

**Study the effect of Melatonin as adjuvant therapy in the treatment
of covid 19 in a sample of cases in kirkuk city / Iraq**

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Abstract:

Coronaviruses are viruses with R.N.A structure which causing an infection for both animals and humans. And this will lead to affecting the gastrointestinal , central nervous system, and respiratory system , like (MERS-CoV) Middle East respiratory syndrome coronavirus and Severe acute respiratory syndrome corona virus (SARS-CoV) that are very fatal causing hundreds of death during last two decades

The aim of this study was to compare the effect of melatonin on the severity of symptoms among covid 19 patients .

Methods : This study was a case – control which is conducted at Kirkuk city through the outbreak of covid19

The total sample was 40 . 20cases diagnosed covid- 19 positive received melatonin 3mg bedtime in addition to the normal protocol of covid19 which consist of: azithromycin 500mg, paracetamol 500mg, dexamethasone 6mg, supplements

While the remaining 20 cases with covid-19 positive received the same treatment but without any melatonin .The conditions of the cases evaluated according to the covid-19 scale

The results show that most of cases have a mild to moderate symptoms (9- 45.0%) , while for control groups , the symptoms mainly concentrated on moderate type with a p- value = 1.000.

There is a significant relation between recovery period and the disease occurrence because (18- 90.0%) of cases were recovered within less than 5 days with a p- value = 0.000

The study concluded that melatonin has a direct effect on the severity of the disease and symptoms present .

The study recommended that more advanced studies should be done to evaluate the effect of melatonin on other aspect of the disease and among large group of population

Key words: compare , symptoms , covid19 , effect

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Introduction

Coronavirus, characterized by affecting the cardio-vascular system leading to a severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2), which is a newly and recently discovered leading to declared pandemic in March 2020 documented by (W.H.O) the World Health Organization. It usually affects the respiratory system, resulting to an severe infection which affects the respiratory dysfunction and the lung failure. It infects human beings through all age groups. The corona virus takes a more fatal and long course in individuals especially those who are suffering from with chronic metabolic diseases like obesity, hypertension, and diabetes mellitus. ^[1,2]

It is documented that COVID-19 virus has been that infected through many thousands and hundreds of years which are killed all over the world. This highly percentage of contagious infection state will be continues to include all population and has reached its peak level in different countries. ^[3]

There is no clearly clinical treatment for patients with COVID-19, and several antiviral, anti-inflammatory molecules are being under tested, with the various presence of vaccines. However, the pandemic of SARS-CoV-2 is clearly improving, it is expected that a new epidemic may occurs. Thus, it is the need for looking to a future effective treatment of COVID-19. ^[4,5]

The main pharmacological features of melatonin are well noticed. In spite of that, there is a remarkable clinical trials which are still under the study about melatonine security, efficacy, and the absence of side effects in the long and short term, with the effective doses of it. ^[6,7]

Melatonin have various functions which are a- signaling synthesized hormone b- the secreted root is by the pineal gland. It is a very powerful antioxidant with immunomodulatory action and has an effective anti-inflammatory action under a different conditions. ^[6,7]

Melatonine has a main characteristic features which is a powerful antioxidant, within proposed regime of treatment protocols in addition to that it is a potential with promising agent which help to get rid Covid-19 infection and assist the immunity in human beings. ^[8,9]

Melatonin's have many various actions against :

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1- Inflammation 2- Oxidation 3- Anti-viral which make it a suitable choice for usage . Melatonin usually is available and can be synthesized easily in huge amounts , also it is a cheap with a very high safety profile in addition to that it can be easily administered . Melatonin is produced inside the body with a small molecule in cases of giving in small amounts which gradually decreasing with advanced age. Under the emergency conditions, melatonin should be given in large doses either alone or in combination with the recommended drugs .^[10,11]

Aim of the study :

This study was done to detect the effect of Melatonin therapy as an adjuvant in the treatment for patient with covid 19 in a sample of cases in Kirkuk city / Iraq.

Material and methods

1- Ethical issues

Agreements permission was obtained from Kirkuk health directorate in order to complete sampling collection .

2- Study setting :-

The research was done in both hospitals (Kirkuk general hospital, and Azadi hospital)

3- Study sample and sampling method :-

This study was a case – control which is conducted at Kirkuk city through the outbreak of covid19 .The total sample was 40 . 20cases diagnosed covid- 19 positive received melatonin 3mg bedtime in addition to the normal protocol of covid19 which consist of: azithromycin 500mg, paracetamol 500mg, dexamethasone 6mg, supplements While the remaining 20 cases with covid-19 positive received the same treatment but without any melatonin The conditions of the cases evaluated according to the covid-19 scale.^[112]

On day 3 and after 1 week from start of symptoms

Cases	Controls	Total sample
20 received melatonin	20 not received	40

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A full explanation of the study aim was explained to them and a written consent was taken from the participants about their agreement before starting the study and they are free to withdraw from the study at any time they need .

