Montelukast Is Effective in Treating Rhabdomyolysis Due to Intoxication: A Randomized Clinical Trial

Mohsen Bijandi,[1] Mitra Rahimi,[2] Shahin Shadnia,[2] Babak Mostafazadeh,[2] Latif Gachkar,[3,4] Maral Ramezani,[5,6] Peyman Erfan Talab Evini[2]

[1]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Toxicological Research Center, Excellence Center and Department of Clinical Toxicology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Infectious Disease, School of Medicine, Loghman Hakim Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Department of Pharmacology, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[6]Traditional and Complementary Medicine Research Center, Arak University of Medical Sciences, Arak, Iran

Keywords. creatine kinase, montelukast, poisoning, rhabdomyolysis

Introduction. Rhabdomyolysis is a clinical syndrome accompanied with biochemical changes that is diagnosed in some patients with acute chemical or drug poisoning. In this regard, the present study aimed to evaluate the effects of Montelukast in the treatment of intoxication-induced rhabdomyolysis.

Methods. This single-blind randomized clinical trial study was conducted in Loghman Hakim Hospital from March 2021 to March 2022. The study participants were 60 individuals evenly distributed into experimental and control groups. The experimental group received Montelukast plus routine treatment and the control group Creatine phosphokinase (CPK), urea, creatinine, aspartate aminotransferase (AST) and alanine transaminase (ALT) levels were monitored daily in both groups for seven days. The variables of age, gender and history of diabetes mellitus and kidney diseases were recorded.

Results. The mean age was 39.9 ± 16.87 and 38.2 ± 16.3 years in the control and intervention groups, respectively. Montelukast significantly ($P < .05$) reduced CPK levels on days five and seven, urea on days three, four, five and seven, and creatinine on days two to seven. The AST and ALT levels, unlike the control group which has a decreasing trend, increased first in the Montelukast group and then decreased on the sixth and seventh days.

Conclusion. The results showed that Montelukast effectively reduced CPK, urea and creatinine levels, as well as the recovery time in patients with poison-induced rhabdomyolysis. In other words, Montelukast is effective in the treatment of rhabdomyolysis.

IJKD 2023;17:199-204
www.ijkd.org
DOI: 10.52547/ijkd.7222

Original Paper

INTRODUCTION

Rhabdomyolysis is a potentially devastating condition of skeletal muscle characterized by the decomposition of muscle tissue and the release of intracellular substances. Since skeletal muscle makes up about 40% of the body mass, such a condition can lead to the accumulation of cellular contents.[1] Clinical manifestations of the disease, which can vary from person to person, include muscle weakness, pain, and dark urine due to elevated levels of serum enzymes such as creatine kinase (CK), lactate dehydrogenase (LDH), or aspartate aminotransferase (AST), and acute kidney injury (AKI).[1]

Various factors such as physical or traumatic injury, genetic factors,[1,2] toxic and pharmacological

agents such as cocaine, amphetamines, neuropsychiatric drugs, lead, opioids, alcohols, clomipramine and acetaminophen induce rhabdomyolysis.[1,3-6] Treating the underlying causes of muscle injury is the first step in the treatment of this condition. In addition, measures to prevent acute kidney injury and its metabolic abnormalities (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia & hyperuricemia) are crucial. Other routine therapeutic measures include volume replacement, urinary alkalinization, and mannitol administration.[1,7,8]

Montelukast is a cystinyl leukotriene (cysLT) receptor antagonist with anti-inflammatory effects, used in the treatment of asthma.[9] Due to the anti-inflammatory effects of this drug, Montelukast is also used in the treatment of other diseases such as stroke, rheumatoid arthritis, ischemic reperfusion injury and Parkinson's disease.[9-12] Studies in animal models indicated that Montelukast is also effective in treating poisonings (e.g., alcohol and cadmium poisoning), by reducing the serum levels of aspartate aminotransferase (AST) and alanine transaminase (ALT), Malondialdehyde, Nitric Oxide and Total Antioxidant Capacity.[13,14]

Due to the fatality of the disease, this study was designed to evaluate the effectiveness of Montelukast in the treatment of poison-induced rhabdomyolysis.

MATERIALS AND METHODS

Study Design

This single-blind randomized clinical trial was conducted on 60 patients suffering from poison-induced rhabdomyolysis who were referred to Loghman Hakim Hospital from March 2021 to March 2022. At the time of referral, the patients were randomly allocated into intervention and control groups of 30. The intervention group received routine rhabdomyolysis treatments including hydration with or without bicarbonate and 20 mg oral Montelukast daily; and, the control group received only routine treatments.

