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Montelukast as an Add-on Drug in Induced Azotemia in Humans Following Gastroenteritis

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Abstract

Background: Gastroenteritis, as a rare and heterogeneous condition, is characterized by patchy or diffuse infiltration of gastrointestinal tissue. Induced azotemia in humans following gastroenteritis has been evaluated in some studies.
Objectives: The aim of present study was to evaluate the effect of montelukast on induced azotemia in humans following gastroenteritis.
Methods: This study examined children with gastroenteritis with moderate dehydration and more than 3 years of age. The cases had a glomerular filtration rate (GFR) less than 90 and were evaluated in two groups of control (n = 20) and intervention (n = 20). Montelukast (5-mg tablets) was given to patients in the intervention group for 5 days. Normal saline at a rate of 20 cc/kg was given to both groups within 20 minutes until clinical symptoms improved. Finally, the improvement of renal function was evaluated and compared between the 2 groups using SPSS.
Results: Out of 40 evaluated patients, the mean age of the control and intervention groups was 5.52 and 5.15 years, respectively. Also, 13 cases (65.0%) in the control group and 9 cases (45.0%) in the control group were males. The mean creatinine (Cr) was significantly reduced after treatment in the intervention group (P = 0.001). Also, the mean GFR after treatment was significantly higher in the intervention group (P = 0.001), and GFR improvement duration was significantly lower in the intervention group (P = 0.002).
Conclusions: Montelukast as an add-on drug was effective in reducing the time of GFR enhancement; thus, we can consider it as an add-on drug in azotemia.

Keywords: Montelukast, Azotemia, Gastroenteritis

1. Background

As a diarrheal disease, gastroenteritis causes more than 0.5 million deaths in cases of less than 5 years of age (1, 2). The higher rate of deaths occurs in the middle- and low-income countries (3), showing the importance of this condition in these countries. The World Health Organization (WHO) defines acute gastroenteritis as defecation of 3 or more liquids or loose stools per day for 3 or more days and less than 14 days (4). In addition, the American Academy of Pediatrics (AAP) describes acute diarrhea as a rapid onset condition with some other signs, such as fever, vomiting, abdominal pain, or nausea (5). However, gastroenteritis is a common diagnosis for pediatric cases presenting to the emergency department (ED). In children less than 5 years of age, diarrhea is a cause of as many as 150 000 hospitalizations and 3.7 million visits by physicians annually in the USA (6, 7).

The most common reason for hospitalization in these cases with acute gastroenteritis is the greater severity of dehydration or mild dehydration with bad social factors (8). These cases with acute gastroenteritis may have increased bowel sounds, abdominal pain, and diffuse abdominal tenderness; thus, these patients need more evaluation to reject other causes (9). After the gastroenteritis diagnosis, the physician should make diagnostic and therapeutic measures such as laboratory evaluation, child rehydration, and administration of an antiemetic agent. These patients with acute dehydration also may develop other complications such as acute renal failure (ARF) and azotemia (10, 11).

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The development of azotemia and ARF in children and young children with acute gastroenteritis may lead to a possible detection of azotemia as a pre-renal azotemia condition resulting from diarrhea that leads to dehydration (2). Patients' symptoms depend on the depth of involvement and gastrointestinal tract segment which is involved (12, 13). As a leukotriene receptor antagonist, montelukast may positively influence the inflammatory condition of patients with gastroenteritis and their dehydration, leading to improved renal function in patients, as the effect of montelukast on renal dysfunction has been investigated in some studies (14-16). Accordingly, montelukast as an add-on drug may be effective in improving the condition of patients with azotemia.

2. Objectives

The present study aimed to evaluate montelukast as an add-on drug on induced azotemia in humans following gastroenteritis.

3. Methods

3.1. Study Setting

This study was conducted on patients with induced azotemia following gastroenteritis, who were referred to Amirkabir Hospital.

3.2. Study Population

The study population was patients with induced azotemia following gastroenteritis. Of the 45 cases, 5 cases were excluded from the study because 3 cases did not take montelukast and 2 cases did not sign informed consent; thus, we enrolled 40 patients in 2 groups of intervention (n = 20) and control (n = 20).

3.3. Randomization

Randomization of the study was performed using cards. To hide the cards, they were placed in the envelope and turned over several times so that the order was not clear. Upon arrival, each participant selected a card, and the group was determined. The selected card was discarded, and this was done in the same way for individuals to achieve the desired sample size.

3.4. Intervention

In both groups, normal saline was given at a rate of 20 cc/Kg within 20 minutes until clinical symptoms improved; also, in the intervention group, 5-mg tablets of montelukast were given for 5 days.