4- Study period :

The study was conducted between August 2020 to October 2020 .

5- Data collection tool :

A special regime treatment was followed for the participants and regular follow up them regarding their improvement and symptoms .

6- The reliable index of the regime treatment : The treatment was presented to (4) experts , 2 of them were medical physicians and the remaining 2 were from statistical field .

7- The data analysis methods :-

The statements presented with yes and no answer , the frequency and percentage will be calculated . The tables were presented with numbers and p value which detect the use of specific statistical test that is Chi- square test in order to determine the association between the presented variables and this p value with the level of (< 0.005) is regarded as a significant value

Discussion:

For table 2 , the current study show that that most of cases have a mild to moderate symptoms in comparison to control groups , the symptoms mainly concentrated on moderate type .

Another similar study was reported by Kobra Bahrapour/ etal. ^[13] about the effect of melatonin potentials against COVID-19 viral infections in order to determine the main role of melatonin in the management of corona virus . they mentioned that melatonin uses was very effective in decreasing the death and virus-mediated stroke, and the viral potency was reducing by modulating the IL-2 and IFN- γ concentrations during Venezuela equine encephalomyelitis (VEE) virus infection in mice . In addition to that melatonin has also been documented to reduce acute lung damage in respiratory syncytial virus models, by inhibition the pro-inflammatory cytokine release and oxidative damage

Another study was taken by Ahmet Ozer Schirli etal / .^[14] in turkey in order to determine the melatonin effectiveness in the treatment of covid 19 patients , and to get rid the main health problem within corona virus epidemics .

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They found that melatonin, is a very a safe drug, which may prevent and protect acute symptoms severity and the side effects of the other antiviral drugs in COVID-19 cases. In conclusion, they published that the melatonin usage that is decreased in the immune-compromised patients and elderly people, should be considered as an adjuvant therapy in spite of its immunomodulatory effect and CD147 suppressor feature

They concluded in their research that melatonin may be a candidate drug to support and provide relief from the clinical signs and symptoms of COVID-19 even though its having an antioxidant effect which cannot eliminate or stop the viral transcription or replication or as shown in the figure below

Regarding table 3 about the recovery period, the current study show that there is a significant association between the disease occurrence and the recovery period because most of cases were recovered within the period less than 5 days.

ussel J. Reiter/ *etal.* ^[15] found in their study about therapeutic algorithm for the usage of melatonin in covid19patients that melatonin is having an a molecule that regulates the overreaction of the innate immune response negatively and excess inflammation, promoting adaptive immune activity. COVID-19 outbreaks c has infected thousands and hundreds of people and killed many individuals all over the world and the high mortality rate is due to uncontrolled destructive inflammation and innate immune response.

Further more, the indole which is an endogenous molecule, that is produced in small amounts, whose synthesis will lead to diminishes with increased age.

This important successful finding support the melatonin use in patients with COVID-19. and the role of melatonin should be given very careful either for prophylactic use or in order to treatment alone or in combination with other drugs, and assist the therapeutic algorithm for its action.

Further similar study was conducted by Fedor Simko *etal* / ^[16] regarding the Melatonin as a putative protection against the occurrence of myocardial injury in COVID-19 infection.

They mentioned that the COVID-19) corona virus disease 2019 (reached its pandemic proportions especially in March 2020 with high, rapid spread dissemination and serious social and health outcomes. In the middle of August, the population of infected patients all over the

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world has risen to more than 20 million with about 750 000 deaths. The number of severely affected cases in some countries overwhelms the real capacities of hospitals and health centers irrespective to its demands. The main serious complication was acute respiratory distress syndrome (ARDS), as the dangerous frequent fatal impacts which has been under study investigation since the beginning of the outbreak. Yet, cardiovascular problems that are regarding the second, commonly occurring complication because of its poorly prognosis, which has received much less concentration and still remains ill defined

Conclusion:

- 1- Melatonin have a direct effect on covid 19 patients through the degree of symptoms severity .
- 2- Melatonin also have an effect on the recovery period .
- 3- Melatonin can be used as an adjuvant therapy in pandemics .

