Research Article

The Potential of Melatonin and N-Acetylcysteine on Remdesivir Induced Liver Injury in Covid 19 Patients

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Abstract | The Covid-19 pandemic has been a problem in recent years. The first FDA approved drug in the treatment of this disease was Remdesivir, which, despite its many benefits, has harmful effects on the liver. Melatonin and N-acetylcysteine, two drugs that have previously been shown to protect the liver with their antioxidant properties, may reduce the hepatic toxicity induced by Remdesivir. Given that few studies have been performed on the role of oral melatonin and N-acetylcysteine on reducing the hepatic adverse effects of Remdesivir, we decided to conduct this clinical trial study. In this double-blind, randomized clinical trial study, 70 patients with Covid-19 in Besat Hospital, Tehran, Iran, during 2022, were enrolled. Patients were randomly divided into two groups of 35 each. Both groups were administered Remdesivir with same protocol. In this period, the first group received N-acetylcysteine 600 mg tablet twice daily and melatonin 6 mg tablet at bedtime. The second group received placebos with the same appearance. Liver enzymes of all patients were serially evaluated and then demographic and lab datas were extracted. Mann-Whitney test, Chi-square test and independent t-test were used for analysis of data. $P < 0.05$ was considered statistically significant. No significant difference was seen between case and control groups regarding age, gender, BMI and severity of the disease at the time of hospital admission ($P > 0.05$), which shows a random classification of two groups. The mean AST, ALT, ALP and CBC of patients in case group decreased compared to the control group but the difference was not statistically significant ($P > 0.05$). In patients with COVID-19 that received Remdesivir, oral administration of melatonin and NAC did not significantly decrease either the patients liver enzymes or CBC level in 6 day of enrolment compared with placebo. Further studies with longer duration and different doses are recommended.

Keywords | Remdesivir, Melatonin, N-acetyl cysteine, Liver injury, Covid-19

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INTRODUCTION

In December 2019, an acute respiratory illness broke out in Wuhan, China (Yuki et al., 2020; Hassanzadeh Khanmiri et al., 2022; Widoyo et al., 2022). The disease spread rapidly and infected more than 470 million people and caused more than 6 million deaths by March 2022 (WHO, 2021; Karimi et al., 2021; Ijaz et al., 2021; Hatami et al., 2022). The disease named novel covid19 and caused by SARS CoV-2 virus, which belongs to the coronaviridae family and causes a range from asymptomatic to fever, cough, dyspnea, pneumonia and death (Sharma et al.,

2021). Four stages are known for the disease: The first stage includes an upper respiratory tract infection, the second stage is the onset of shortness of breath and pneumonia, in the third stage cytokine storm occurs, and the fourth stage will be recovery or death. Depending on the stage of the disease and the patient's clinical condition, several drugs are used for treatment, including antivirals and immunomodulatory drugs (Stasi et al., 2020).

Remdesivir is the first FDA-approved drug for treating covid19 patients that originally developed for the treatment of Ebola virus. It is a nucleotide analogue with broad-spectrum antiviral properties that its effectiveness in treating hospitalized covid-19 patients has been observed in several clinical trials (Lamb, 2020).

In a meta-analysis performed by Elsawah et al. (2021) it was observed that treatment with Remdesivir increase recovery rates on day 14 by 50% in patients with severe cases and reduced mortality rate by 36% in all hospitalized patients.

Despite the benefits of Remdesivir, its hepatic adverse effect should be considered. There is some evidence that the use of Remdesivir can causes liver injury and a low to moderate increase in liver enzymes. Therefore, routinly it is recommended that liver enzymes be checked serially and if the liver enzymes increase more than 10 times injection should be discontinued (Zampino et al., 2020; Aleem et al., 2021).

Melatonin (N-acetyl 5-methoxytryptamine) is a hormone synthesized from the amino acid tryptophan, which in addition to regulating the circadian rhythms, has protective effects on liver diseases and injuries caused by drugs, alcohol and chemical contaminants by preventing oxidative damage, improving mitochondrial physiology, and suppressing liver fibrosis (Zhang et al., 2017; Stacchiotti et al., 2019).

NAC is derived from the amino acid cystein that neutralizes oxygen free radicals and has antioxidant properties. It acts as a glutathione substitute and, in direct combination with active metabolites, stores cytoplasmic and mitochondrial glutathione reserves as a sulfate source and prevents liver damage (Moosa et al., 2021; Walayat et al., 2021).

Since it is important to administer Remdesivir without any side effects for covid-19 patients, we decided to conduct this clinical trial to evaluate the propable role of melatonin and NAC to protect the liver.

MATERIALS AND METHODS

Study design

This randomized, double-blind, placebo-controlled clinical trial study was conducted on hospitalized patients diagnosed with covid-19 in Besat Hospital, Tehran, Iran, in 2022. This study was reviewed and approved by the Ethics Committee of AJA University of Medical Sciences and was performed after obtaining informed consent from all patients (Clinical Trial Registration Code: IRCT20210926052586N2).

