

References

1. Rosenfeldt, V, Vesikari T, Pang XL, Zeng SQ, Tvede M, Paerregaard A. Viral etiology and incidence of acute gastroenteritis in young children attending day-care centers. *Pediatr Infect Dis J* 2005;24(11):962-5. <https://doi.org/10.1097/01.inf.0000183748.41027.a4>
2. Qiu FZ, Shen XX, Li GX, Zhao L, Chen C, Duan SX, Guo JY, et al. Adenovirus associated with acute diarrhea: a case-control study. *BMC Infect Dis* 2018;18(1): 450. <https://doi.org/10.1186/s12879-018-3340-1>
3. Liu X, Meng L, Li J, Liu X, Bai Y, Yu D, et al. Etiological epidemiology of viral diarrhea on the basis of sentinel surveillance in children younger than 5 years in Gansu, northwest China, 2009-2013. *J Med Virol* 2015;87(12):2048-53. <https://doi.org/10.1002/jmv.24283>
4. Karakus YT, Bircan S, Saime E. Incidence of rotavirus and adenovirus 40/41 in children and infants. *Eur J Med Sci* 2014;1(1):22-25. <https://doi.org/10.12973/ejms.2014.104p>
5. Bozdayi G, Dogan B, Dalgic B, Bostanci I, Sari S, Battaloglu NO, et al. Diversity of human rotavirus G9 among children in Turkey. *J Med Virol* 2008;80(4):733-40. <https://doi.org/10.1002/jmv.21120>
6. Soriano-Gabarró M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. *Ped Infect Dis J* 2006;25(1):S7-S11. <https://doi.org/10.1097/01.inf.0000197622.98559.01>
7. Elliott EJ. Acute gastroenteritis in children. *BMJ* 2007;334(7583):35. <https://doi.org/10.1136/bmj.39036.406169.80>
8. Karamyyar M, Gheibi S, Noroozi M, Valeshabad AK. Therapeutic effects of oral zinc supplementation on acute watery diarrhea with moderate dehydration: a double-blind randomized clinical trial. *Iran J Med Sci* 2013;38(2):93-9.
9. Patro B, Golicki D, Szajewska H. Meta-analysis: zinc supplementation for acute gastroenteritis in children. *Aliment Pharmacol Ther* 2008; 28(6):713-23. <https://doi.org/10.1111/j.1365-2036.2008.03787.x>
10. Rodriguez-Baez N, O'Brien R, Qiu SQ, Bass DM. Astrovirus, adenovirus, and rotavirus in hospitalized children: prevalence and association with gastroenteritis. *J Pediatr Gastroenterol Nutr* 2002;35(1):64-8. <https://doi.org/10.1097/00005176-200207000-00014>
11. Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra JH, Shamir R. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: executive summary. *J Pediatr Gastroenterol Nutr* 2008;46(5):619-21. <https://doi.org/10.1097/MPG.0b013e318272b67b>
12. Guarino A, Ashkenazi S, Gendrel D, Vecchio AL, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *J Pediatr Gastroenterol Nutr* 2014;59(1):132-52. <https://doi.org/10.1097/MPG.0000000000000375>
13. Regagnon C, Chambon M, Archimbaud C, Charbonné F, Demeocq F, Labbé A, et al. Rapid diagnosis of rotavirus infections: comparative prospective study of two techniques for antigen detection in stool. *Pathol Biol* 2006; 54(6):343-6. <https://doi.org/10.1016/j.patbio.2005.12.002>
14. Tuerk MJ, Fazel N. Zinc deficiency. *Curr Opin Gastroenterol* 2009;25(2):136-43. <https://doi.org/10.1097/MOG.0b013e328321b395>
15. Patel AB, Mamtani M, Badhoniya, N, Kulkarni H. What zinc supplementation does and does not achieve in diarrhea prevention: a systematic review and meta-analysis. *BMC Infect Dis* 2011;11(1):122. <https://doi.org/10.1186/1471-2334-11-122>
16. Grahn BH, Paterson PG, Gottschall-Pass KT, Zhang Z. Zinc and the eye. *J Am Coll Nutr* 2001;20(2):106-18. <https://doi.org/10.1080/07315724.2001.10719022>