Recommendation :

- 1- Advanced educational program through the social media about the effect of melatonin on the diseased patients .
- 2- further wide range studies should be done to include a large sample to detect melatonin affectivity on the patients .
- 3- financial with the governmental assistance to support these studies .

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
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The characteristic features	Number N=40	Percent %
Gender		
Male	23	57.5%
female	17	42.5%
Age (years)		
< 30	18	55.0%
>30	22	45.0%
Employment		
Yes	27	67.5%
No	13	32.5%
Educational level		
Illiterate	18	45.0%
Read and write	7	17.5%
Primary	10	25.0%
Secondary and above	5	12.5%

Table 1 show that most of patients were male (57.5 %) , aging above 30 years (55.0 %) , employed (67.5%) , and they are illiterate (45.0%).

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Table 2 Distribution of study patients according to degree of coiv-19 symptoms

Degree of symptoms	Patients N= 20	Control N=20	Total N= 40	P- value
Mild	9 (45.0%)	8 (40.0%)	17 (42.5%)	0.749
Moderate	9 (45.0%)	9 (45.0%)	18 (40.0%)	1.000
Sever	2 (10.0%)	3 (15.0%)	5 (12.5%)	0.633
Total	20 (100.0)	20 (100.0%)	40 (100.0%)	

$\chi^2 =$ was used

Table 2 show that most of cases have a mild to moderate symptoms (9- 45.0%) , while for control groups , the symptoms mainly concentrated on moderate type (p- value = 1.000)

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Table

Recovery period	Patients have N= 20	Control N=20	Total N= 40	P- value
< 5 days	18 (90.0%)	0 (0.0%)	18 (45.0%)	0.000
6-10 days	2 (10.0%)	5 (25.0%)	7 (17.5%)	0.212
>5 days	0 (0.0%)	15 (75.0%)	15 (37.5%)	0.000
Total	20 (100.0)	20 (100.0%)	40 (100.0%)	

3 patients distribution regarding the recovery period

$\chi^2 =$ was used

Table 3 show that there is a significant relation between recovery period and the disease occurrence because (18- 90.0%) of cases were recovered within less than 5 days with a p- value = 0.000, on the other hand (15- 75.0%)of control groups were recovered within the period more than 5 days with a p- value =0.000.

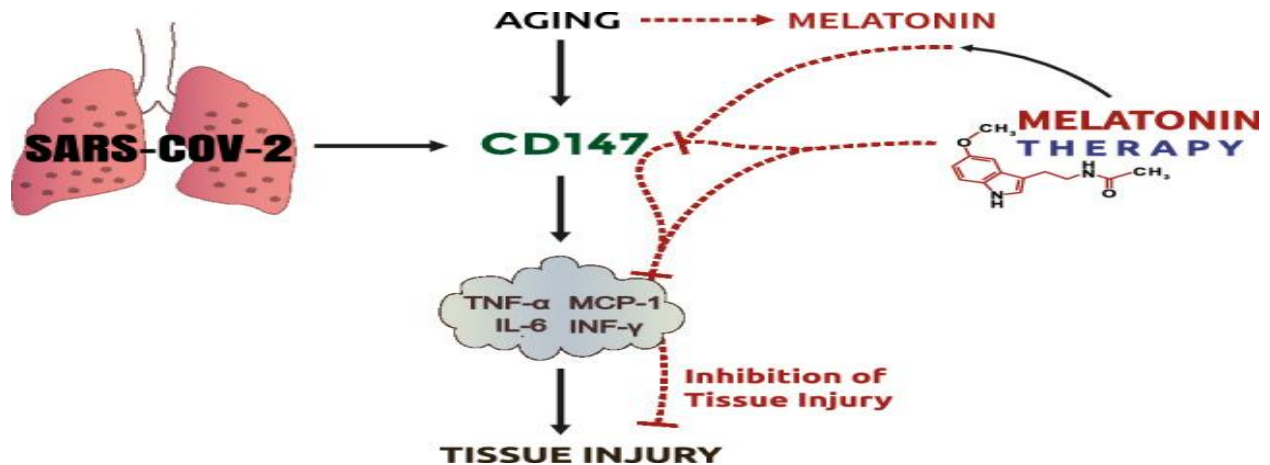


Figure 1 SARS-CoV-2 causes tissue damage by increasing TNF- α , MCP-1, IL-6 and INF- γ levels through CD147. Due to both the excess of CD147 levels and the decrease in melatonin levels in elder people, tissue damage is more severe with cytokine storm. Melatonin therapy may have the ability to inhibit tissue damage by causing a decrease in CD 147 levels and thus cytokine level