Creatine phosphokinase (CPK), urea, creatinine (Cr), AST and ALT levels were monitored daily in both groups for seven days. The variables of age, gender and history of diabetes mellitus, and kidney disease were recorded. Poisoned patients with creatine phosphokinase (CPK) levels above 1000 (mcg/L) were included in the study. The exclusion criteria included those patients who were discharged from the hospital with personal consent. CPK levels lower or equal to the commencement of treatment were regarded as the time that the progression of rhabdomyolysis has been stopped, and CPK levels below 1000 mcg/L were considered the recovery time.

Ethical Considerations

Written informed consent was secured from the study participants, and a phone number was assigned to answer their questions when needed. To conduct the study, research code of ethics was issued by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.441), and the code of Iranian Registry of Clinical Trials center was also obtained (IRCT20210720051946N2).

Statistical Analysis

The study sample size was calculated at confidence level of 95%, power of 80%, and the effect size of 8% in G power software version 3.1.9.2. Data were analyzed by SPSS software version 18. First, Kolmogorov-Smirnov test was used to examine normal distribution in the statistical population, then the central and descriptive indices were calculated. Parametric tests such as independent t-test and non-parametric chi-square test were used according to the distribution of samples. $P < .05$ was considered significant for all tests.

RESULTS

The results indicated that there were 24 (80%) men and 6 (20%) women in the control group and 27 (90%) men and 3 (10%) women in the intervention group. The mean age was 39.9 ± 16.87 and 38.2 ± 16.3 years in in the control and intervention groups, respectively. The study participants had no history of kidney diseases, and one participant in the control group had a history of diabetes mellitus. Chi-square test results did not show significant differences between the two groups in terms of age, sex, history of diabetes mellitus and kidney diseases.

The results of CPK, urea and Cr levels are shown in Table 1. A comparison of CPK values showed that there was a significant ($P < .05$) decrease in the intervention group (receiving Montelukast) on the fifth and seventh days of the intervention

Table 1. Laboratory Data of CPK, Urea and Creatinine in Patients with Rhabdomyolysis in the First to Seventh Days

	CPK			Urea			Cr		
	Control Group	Montelukast Group	*P*	Control Group	Montelukast Group	*P*	Control Group	Montelukast Group	*P*
1th day	4322.2 ± 4798.2	2956.3 ± 1483.5	> .05	54.7 ± 35.3	37.9 ± 25.8	> .05	1.7 ± 1.03	1.3 ± 0.6	> .05
2th day	3933 ± 4502.6	2378.6 ± 2085.4	> 0.05	59.9 ± 50.3	34.3 ± 30.5	> .05	1.7 ± 1.3	1.2 ± 0.8	< .05*
3th day	2614 ± 1361.01	2265.9 ± 2856.2	> .05	63.4 ± 60.3	33.8 ± 33.5	< .05*	2 ± 2.06	1.2 ± 0.9	< .05*
4th day	2141.9 ± 1271.3	1531.5 ± 1710.7	> .05	69.8 ± 77.04	31.8 ± 20.2	< .05*	2.2 ± 2.5	1.02 ± 0.3	< .05*
5th day	1791.8 ± 1275.5	1171.4 ± 787.3	< .05*	77 ± 74.8	47.4 ± 44.5	< .05*	2.4 ± 2.5	1.3 ± 1.1	< .05*
6th day	1797 ± 1242.8	806.4 ± 860.2	> .05	106.8 ± 88.9	67.4 ± 74.7	> .05	3.3 ± 3.1	1.6 ± 1.5	< .05*
7th day	1752.3 ± 1342.5	567.8 ± 135.7	< .05*	120.8 ± 102.4	19.5 ± 3.1	< .05*	4.1 ± 4.1	0.85 ± 0.05	< .05*

(Figure 1). In addition, urea levels were significantly ($P < .05$) decreased in the third, fourth, fifth and seventh days in the intervention group. Also, in this group, creatinine values showed a significant ($P < .05$) decrease in the second to seventh days.

The median time to stop the progression of rhabdomyolysis in both groups was the second day. On the second day, there was no significant difference between the two groups in terms of the frequency of cases in which illness progression ceased. In the control group, the median recovery time occurred on the fifth day, while in the intervention group (montelukast recipients), it occurred on the third, fourth, and fifth days. In addition, the frequency of individuals having creatinine levels exceeding 2 mg/dL on all trial days was reduced in the intervention group.