3.5. Measurements

This clinical trial study was conducted on 2 groups; routine treatment was given to both groups, and montelukast was only used in the intervention group for 5 days. At the beginning of the study, the study procedure (including randomization of the study) was fully explained to the parents. They were assured that the information would be kept confidential. It was also mentioned that the drugs have minor side effects (including abdominal pain, dizziness, fever, nasal congestion, skin lesions, urticaria, cough, and sinusitis) and may occur at any stage of the study. The participants were able to leave the study at any time.

The glomerular filtration rate (GFR) recovery time (GFR = 0.43 $\times$ Height (cm)/creatinine [Cr]), blood urea nitrogen (BUN), Cr, and GFR values were evaluated before and after treatment. We examined patients with daily visits, asking parents questions and performing clinical examinations for signs of dehydration.

3.6. Ethical Considerations

The Ethics Committee of Arak University of Medical Sciences approved this study (code: IR.ARAKMU.REC.1399.204). This study was also registered on the Iranian Registry of Clinical Trials website (code: IRCT20201005048940N1). The present study did not influence patients' treatment process; the result of the assessment was only reported to patients.

3.7. Statistical Analysis

The results were analyzed using SPSS version 24 (SPSS Inc, Chicago, Ill, USA) at a 95% confidence level. Quantitative variables were compared by the independent *t*-test; in addition, qualitative variables were compared by the chi-square test.

4. Results

4.1. Clinical Characteristics

Based on our inclusion and exclusion criteria, 40 cases with induced azotemia following gastroenteritis were enrolled and analyzed based on our aims. Our cases were randomly divided into intervention and control groups. In the intervention and control groups, there were 9 (45.0%) and 13 (65.0%) male members, respectively (P = 0.101). The mean $\pm$ SD of age in total and intervention and control groups was 5.34 $\pm$ 2.83, 5.15 $\pm$ 2.54, and 5.52 $\pm$ 3.13 years, respectively (P = 0.761; Table 1).

Table 1. Age and Gender in the 2 Groups

Variables	Groups			Statistical Value
	Intervention	Control	Total	
Age (mean ± SD)	5.15 ± 2.54	5.52 ± 3.13	5.34 ± 2.83	0.761 [a]
Gender				0.101 [b]
Male	9 (45.0)	7 (35.0)	23 (57.5)	
Female	11 (55.0)	13 (65.0)	17 (42.5)	

[a] Independent sample *t*-test
[b] Chi-square test

4.1.1. BUN

The mean ± SD of BUN after treatment was significantly higher in the control group (52.59 ± 8.69 vs. 23.59 ± 8.69; P = 0.0001). Also, this index after treatment was significantly lower in the intervention group than before (22.81 ± 4.97 vs. 92.52 ± 4.17; P = 0.001). Also, the difference between before and after treatment was significant in the overall statistical evaluation (P = 0.395; Table 2).

Table 2. Comparison of Blood Urea Nitrogen Before and After Treatment in the 2 Groups

BUN	Time		P-Value
	Before	After	
Control	23.59 ± 8.79	52.59 ± 8.69	0.001
Intervention	92.52 ±4.17	22.81 ± 4.97	0.001

4.1.2. Cr

The mean ± SD of Cr was significantly higher in the control group before treatment than after treatment (0.35 ± 0.08 vs. 0.86 ± 0.12; P = 0.001). In addition, it was significantly higher in the intervention group before treatment (0.05 ± 0.08 vs. 0.46 ± 0.14; P = 0.001). However, there was no statistically significant difference between the 2 groups in the overall statistical evaluation before and after treatment (P = 0.293; Table 3).

4.1.3. GFR

GFR after treatment was significantly higher in the control group (72.98 ± 9.87 vs. 60.07 ± 9.83; P = 0.001). Also, GFR after treatment was significantly higher in the intervention group (60.07 ± 17.68 vs. 81.49 ± 10.43; P = 0.001). In addition, there were statistically significant differences between the 2 groups in the overall statistical evaluation before and after treatment (P = 0.002; Table 4). In addition, the mean ± SD of GFR recovery time in children was statistically and significantly higher in the control group than in the intervention group (P = 0.002; Table 5).

5. Discussion

We observed that the GFR of patients significantly increased in the intervention group; in addition, the time of GFR recovery was reduced in this group compared with the control group. Sahib et al. evaluated the efficacy of montelukast in acute renal impairment and observed that montelukast had a protective effect against acute renal damage due to diclofenac (17). This protective effect is also demonstrated in the present study; however, in the present study, we also observed a protective effect against gastroenteritis-induced azotemia. Also, Wan et al. evaluated the effect of montelukast in patients with eosinophilic gastroenteritis, showing that this drug can be used to treat this group of patients (18). Similar to our study, this study referred to an anti-inflammatory effect of montelukast, but in this study, the tissue was the gastrointestinal tract, while in our study, the tissue was the kidney. In the study by Beytur et al., the protective and therapeutic effects of montelukast on cisplatin-induced renal injury in rats were investigated, showing that montelukast had a therapeutic effect on acute renal injury following cisplatin (19). Although this study was also based on an animal model, it was similar to the present study regarding the effectiveness of treatment with montelukast on acute kidney injury.

