Original Article

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Magnesium Sulfate and Moderate-Intensity Training Improve Lithium-Induced Liver Injury in Male Rats

Elham Shoghi [1], Tahereh Safari [1,2*], Abbas Ali Niazi [3], Parsa Niyazi [1] Hossein Bagheri [4], Mohamad Mahdi Vahedi [5], Rana Hashemi [1], Fatemeh Maghool [6] Mohadece Chahkandi [7]

1. *Department of Physiology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran*
2. *Pharmacology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran*
3. *Department of Pathology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran*
4. *Department of Medical English, Zahedan University of Medical Sciences, Zahedan, Iran*
5. *Department of Pharmacology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran*
6. *Poursina Hakim Digestive Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*
7. *Cellular and Molecular Research Center, Research Institute of Cellular, Zahedan University of Medical Sciences, Zahedan, Iran*

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Corresponding Information:
Tahereh Safari,
Department of Physiology, School of medicine, Zahedan University of Medical Sciences, Zahedan, Iran
E-Mail:safaritahereh2@gmail.com

ABSTRACT

Background & Objective: Liver damage is a common complication of lithium (Li). The present study investigates the preventive role of $MgSo_4$ and moderate-intensity training MIT on Li hepatotoxicity in male rats.

Materials & Methods: Seventy-two male rats were distributed into 12 groups, control, Li10 mg/kg/day/ip, $MgSo_4$ 80 mg/kg/day/ip; MIT; Li40 mg/kg/day/ip; Li10+$MgSo_4$; Li10+MIT; Li10+$MgSo_4$+MIT, $MgSo_4$+MIT, Li40+$MgSo_4$, Li40+MIT, Li40+$MgSo_4$+MIT. All animals were under the exercise protocol for 6 weeks and received the drugs daily. Then, a blood sample was taken from the heart to measure Cholesterol, Triglyceride, LDL, HDL, AST, and ALT. The liver was excised and then put in 10% formalin to be sent to the lab for pathological investigations.

Results: Compared to the control group, Li 10 and 40 mg/kg cause severe liver injury, $p<0.05$. Instead, $MgSo_4$ and 6 weeks of MIT (Li10+$MgSo_4$, Li10+MIT, and Li10+$MgSo_4$+MIT), Li40+$MgSo_4$, Li40+MIT, Li40+$MgSo_4$+MIT, in comparison with Li10mg/kg and Li40 mg/kg, reduces damage and improves the liver function, $p<0.05$.

Conclusion: $MgSo_4$ and exercise reduce Li-related, improved integrity together with liver function.

Keywords: *: Lithium, hepatotoxicity, magnesium sulfate, moderate-intensity training*

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Introduction

Lithium salts (Li) are widely used to treat mental disorders (1, 2). Li has been shown to reduce the likelihood of recurrence and severity of illness in periodic mood disorders (2). Li is easily absorbed from the gut and distributed in all tissues (1). There are reports that, in the long term, Li causes serious damage to body tissues, including the liver tissue (3, 4). It is known that Li damages the organization and function of the liver, and the recipient of this drug is at risk of hepatotoxicity following subsequent complications (3).

The obligation of free radicals and oxidative stress in the pathogenesis of heavy metals and toxic substances, including Li, has been reported (5). It has been reported that the consumption of lithium causes the creation of free radicals, including Reactive Oxygen species (ROS), by inducing oxidative stress (5). Free radicals produced by damaging the antioxidant system cause liver tissue damage (5). Administration of Li increases the activity of Na^+/K^+_{ATPase} and drug-metabolizing enzymes (6).

Among all mineral elements, magnesium plays a key role in energy metabolism, metabolic pathways, and signaling (7). Magnesium deficit is frequently linked with liver diseases, and may affect nutrient uptake, low serum albumin, or hormone deactivation. Magnesium deficiency cause trouble in mitochondrial function, defective protein kinase C (PKC) translocation, inflammatory answers, oxidative stress, or metabolic complaints. Additionally, magnesium supplementation can recover liver function in certain liver illnesses (8).