AST and ALT levels showed a gradual increas until the fifth day in the intervention group (montelukast receipiants) which then decreased, while in the control group there was a decreasing trend in AST (Figure 2).On the other hand ALT in the control group had an increase on the second day and then a downward trend was observed (Figure 3).

DISCUSSION

Montelucast acts as an antagonist with high-affinity binding to the cysteine leukotriene receptor for leukotrienes D4 and E4.[15] These leukotrienes are secreted by different types of cells, such as mast cells, and are involved in the inflammatory process that causes asthma and allergic rhinitis symptoms.[15] In addition, the effects of Montelukast as an anti-inflammatory drug have been considered in various studies.[16] Coskun *et al.* in a study on the effects of montelukast on sepsis in rats reported that the observed effects of the drug on the heart, liver, lungs, and kidneys of rats expresed an improved systemic inflammatory response and a reduction in organ failure.[16]

The results of the present study showed that the use of Montelukast in intoxication-induced rhabdomyolysis significantly reduced urea, creatinine and CPK levels and the recovery time. Some of the studies that were in line with the findings of the present studies are presented here.

Hormati *et al.* in their study of the radioprotective effects of montelukast on gamma radiation-induced nephrotoxicity, showed that montelukast

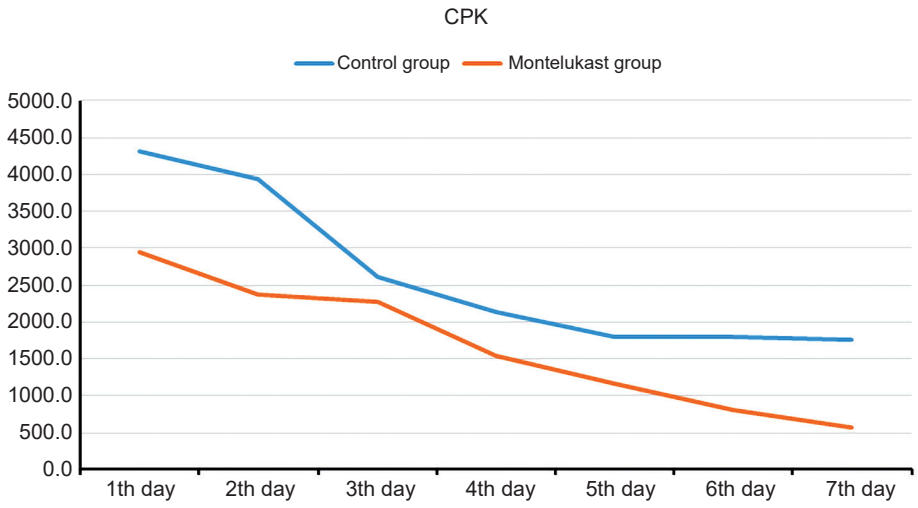

Figure 1. CPK Level Trend in Control Group and Montelukast Treatment Group in 7 Days of Intervention

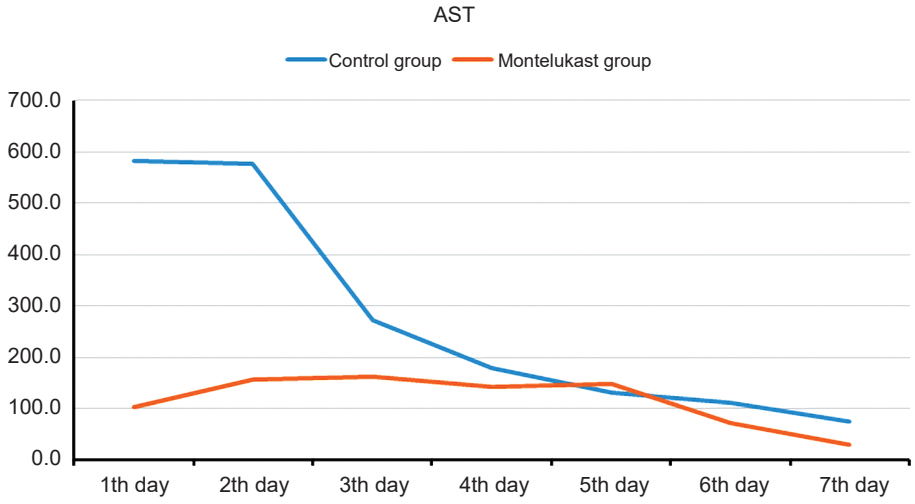

Figure 2. AST Level Trend in Control Group and Montelukast Treatment Group in 7 Days of Intervention

