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LETTERS TO THE EDITOR

What if melatonin could help patients with severe COVID-19?

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In March 2020, a protocol recommending the prescription of melatonin, among other sleep- and biorhythms-promoting measures, to hospitalized patients with coronavirus disease 2019 (COVID-19) with sleep problems or delirium was sent from the consultation-liaison psychiatrist to the medical staff of the Fundación Jiménez Díaz University Hospital (FJDUH) in Madrid, Spain. Several authors have suggested a potential benefit of melatonin use in COVID-19.[1–4] In addition to its circadian function, melatonin is thought to have several health-promoting properties, including immune response modulation and anti-inflammatory and antioxidant properties.[5] We here report a retrospective analysis showing an association of melatonin with survival in a sample of 2,463

Table 1—Unmatched and matched groups of melatonin and non-melatonin patient characteristics, and comparison of mortality and hospital stay between matched groups.

Variable	Melatonin (n = 224)	Unmatched Comparisons		Matched Comparisons		
		Non-Melatonin (n = 1,952)	*P* Value	Non-Melatonin (n = 224)	*P* Value	Effect[b] (95% CI)
Demographics and clinical history						
Age[a]	69.0 (22.5)	74.0 (28.0)	.054	70.0 (25.0)	.982	—
Female	96 (42.9%)	917 (47.0%)	.271	97 (43.3%)	> .99	—
CVD	61 (27.2%)	594 (30.4%)	.362	62 (27.7%)	> .99	—
DM	53 (23.7%)	378 (19.4%)	.150	39 (17.4%)	.128	—
Hypertension	113 (50.4%)	1,052 (53.9%)	.363	112 (50.0%)	> .99	—
Lung disease	54 (24.1%)	443 (22.7%)	.694	58 (25.9%)	.743	—
Dyslipidemia	95 (42.4%)	738 (37.8%)	.204	80 (35.7%)	.175	—
Smoking habit	14 (6.2%)	152 (7.8%)	.492	20 (8.9%)	.372	—
Treatment-related						
ICU/IRCU stay	53 (23.7%)	112 (5.7%)	<.001	43 (19.2%)	.300	—
Dexamethasone	42 (18.8%)	109 (5.6%)	<.001	32 (14.3%)	.252	—
Tocilizumab	67 (29.9%)	177 (9.1%)	<.001	71 (31.7%)	.759	—
Cyclosporine	138 (61.6%)	677 (34.7%)	<.001	145 (64.7%)	.557	—
Methylprednisolone	183 (81.7%)	1,167 (59.8%)	<.001	192 (85.7%)	.306	—
Anakinra	11 (4.9%)	13 (0.7%)	<.001	7 (3.1%)	.470	—
Nasal cannula oxygen	184 (82.1%)	1,272 (65.2%)	<.001	171 (76.3%)	.162	—
High-flow oxygen	34 (15.2%)	82 (4.2%)	<.001	26 (11.6%)	.332	—
Clinical evolution						
Hospital stay, d	13.7 (23.1)	5.9 (6.7)	<.001	8.9 (10.9)	<.001	4.8 (2.3–6.2)
Mortality	24 (10.7%)	340 (17.4%)	.014	53 (23.7%)	<.001	0.39 (0.23–0.65)

[a]Expressed as median (interquartile range). [b]Median differences for hospital stay and odds ratio for death. Hospital stay is expressed as median (interquartile range). Mortality is expressed as frequency (%). CVD = cardiovascular disease, DM = diabetes mellitus, ICU = intensive care unit, IRCU = intermediate respiratory care unit.

patients with COVID-19 hospitalized during the first wave of the pandemic, 265 of whom (10.75%) were given 2–6 mg of oral melatonin at 21 hours during admission (median of first day of administration was day 4, and 25% of patients received melatonin from the first day). Our work and that of Ramlall et al[6] are the first to show real-world clinical data supporting a possible benefit of melatonin in COVID-19.