Physical activity is one of the prominent cases in delaying various diseases, including liver diseases (9-13). There is evidence that exercise can improve oxidative damage and mitochondrial dysfunction with its antioxidant effects, which reduce inflammation, increase growth factors, and reduce liver resistance against factors such as Doxorubicin and iron oxide nanoparticles (14). The essential fact is that exercise prescription and its effects depend on factors such as intensity and duration of physical activity (15). Since the strength of physical activity strongly influences liver function, it is very vital to decide on the intensity of exercise in this patient (16). Likewise, many reports show that regular exercise, including moderate-intensity training (MIT), improves and delays the progress of various diseases (9, 16).

In line with the literature mentioned above, the current research aims to investigate the protective role of $MgSo_4$ and MIT on Li hepatotoxicity in male rats.

Materials and Methods

Animal and Experimental Protocol

In this investigation, 72 Wistar male rats, weighing 174.3 ± 8.2 g, were placed at room temperature of 23-25 °C with 12/12-h light/dark cycles, and permission was to adapt to the circumstances for one week. The rats were nourished with rat food and water ad libitum. The research procedure was confirmed by the Zahedan University of Medical Sciences Ethics Committee (Ethic No. IR.ZAUMS.REC.1400.350).

The animals were classified into 12 groups, each including 6 animals (figure1);

a) Control (C), n=6

b) Magnesium sulfate, $MgSo_4$, (80 mg/kg/day/ip) n=6

c) Moderate-intensity training (MIT) n=6

d) Magnesium sulfate and moderate-intensity training ($MgSo_4$+MIT) n=6

e) Lithium10 (10 mg/kg/day/ip), n=6

f) Lithium10+ magnesium sulfate (Li10+$MgSo_4$) n=6

g) Lithium 10 and moderate-intensity training (Li10+MIT) n=6

h) Lithium 10, magnesium sulfate, and moderate-intensity training (Li10+$MgSo_4$+MIT) n=6

i) Lithium40 (Li40 mg/kg/day/ip) n=6

j) Lithium 40 and magnesium sulfate (Li40+$MgSo_4$) n=6

k) Lithium 40 and moderate-intensity training (Li40+MIT) n=6

l) Lithium 40, magnesium sulfate, and moderate-intensity training (Li40+$MgSo_4$+MIT) n=6

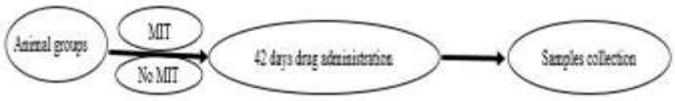


Figure-1: Summary of methods

Before the experiments began, for one week, the rats in the MIT groups were trained to run on a treadmill--type USD5000, Form USD4500 Shenyang Sino-King Equipment Imp. & Exp. Co., Ltd(17).

However, Animals in groups C, Li10, Li40, $MgSo_4$, Li10+$MgSo_4$, and Li40+$MgSo_4$ were in normal laboratory conditions without exercise for 6 weeks. Moreover, the animals were administered an ip injection of Li at a dose of 10, 40 mg/kg/day(18) and $MgSo_4$ at 80 mg/kg/day for six weeks(17).

Forty-eight hours after the last day of exercise, the animals were anesthetized using ketamine, 75 mg/kg/ip, and xylazine 4mg/kg/ip(19). The animals were weighed daily, blood was collected from the heart, while the liver was placed in 10% formalin after removal to be referred to the lab for pathological studies. To separate the serum, the blood was centrifuged for 20 minutes at 6000 rpm.

Exercise Training Protocol

Before MIT, the rats experienced a 5-minute warm-up and a 5- min cool-down intermittently, at the speed of 10 m/min. In concordance with the previous studies, the exercise training procedures were checked by the running speediness of rats on the treadmill. In the first week, the MIT started at 55% of maximum capacity over 31 minutes and then slowly increased until it reached 70% in 46 minutes at the end of the sixth week (17).