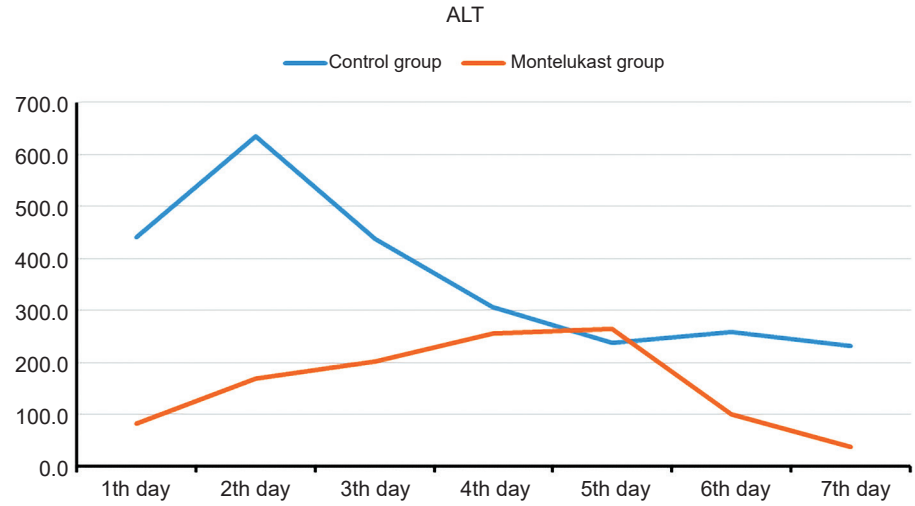

Figure 3. ALT Level Trend in Control Group and Montelukast Treatment Group in 7 Days of Intervention

significantly reduced urea and creatinine levels.[17] The Coskun study also showed that Montelukast reduced urea and creatinine levels in cecal ligation and puncture (CLP)-induced sepsis.[16]

The results reported on the effects of Montelukast on AST and ALT enzymes are different. Some animal model studies, such as the Coskun study, have shown that Montelukast can significantly reduce AST and ALT levels.[16] A study by Zkan *et al.* on hepatic ischemia/reperfusion injury in rats and the protective effects of Montelukast showed that ALT, AST and LDH levels were significantly reduced with Montelukast.[18] Zengin *et al.* in their study on the effects of Montelukast on ethanol-induced liver damage, reported a significant reduction in AST and ALT levels.[14] In a study on the effects of Montelukast on acetaminophen poisoning, Içera *et al.* found that taking Montelukast alone and Montelukast with NAC in acetaminophen poisoning significantly reduced AST and ALT levels.[19]

On the other hand, El-Shehaby's review of Sepsis in Preterm Infants treatment with Montelukast showed that AST and ALT levels were not significantly different from the control group 10 days after treatment and even increased to some extent.[20] In the study by Hareedy *et al.* the results showed that administration of Montelukast alone increased ALT, AST, ALP, CK-MB and creatinine levels compared to the control group.[21] The present study showed that AST and ALT levels, unlike the control group who showed a decreasing trend, in the Montelukast group first increased, and then decreased on the sixth and seventh days. This trend may be due Montelukast-induced liver toxicity, cholestatic and hepatitis in some people.[15,22,23]

CONCLUSION

Finally, our study showed that Montelukast can effectively reduce CPK, urea and creatinine levels in patients suffering from poison-induced rhabdomyolysis, as well as its recovery time. AST and ALT levels showed different changes due to individual differences in response to Montelukast.

ACKNOWLEDGEMENT

The authors would like to thank the Toxicological Research Center of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the study.

AUTHORS' CONTRIBUTION

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

FUNDING AND SUPPORT

This study was supported from Toxicological Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences.