In a study evaluating the efficacy of montelukast in pyelonephritis, Taherahmadi et al. indicated that montelukast led to a rapid improvement in clinical manifestations of pyelonephritis and could be used as an effective adjunctive therapy in these patients (20). Although Our study had a smaller sample size than Taherahmadi study, but like to Taherahmadi study, it showed that the use of Montelukast has an effective role in improving the clinical symptoms of hospitalized patients. The duration of drug use was shorter in our study, which can be justified given that the duration of treatment is different in gastroenteritis and pyelonephritis. Otunctemur et al. evaluated the efficacy of montelukast in mouse model kidney injury and observed that serum urea and Cr levels were significantly

Table 3. Comparison of Creatinine Before and After Treatment in the 2 Groups

Creatinine	Time		P-Value (Paired Sample *t*-test)	P-Value (Independent Sample *t*-test)
	Before	After		
Control	0.86 ± 0.12	0.35 ± 0.08	0.001	0.293
Intervention	0.46 ± 0.14	0.05 ± 0.10	0.001	

Table 4. Mean of the Glomerular Filtration Rate Before and After Treatment in the 2 Groups

GFR	Time		P-Value (Paired Sample *t*-test)	P-Value (Independent Sample *t*-test)
	Before	After		
Control	60.07 ± 9.83	72.98 ± 9.87	0.001	0.002
Intervention	60.07 ± 17.68	81.49 ± 10.43	0.001	

Table 5. Glomerular Filtration Rate Recovery Time in the 2 Groups

Groups	Mean ± SD	P-Value
Control	3.65 ± 1.03	0.002
Intervention	2.5 ± 0.82	

higher in the montelukast group than in the control group (16). However, their mean before and after the intervention was not significantly different between the control and intervention groups, but in the present study, BUN and Cr levels were significantly lower in the intervention group rather than in the control group.

Kose et al. evaluated the efficacy of montelukast in counteracting the effects of amikacin on renal impairment in rats and observed that BUN, Cr, and inflammatory factors significantly increased in the control group than in the treated groups (21). These results are consistent with the present study. In addition, Teslariu et al. evaluated the effect of montelukast on the nephrotoxic effect of gentamicin in a mouse model and indicated that the factors indicating oxidative and inflammatory effects were reduced in the intervention group (22). This indicates the antioxidant effect of montelukast. In the study by Kose et al., the protective and therapeutic effects of montelukast on amikacin-induced renal azotemia in rats were investigated, showing that this drug could be effective in reducing acute renal impairment following amikacin (21). Therefore, the protective role of montelukast on kidney damage was identified in our study, similar to their study. Accordingly, the above studies show that montelukast could be an add-on drug in patients with induced azotemia following gastroenteritis.

5.1. Conclusions

Montelukast could be an effective treatment for induced azotemia following gastroenteritis when used as an add-on drug with routine treatment. It can reduce the time of GFR enhancement. Our study is one of the first studies to evaluate the efficacy of this drug in patients with inflammatory conditions. The majority of studies showed promising and positive efficacy and outcomes. More studies in this field are needed to further investigate the use of montelukast in induced azotemia following gastroenteritis to highlight the duration, dosage, and long-term outcomes of treatment.

Footnotes

Authors' Contribution: P. Y. C. participated in the evaluation and drafted the manuscript. M. H. and F. M. S. participated in designing the evaluation, performed parts of the statistical analysis, and helped to draft the manuscript. F. D. and A. A. re-evaluated the clinical data, revised the manuscript, performed the statistical analysis, and revised the manuscript. F. M. S. and M. R. Z. collected the clinical data, interpreted them, and revised the manuscript. S. K. M. revised the manuscript. All authors read and approved the final manuscript.

Clinical Trial Registration Code: This study was also registered on the Iranian Registry of Clinical Trials website. IRCT20201005048940N1 (https://en.irct.ir/trial/51460).

Conflict of Interests: Our study was funded by Arak University of Medical Sciences; in addition, we have no personal financial interests. We are not one of the editorial board members or a reviewer of this journal.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after its publication. The data are not publicly available due to the possibility of copying information and data.

Ethical Approval: The Ethics Committee of Arak University of Medical Sciences approved

this study. IR.ARAKMU.REC.1399.204 (Link: ethics.research.ac.ir/EthicsProposalViewEn.php?id=156369).

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Informed Consent: Written informed consent was obtained from all participants.

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