Measurements

The Cholesterol, Triglyceride, LDL, HDL, AST and ALT level was measured using quantitative diagnostic kits (Pars Azmoon Co, Iran).

Drugs

Lithium carbonate (CAS-No:554-13-2) and magnesium sulfate (CAS-No:10034-99-8) were purchased from Merck Company in Germany.

Histopathological Procedures

The liver was removed, weighed, and immersed in 10% formalin solution and inserted in paraffin for histopathological staining. The hematoxylin and eosin staining were achieved to examination the tissue. Two pathologists observed the tissues in a blind manner. Liver tissue damage score (LTDS) was checked based on the procedure of Veteläinen RL et al (20).

Histopathology Score of Liver Damage (Table1)

Statistical Analysis

Mean ± SEM was used to report the results. The cholesterol, triglyceride, LDL, HDL, liver weight/g/100g Body Weight, AST, ALT were evaluated by one-way analysis of variance (ANOVA) followed by the LSD test. Similarly, the groups were compared with the Kruskal-Wallis or Mann-Whitney U tests on the liver tissue damage score (LTDS). Via SPSS version 17 (Chicago, IL, USA), $P \leq 0.05$ was assumed statistically meaningful.

Table 1. Amount of inflammatory cells

Histological criteria	Severity	Description	Score
Steatosis	Not found	<10%	**0**
	Mild	10-30%	**1**
	Marked	31-60%	**2**
	Severe	>60%	**3**
Inflammation	None		**0**
	Moderate	Scattered[a]	**1**
	Marked	Foci[a]	**2**
	Severe	Diffuse[a]	**3**
Necrosis	Not Found	0%	**0**
	Mild	<10%	**1**
	Marked	10-50%	**2**
	Severe	>50%	**3**
Fibrosis	Not Found	0%	**0**
	Mild	<10%	**1**
	Marked	10-50%	**2**
	Severe	>50%	**3**

Results

Liver Weight/g/100g Body Weight, Lipid Profile

The average liver tissue weight per 100 g of body weight did not demonstrate any significant difference between groups. Furthermore, no important changes were detected among the different groups in the mean serum cholesterol, triglyceride, LDL, and HDL levels between the different groups (Table 2).

The Serum Levels of AST, ALT, and Liver Tissue Damage Score

Administering lithium with doses of 10 and 40 has caused liver damage and augmented serum levels of liver enzymes (AST and ALT). In evaluation with the control group, serum levels of liver enzymes, AST and ALT, show a noteworthy amplification in levels in the groups receiving Li10 and 40. Administration of $MgSo_4$ and MIT, each individually, with Li improved liver tests and corrects amounts of both enzymes(AST and ALT) in Li10+$MgSo_4$, Li10+MIT, Li40+$MgSo_4$, and Li40+MIT groups, compared to the group receiving lithium 10 and 40 (Li10 and Li40) respectively. Administration of $MgSo_4$ and MIT simultaneously in the Li10+$MgSo_4$+MIT group caused an important decrease in levels of AST and ALT enzymes compared with the Li10mg/kg, $P<0.05$. However, it did not have more effect than prescribing $MgSo_4$ and MIT along with Li 10 mg/kg, Li10+MgSo4+MIT (Table 3). The simultaneous administration of $MgSo_4$ and MIT in the Li40+$MgSo_4$+MIT group decreased the level of AST and ALT compared to the group receiving lithium 40, but there was no significant difference with this group. However, the level of AST and ALT increased compared to the group receiving Li40+$MgSo_4$ and Li40+MIT.