Patients

70 patients were enrolled. All patients were over 18 years of old, have positive SARS-CoV-2 PCR test, hospitalized, and have indication to receive Remdesivir. Liver disease and inability to receive oral medication were considered as exclusion criteria.

Randomization and intervention

Patients were randomly divided into two groups of 35 each. Both groups received 200 mg of Remdesivir on the first day of hospitalization and then 100 mg daily for up to four doses. During this period, the first group (experimental group) received N-acetylcysteine 600 mg teblet twice daily and melatonin 6 mg tablet at bedtime. The second group (placebo group) just received a placebo with the same appearance.

Extraction of data

AST, ALT, ALP, CBC and Cr of all patients were serially evaluated on the day 1, 3 and 6 of hospitalization. The chief complaint, severity of the disease at the time of admission and the patients underlying disease were assessed. Moreover, demographic datas such as age, gender and BMI were extracted from medical records.

Statistical analysis

Data were entered SPSS version 26. At first, all datas normality were examined with Kolmogorov–Smirnov test. Then, based on the variable, Mann-Whitney test, Chi-square test and independent t-test were used for analysis of data. P-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

As shown in Table 1, the mean age of participants in the case and control groups was 63.40±16.39 and 55.17±21.98, respectively (P=0.068). Also, there was no significant difference between the two groups in term of gender of patients (P= 0.641). The mean BMI in the case and control groups was 27.70±4.45 and 26.28±3.28 that was not significantly different (0.130).

Moreover, as demonstrated in Table 1, based on the WHO classification (13), no significant difference were observed between the two groups in term of the severity of the disease (P=0.217).

Table 1: Comparison of two groups in terms of age, gender, BMI and disease severity.

Variable	Intervention (n=35)	Placebo (n=35)	P value [a]
Age (years), Mean±SD	63.41±16.39	55.17±21.98	0.068
Gender, n (%)			0.641
Men	15 (44.1)	18 (50.0)	
Female	19 (55.9)	18 (50.0)	
BMI (kg/m2), Mean±SD	27.70±4.45	26.28±3.28	0.130
Severity, n (%)			0.217
Mild	21 (61.8)	27 (75.0)	
Moderate	5 (14.7)	6 (16.7)	
Severe	8 (23.5)	3 (8.3)	

As shown in Table 2, on day 3 of enrolment the AST and ALP level of patients in intervention group decreased compared to the placebo group, but the difference was not statistically significant (P:0.903 and P:0.858). Also, the ALT and CBC level in the intervention group patinets increased less than the control group but there was no significant difference (P:0.191 and P:0.518).

As Table 3 shows, on day 6 of enrolment the AST and ALP level of patients who received Melatonin and NAC numerically decreased more than the placebo group, but the difference was not significant (P:0.242 and P:0.110). Also, the level of ALT and CBC in subjects who received intervention increased less than the placebo group but no significant difference was observed between them (P:0.100 and P:0.055).

Remdesivir is a broad-spectrum antiviral drug that has been reported causes liver injury in some patients with covid19 who have received it. It is metabolised in the liver to form remdesivir triphosphate, this metabolite is a nucleotide analogue that competes with ATP and inhibits RNA-dependent RNA polymerase which is essential for viral replication. Therefore, it seems that this drug can causes liver injury by the mechanism of hepatocytes mitochondrial damage (Wong et al., 2021).

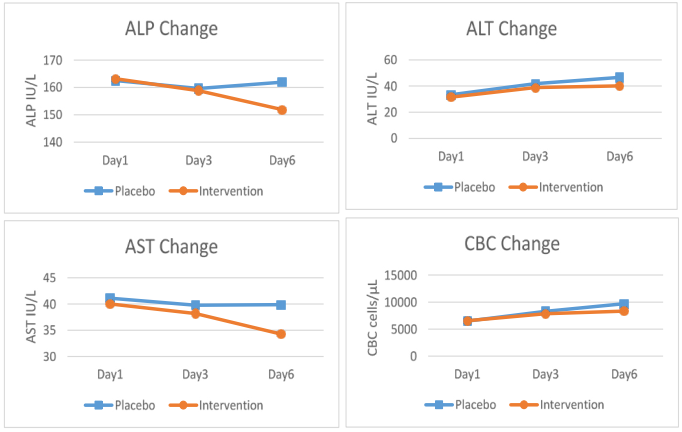

Figure 1: AST, CBC, ALP and ALT change.

Melatonin and NAC are two substances that with their antioxidant and anti-inflammatory effects have important role in reducing liver toxicity caused by medications (Zhang et al., 2017; Stacchiotti et al., 2019).