To reduce the possibility of a biased, biologically nonrelevant association of melatonin with survival, we excluded from the sample patients who died during the first 72 hours of admission without taking melatonin and patients who started on melatonin in the last 7 days of their admittance, having completed 75% of their stay. The remaining sample comprised 224 patients who received melatonin and 1,952 patients who did not receive melatonin. Both groups included patients admitted in the intensive care unit (or intermediate respiratory care unit), with the patients of the melatonin group having more probability of intensive care unit/intermediate respiratory care unit admission (**Table 1**). To control for baseline differences between the 2 groups we performed a propensity score matching. The melatonin group showed a much lower mortality rate (10.7% vs 23.7%) compared with the non-melatonin matched group, with an odds ratio of 0.39 (**Table 1**). We had data available on CURB-65 (confusion, blood urea nitrogen >19 mg/dL, respiratory rate ≥30 breaths/minute, low blood pressure, and age ≥ 65 years; a validated scale of clinical severity[7]) for 343 (76.5%) out of 448 patients in the matched groups, 179/224 in the melatonin group, and 164/224 in the non-melatonin matched group. No differences were found between the 2 groups in the distribution of their CURB-65 scores, suggesting that they were similar in terms of illness severity at admission.

One possible pathophysiological mechanism to explain age-related vulnerability to COVID-19 is the progressive loss of endogenous melatonin with aging.[8] The circadian disruption that intensive care unit patients[9,10] and other hospitalized patients experience also likely contributes to the pathophysiology of acutely ill patients with COVID-19. The circadian rhythm strengthening of melatonin and other measures, such as appropriate daytime lighting and activity, could be of benefit not only for the management of COVID-19 but also for other diseases.

This report shows the first set of data of a bigger analysis we are performing on the effect of melatonin on the clinical evolution of patients admitted in the FJDUH throughout the pandemic. We are aware that a retrospective analysis prevents us from establishing a causal association between melatonin and survival. Prospective studies are already on their way[11,12] to assess the utility of melatonin as an adjunctive treatment for COVID-19. However, with no time to lose and given its safety profile and low cost, our data may help the clinician to consider the use of melatonin in patients with COVID-19.

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REFERENCES

1. Zhang R, Wang X, Ni L, et al. COVID-19: melatonin as a potential adjuvant treatment. *Life Sci.* 2020;250:117583.
2. Bahrampour Juybari K, Pourhanifeh MH, Hosseinzadeh A, Hemati K, Mehrzadi S. Melatonin potentials against viral infections including COVID-19: current evidence and new findings. *Virus Res.* 2020;287:198108.
3. Shneider A, Kudriavtsev A, Vakhrusheva A. Can melatonin reduce the severity of COVID-19 pandemic? *Int Rev Immunol.* 2020;39(4):153–162.
4. Artigas L, Coma M, Matos-Filipe P, et al. In-silico drug repurposing study predicts the combination of pirfenidone and melatonin as a promising candidate therapy to reduce SARS-CoV-2 infection progression and respiratory distress caused by cytokine storm. *PLoS One.* 2020;15(10):e0240149.
5. Tordjman S, Chokron S, Delorme R, et al. Melatonin: pharmacology, functions and therapeutic benefits. *Curr Neuropharmacol.* 2017;15(3):434–443.
6. Ramlall V, Zucker J, Tatonetti N. Melatonin is significantly associated with survival of intubated COVID-19 patients. *medRxiv.* Preprint posted online October 18, 2020.
7. Rodriguez-Nava G, Yanez-Bello MA, Trelles-Garcia DP, Chung CW, Friedman HJ, Hines DW. Performance of the quick COVID-19 severity index and the Brescia-COVID respiratory severity scale in hospitalized patients with COVID-19 in a community hospital setting. *Int J Infect Dis.* 2021;102:571–576.
8. Simko F, Reiter RJ. Is melatonin deficiency a unifying pathomechanism of high risk patients with COVID-19? *Life Sci.* 2020;256:117902.
9. Fan EP, Abbott SM, Reid KJ, Zee PC, Maas MB. Abnormal environmental light exposure in the intensive care environment. *J Crit Care.* 2017;40:11–14.
10. Maas MB, Iwanaszko M, Lizza BD, Reid KJ, Braun RI, Zee PC. Circadian gene expression rhythms during critical illness. *Crit Care Med.* 2020;48(12):e1294–e1299.
11. Acuña-Castroviejo D, Escames G, Figueira JC, de la Oliva P, Borobia AM, Acuña-Fernández C. Clinical trial to test the efficacy of melatonin in COVID-19. *J Pineal Res.* 2020;69(3):e12683.
12. Ziaei A, Davoodian P, Dadvand H, et al. Evaluation of the efficacy and safety of melatonin in moderately ill patients with COVID-19: a structured summary of a study protocol for a randomized controlled trial. *Trials.* 2020;21(1):882.

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