Li10 mg/kg and 40mg/kg have caused severe damage to the liver tissue in comparison with the control group, $P<0.05$. The results indicate that the administration of $MgSo_4$ and MIT with Li10 (Li10+$MgSo_4$, Li10+MIT) has reduced the damage and improved tissue structure, $P<0.05$. Moreover, the results show that the simultaneous administration of $MgSo_4$ and MIT (Li10+$MgSo_4$+MIT) improved the injury compared with the Li10 group, but it did not have a greater effect than their administration alone with Li in the (Li10+$MgSo_4$, Li10+MIT) group. In the groups receiving Li40, the administration of $MgSo_4$ and MIT (Li40+$MgSo_4$, Li40+MIT) alone significantly reduced the liver damage compared with the Li40 group. Despite expectation, the administration of the two mediators together (Li40+$MgSo_4$+MIT) did not improve the liver damage. However, unexpectedly, it aggravated the damage and showed a significant difference with the Li40mg/kg group, $P<0.05$ (Table 3, Figure 2).

Table 2. Liver Weight/g/100g Body Weight, Lipid Profiles

Groups	liver weight/g/100g Body Weight	Cho mg/dl	TG mg/dl	LDL mg/dl	HDL mg/dl
Control	5.42±0.20	50.40±2.11	54.80±11.66	17.40±1.20	29.80±1.49
$MgSo_4$	4.17±0.39	58.50±0.76	56.00±7.55	23.50±1.28	28.16±1.01
MIT	4.42±0.22	44.60±2.22	32.20±6.02	15.60±0.60	25.80±1.49
Li10	4.82±0.12	36.20±8.66	56.40±11.58	14.60±1.43	23.00±2.68
Li40	5.16±0.39	54.50±7.89	68.50±17.02	20.00±2.03	26.16±3.70
$MgSo_4$+MIT	4.30±0.35	44.50±5.00	61.50±12.91	16.75±1.10	23.25±3.35
Li10+MgSo4	4.43±0.15	46.66±4.94	46.50±5.77	15.83±1.49	28.00±3.78
Li10+MIT	4.29±0.46	57.50±8.42	68.50±19.58	21.25±4.25	33.00±5.40
Li10+ $MgSo_4$+ MIT	4.70±0.16	45.00±4.07	49.83±6.62	15.83±1.22	23.33±2.38
Li40+$MgSo_4$	5.09±0.60	48.66±4.11	66.83±8.30	16.00±1.91	24.16±2.86
Li40+MIT	5.47±0.11	49.50±4.31	54.00±5.57	27.00±9.39	26.83±2.40
Li40+$MgSo_4$+MIT	4.65±0.25	42.00±2.88	47.80±4.57	14.20±1.24	24.20±2.20

Means ± SEM, Li = Lithium. $MgSo_4$ = magnesium sulfate, Moderate-intensity training = MIT, Cholestrol=Cho Low density lipoprotein=LDL, High density lipoprotein=HDL

Table 3. AST, ALT, and LTDS

Groups	AST IU/L	ALT IU/l	LTDS
Control	59.8±14.28	74.80±2.90	00.00±00.00
$MgSo_4$	161.16±13.58	82.83±3.17	00.00±00.00
MIT	132.20±12.43	66.4±2.87	00.00±00.00
Li10	123.6±9.79*	166.00±3.74$^{*\$}$	2.66±0.33*
Li40	159.50±14.35*	227.5±9.99*	2.83±0.16*
$MgSo_4$+MIT	144.00±21.84	81.00±5.21	0.04±0.05
Li10+MgSo4	89.83±8.27^{a}	71.66 ±4.77^{a}	00.00±00.00^{a}
Li10+MIT	78.50±19.93^{a}	73.00±7.79^{a}	00.00±00.00^{a}
Li10+$MgSo_4$+MIT	88.16±5.75^{a}	79.83±4.30^{a}	00.00±00.00^{a}
Li40+$MgSo_4$	93.33±2.67$^{\#}$	92.5±2.36$^{\#}$	1.33±0.61$^{\#}$
Li40+MIT	89.50±3.51$^{\#}$	80.83±3.82$^{\#}$	0.45±0.39$^{\#}$
Li40+$MgSo_4$+MIT	137.60±5.93	194.40±5.23	3.20±0.20$^{\#}$