NAC has an antioxidant function by acting as a glutathione precursor, which is a potential antioxidant, also by breaking down thiol proteins and releasing free thiols that have antioxidant activity. Moreover, NAC sometimes acts as a direct antioxidant for some oxidants such as NO2 and HOX when glutathione and cysteine stores are depleted (Aldini et al., 2018).

Table 2: AST, ALT, ALP, CBC change after 3 days of enrolment.

Variable	Intervention			Placebo			P value
	Day 1	Day 3	Change	Day 1	Day 3	Change	
AST (IU/µL), Mean ± SD	40.03±20.37	38.21±22.15	-1.82	41.14±19.37	39.78±15.34	-1.36	0.903
ALT (IU/µL), Mean±SD	31.56±21.22	38.82±24.77	7.26	33.33±14.68	41.78±21.84	8.44	0.191
ALP (IU/µL), Mean ± SD	163.18±49.41	158.82±66.66	-4.35	162.50±34.76	159.61±26.65	-2.89	0.858
CBC (cells/µL), Mean ± SD	6539.12±3504.16	7855.88±3041.25	1316.76	6472.22±2859.73	8305.56±3255.45	1833.33	0.518

Table 3: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), complete blood count (CBC) chang after 6 days of enrolment.

Variable	Intervention			Placebo			P value
	Day 1	Day 6	Change	Day 1	Day 6	Change	
AST(IU/µL), Mean±SD	40.03±20.37	34.30±13.90	-5.73	41.14±19.37	39.89±14.97	-1.25	0.242
ALT(IU/µL), Mean±SD	31.56±21.22	40.18±21.70	8.61	33.33±14.68	46.60±19.21	13.26	0.100
ALP(IU/µL), Mean±SD	163.18±49.41	151.91±62.47	-11.26	162.50±34.76	161.94±41.09	-0.56	0.110
CBC (cells/µL), Mean±SD	6539.12±3504.16	8316.47±2898.02	1777.35	6472.22±2859.73	9677.78±3734.34	3205.56	0.055

On the other hand, melatonin's functions as an antioxidant include: direct free radical scavenging, stimulation of antioxidative enzymes, increasing the efficiency of mitochondrial oxidative phosphorylation, reducing electron leakage and augmenting the efficiency of other antioxidants (Reiter et al., 2003).

In this double-blind, case control clinical trial, we examined the efficacy oral NAC and Melatonin in dose of 1200mg and 6mg daily in the management of Remdesivir liver injury in COVID-19 patients. The results of our study showed that the use of NAC and Melatonin along with Remdesivir in Covid 19 patients, can slows down the elevation of liver enzymes level. However, this was not statistically significant.

In a clinical trial that was reported by Cichoz-Lach *et al*, demonstrated that adding of Melatonin to treatment regimen of patients with NASH cannot sigificantly decrease AST, ALP or ALP level (Cichoz-Lach et al., 2010). In contrast Chojnacki et al. (2017) showed that for patient taking Atorvastatin 20mg daily for hyperlipidemia receiving daily dose of 10mg of Melatonin orally can reduce Liver enzymes compared to Placebo group. Also, in a study by Pakravan et al. (2017) was found that administration of Melatonin in a duration of 6 weeks in patients with NAFLD can reduce AST significantly compared to the placebo group but ALT level was not changed significantly.

Gokcimen et al. (2007) in an animal intervention study after histopathological examination found that N-acetylcysteine had no protective effect on the liver in doxorubicin induced hepatotoxicity. In contrast, Baniasadi et al. (2010) showed that receiving 600mg NAC orally twice a day can protect liver against anti TB drug induced damage. Moreover, Carother et al. (2020) showed that IV administration of NAC with discontinuation of Remdesivir can have important role in reduction of AST and ALT and improved acute liver failure due to Remdesivir infusion.

CONCLUSIONS AND RECOMMENDATIONS

The limitation of our study was that, it was conducted at a single centre with a relatively small sample size. And also, it was difficult to distinguish whether the increase in patients' liver enzymes was due to the injection of remedsivir or Covid-19 disease itself. In conclusion, in this clinical trial of oral administration of melatonin and NAC doses of 6mg and 1200mg in patients with Covid-19, no significant difference in either the CBC level or liver enzymes decline after 6 days of enrolment was observed.

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NOVELTY STATEMENT

To administer Remdesivir without any side effects for covid-19 patients, we decided to conduct this clinical trial to evaluate the role of melatonin and NAC to protect the liver.

AUTHOR'S CONTRIBUTION

This study was performed due to the widespread prevalence of covid19 in our region and the fact that so far almost no study has been done to find a way to reduce the hepatotoxicity caused by Ramed Sivir. All authors read and approved the final manuscript.

Ethical approved

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Informed consent

Informed consent was obtained from all patients before the study.

Conflict of interest

The authors have declared no conflict of interest.

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