CONFLICT OF INTEREST

The authors declare that they have no competing interests

REFERENCES

1. Cabral BMI, Edding SN, Portocarrero JP, Lerma EV. Rhabdomyolysis. Disease-a-Month. 2020;66(8):101015.
2. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. Journal of neurology. 2020;267(4):877-82.
3. Pajoum A, Fahim F, Akhlaghdoust M, Zamani N, Amirfirooz Z, Dehdehasti M. Rhabdomyolysis and acute poisoning; a brief report. Emergency. 2018;6(1).
4. Ansari B, Dorooshi G, Lalehzar SS, Taheri A, Meamar R. Rhabdomyolysis and muscle necrosis induced by lead poisoning. Advanced biomedical research. 2020;9.
5. Rogliano P-F, Voicu S, Labat L, Deye N, Malissin I, Laplanche J-L, et al. Acute poisoning with rhabdomyolysis in the intensive care unit: Risk factors for acute kidney injury and renal replacement therapy requirement. Toxics. 2020;8(4):79.
6. Santana NOd, Góis AFTd. Rhabdomyolysis as a manifestation of clomipramine poisoning. Sao Paulo Medical Journal. 2013;131:432-5.
7. Nelson LS, Hoffman RS, Howland MA, Lewin NA, Goldfrank LR. Goldfrank's toxicologic emergencies: McGraw Hill Professional; 2018.
8. Bieber SD, Jefferson J. Chapter 12-rhabdomyolysis. Nephrology Secrets, fourth ed Elsevier. 2019:89-93.
9. Chen X, Zhang X, Pan J. Effect of montelukast on bronchopulmonary dysplasia (BPD) and related mechanisms. Medical science monitor: international medical journal of experimental and clinical research. 2019;25:1886.
10. Dong H, Liu F, Ma F, Xu L, Pang L, Li X, et al. Montelukast inhibits inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. International Immunopharmacology. 2018;61:215-21.

11. Bilgiç Mİ, Altun G, Çakıcı H, Gideroğlu K, Saka G. The protective effect of Montelukast against skeletal muscle ischemia reperfusion injury: An experimental rat model. Turkish Journal of Trauma and Emergency Surgery. 2018;24(3):185-90.
12. Nagarajan VB, Marathe PA. Effect of montelukast in experimental model of Parkinson's disease. Neuroscience Letters. 2018;682:100-5.
13. Kaviani F, Jalali M, Hoveizi E, Jamshidian J, Ahmadizadeh M. Montelukast Protects Against Renal Damage Due to Cadmium Toxicity: In vivo and In vitro Experiments. Iranian Journal of Toxicology. 2021;15(4):223-32.
14. Zengin Y, İcer M, Gunduz E, Dursun R, Turkcu G, Yuksel H, et al. Protective Effect of Montelukast Sodium in Acute Ethyl Alcohol-induced Hepatic Injury in Rats. West Indian Medical Journal. 2021;69(5).
15. Wermuth HR, Badri T, Takov V. Montelukast. StatPearls [Internet]: StatPearls Publishing; 2021.
16. Coskun AK, Yigiter M, Oral A, Odabasoglu F, Halici Z, Mentes O, et al. The effects of Montelukast on antioxidant enzymes and proinflammatory cytokines on the heart, liver, lungs, and kidneys in a rat model of cecal ligation and puncture–induced sepsis. TheScientificWorldJOURNAL. 2011;11:1341-56.
17. Hormati A, Ahmadpour S, Afkhami Ardekani M, Khodadust F, Refahi S. Radioprotective effects of montelukast, a selective leukotriene CysLT1 receptor antagonist, against nephrotoxicity induced by gamma radiation in mice. Journal of biochemical and molecular toxicology. 2020;34(6):e22479.
18. Özkan E, Yardimci S, Dulundu E, Topaloğlu Ü, Şehirli Ö, Ercan F, et al. Protective potential of montelukast against hepatic ischemia/reperfusion injury in rats. Journal of Surgical Research. 2010;159(1):588-94.
19. İçer M, Zengin Y, Gunduz E, Dursun R, Durgun HM, Turkcu G, et al. Is montelukast as effective as N-acetylcysteine in hepatic injury due to acetaminophen intoxication in rats? Experimental and Toxicologic Pathology. 2016;68(1):55-9.
20. El-Shehaby N, El-Shahawy H, Nasef N, El-Sallab S, El-Halaby H. Role of Montelukast in Modulation of Response to Sepsis in Preterm Infants: A Randomized-controlled Trial. 2021.
21. Hareedy MS, Ahmed EA, Ali MF. Montelukast modifies simvastatin-induced myopathy and hepatotoxicity. Drug Development Research. 2019;80(7):1000-9.
22. Lebensztejn DM, Bobrus-Chociej A, Kłusek M, Uscinowicz M, Lotowska J, Sobaniec-Lotowska M, et al. Hepatotoxicity caused by montelukast in a paediatric patient. Przeglad Gastroenterologiczny. 2014;9(2):121.
23. Harugeri A, Parthasarathi G, Sharma J, D'Souza G, Ramesh M. Montelukast induced acute hepatocellular liver injury. Journal of Postgraduate Medicine. 2009;55(2):141.

Correspondence to:
Peyman Erfan Talab Evini, MD
Toxicological Research Center, Excellence Center & Department of Clinical Toxicology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
E-mail: peyman1346erfan@sbmu.ac.ir

Received February 2023
Revised April 2023
Accepted June 2023