Means ± SEM, the character of *shows significant differences ($p \leq 0.05$) associated with the control group, the character of "a" designates a significant difference from the Li10 mg/kg group, the character of # designates a significant difference from the Li40mg/kg/d group, the character of $ indicates significant difference from the Li40mg/kg/d group, Li = Lithium. $MgSo_4$ = magnesium sulfate, Moderate-intensity training = MIT, Cholesterol = Cho Low density lipoprotein = LDL, High density lipoprotein = HDL

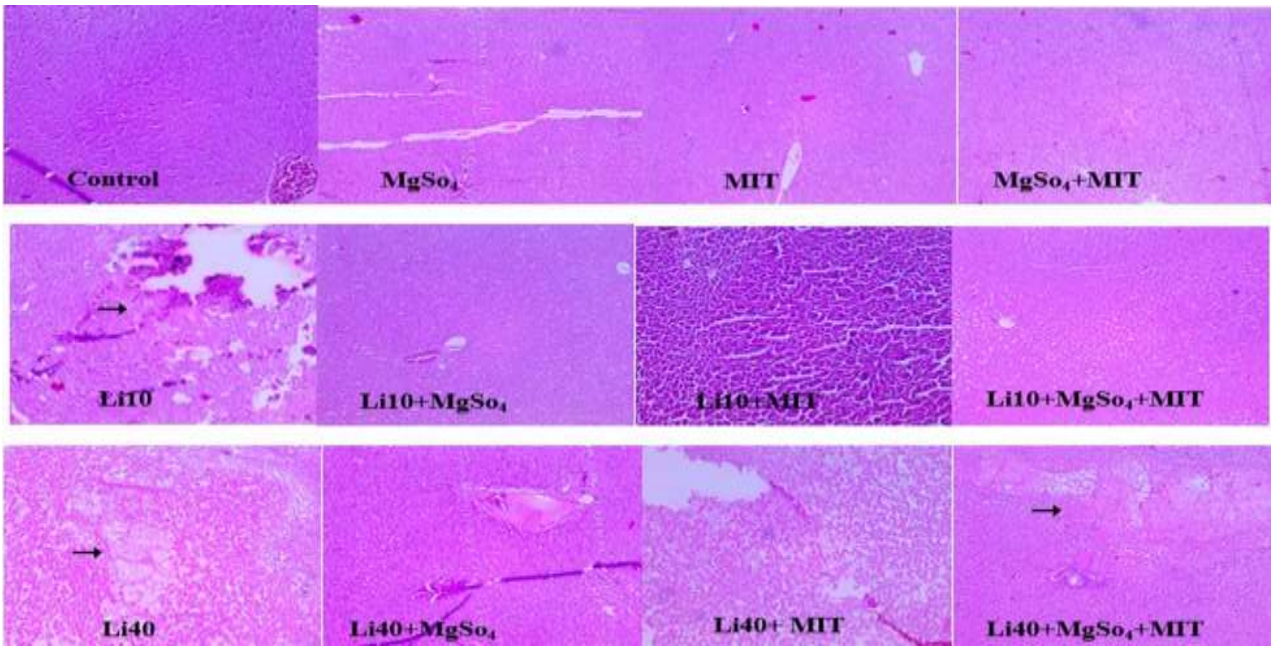


Figure 2: The pathology pictures (×100) of liver tissue. The groups have been treated saline, $MgSo_4$, MIT, $MgSo_4$+MIT, Li10 mg/kg/d, Li10+$MgSo_4$ 80mg/kg, Li10+MIT, Li10+$MgSo_4$+MIT, Li40mg/kg/d, L40+$MgSo_4$, Li40+MIT and Li40+$MgSo_4$+MIT for 6 weeks.

Discussion

The current research suggested that Li with doses of 10 and 40mg/kg causes severe liver damage; on the other hand, the administration of $MgSo_4$ and 6 weeks of MIT reduces damage and improves liver function; it is noteworthy that the administration of $MgSo_4$ and 6 weeks exercise training did not improve the liver functioning after treatment with Li40mg/kg; however, it worsened the liver functioning unexpectedly.

Transaminases or aminotransferases are known as very specific liver marker enzymes. These enzymes reversely act in the conversation of amino acids between α-amine and alpha-κ, at the relationship among the metabolism of proteins and carbohydrates (21). Vijayta Dani Chadha et al. reported that the levels of both liver enzymes (AST, ALT) increased with Li administration (22), which is consistent with the results of this study. An increase in these transferases confirms liver damage (22). Although the mechanism of Li damage has not yet been correctly determined, one of the mechanisms involved in damage induction is oxidative stress (22, 23). In this regard, some documentation have been found that Li causes the generation of oxygen free radicals by damaging the mitochondria membrane. This event causes the consumption of SOD and the reduction of the tissue level of this enzyme and increases the possible damage caused by the oxidative stress related to Li (24, 25).

Regarding the antioxidant effects of $MgSo_4$, several studies have shown that $MgSo_4$ reduces kidney damage related to gentamicin, cisplatin, and metabolic syndrome (26-28). Magnesium is a scavenger of free radicals and can reduce possible tissue damage by reducing the superoxide ion and improving the function of various tissues, including the kidney and liver (29). Similarly, it has been reported that exercise recovers liver function after administration of iron oxide nanoparticles (30). During exercise, many events may help the skeletal muscles use energy and intensify the breakdown of glucose and fatty acids. In addition, during muscle activity, mechanisms are activated that can affect liver cells (31), change gene expression in liver hepatocytes, and prevent hyperglycemia and hepatic steosis(32). Regular exercise with antioxidants causes the reduction of ROS and leads to the peroxidation of fatty acids in liver cells (33). It has also been reported that 30 days of moderate training increases the level of antioxidants, including GSH and CAT, reducing fibrosis in kidney tissue and decreasing nephrotoxicity caused by gentamicin (34). The outcomes of all these studies are congruent with the present study. In this regard, there are reports that $MgSo_4$ and exercise can reduce oxidative stress, improving kidney damage with an additive effect, although this effect was not seen in the present study (29). Therefore, the reduction of ALT and AST levels in the current study in the groups treated with $MgSo_4$ and MIT indicates their protective role against Li-induced liver damage. Similarly, administering $MgSo_4$ improves and regulates protein metabolism and regulates ALT and AST levels. Therefore, it can be concluded that $MgSo_4$ and MIT, with their antioxidant effects, bring back and improve integrity and liver function.

Regarding the aggravation of liver tissue damage after the simultaneous administration of $MgSo_4$ and MIT with lithium 40mg/kg, no clear reason or explanation could be found. Likewise, there is some evidence that long-term exercise increases the

excretion of magnesium and decreases it in soft tissues (35). Considering the exacerbation of liver complications of lithium in a dose of 40mg/kg simultaneously with the administration of $MgSo_4$ and MIT, it is possible to decrease the level of tissue magnesium concurrently with exercise, which could not prevent lithium hepatotoxicity and aggravated the toxicity.

Conclusion

This study found that $MgSo_4$ and MIT significantly reduce the hepatotoxicity caused by lithium. Consequently, it is suggested to determine the mechanism of acting on these two factors in future studies to focus on the antioxidant and anti-inflammatory effects of $MgSo_4$ and MIT.

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Conflict of interest

The authors announce no conflicts of interest about this article's authorship and/or publication.

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Ethics approval and consent to participate

The research registration code is (Ethic No. IR.ZAUMS.REC. 1400.350)

Authors' contribution

Substantial contributions to the conception or design of the work:ESh, TS

The acquisition, analysis, or interpretation of data for the work:ESh, TS

Drafting the work or revising it critically for important intellectual content:TS, ESh, AAN, MCh

Final approval of the version to be published:ES, AAN, PN, HB, RH, FM, MCh, TS

Agreement to be accountable for all aspects of the work in ensuring that questions lated to the accuracy or integrity of any part of the work: ESh, AAN, PN, HB, MMV, RH, FM, TS

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