Journal of Travel Medicine

International Society of Travel Medicine
Established 1991
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Journal of Travel Medicine, 2022, 1–3
https://doi.org/10.1093/jtm/taab195
Research Letter

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Melatonin does not reduce mortality in adult hospitalized patients with COVID-19: a multicenter retrospective observational study

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Submitted 27 November 2021; Revised 10 December 2021; Editorial Decision 14 December 2021; Accepted 14 December 2021

Key words: melatonin, treatment, efficacy, mortality, death, SARS-CoV-2, COVID-19

Melatonin is an hormone secreted from the pineal gland indicated in the treatment of insomnia and circadian sleep disturbances.[1] In the needed search for an effective treatment for patients with COVID-19,[2] this molecule has been previously proposed as a potential useful treatment against COVID-19 thanks to its antioxidant, immunomodulatory, anti-inflammatory and potential SARS-CoV-2 main protease inhibition activities.[3–6] However, while a recent randomized clinical trial[7] involving patients hospitalized with mild to moderate COVID-19 suggests that oral melatonin administration as an adjuvant therapy added to the standard of care may improve respiratory symptoms and time of patient discharge vs standard of care alone, another randomized trial found no substantial improvement in patients hospitalized for severe COVID-19.[8] In this report, we used data from a multicenter retrospective study involving patients hospitalized for laboratory-confirmed COVID-19 in Greater Paris University hospitals, as detailed elsewhere,[9] and sought to examine the association between melatonin use and mortality in this population. Observational studies examining the potential usefulness of existing treatments against COVID-19 can be crucial to help prioritize molecules in clinical trials.

This multicenter observational retrospective cohort study was conducted at 36 AP-HP hospitals from the beginning of the epidemic in France, i.e. 24 January 2020, until 31 October 2021, using data from the AP-HP Health Data Warehouse ['Entrepôt de Données de Santé (EDS)'].[9,10] We included all adults aged 18 years or over who have been hospitalized in these medical centers for COVID-19. COVID-19 was ascertained by a positive reverse transcriptase–polymerase chain reaction test from analysis of nasopharyngeal or oropharyngeal swab specimens.

Data were obtained for demographic characteristics and medical risk factors associated with severe COVID-19, including: sex; age, categorized into three groups (18–70, 71–80, 81+); hospital, which was categorized into four classes following the administrative clustering of AP-HP hospitals in Paris and its suburbs based on their geographical location (i.e. AP-HP Centre—Paris University, Henri Mondor University Hospitals and at home hospitalization; AP-HP Nord and Hôpitaux Universitaires Paris Seine-Saint-Denis; AP-HP Paris Saclay University and AP-HP Sorbonne University); hospitalization period categorized using terciles; obesity, defined as having a body mass index ≥ 30 kg/m^2 or an ICD-10 diagnosis code for obesity (E66.0, E66.1, E66.2, E66.8, E66.9); number of medical conditions associated with severe COVID-19, including diabetes mellitus (E11), diseases of the circulatory system (I00–I99), diseases of the respiratory system (J00–J99), neoplasms (C00–D49) and diseases of the

Table 1. Association between melatonin use and risk of death in adult patients hospitalized for COVID-19 ($N = 58\,562$)

	Number of events/Number of patients	Crude logistic regression	Multivariable logistic regression analysis[a]	Multivariable logistic regression analysis[b]
	N/N (%)	OR (95%CI; *P*-value)	AOR (95% CI; *P*-value)	AOR (95% CI; *P*-value)
No use of melatonin	6487/58 290 (11.1%)	Ref.	Ref.	Ref.
Melatonin use at baseline	82/272 (30.1%)	3.45 (2.66–4.47; < 0.001*)	1.26 (0.96–1.66; 0.100)	0.81 (0.61–1.08; 0.149)

[a]Adjusted for age and sex [df = 4; all $GVIF^{(1/(2*df))} < 1.1$]. [b]Adjusted for age, sex, hospital, hospitalization period, obesity, any sleep, anxiety, depression or dementia disorders, number of comorbid medical conditions, severe COVID-19 and medication according to compassionate use or as part of a clinical trial [df = 15; all $GVIF^{(1/(2*df))} < 1.3$]. *Two-sided *P*-value is significant ($P < 0.05$). df, degrees of freedom; GVIF, generalized variance inflation factor.

blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89); COVID-19 severity at admission (as defined in eText 1) and any medication prescribed according to compassionate use or as part of a clinical trial (detailed in eText 1). To assess possible confounding by indication bias for melatonin prescription, we recorded whether patients had any record of insomnia (G47), mood disorders (F30-F39), anxiety disorders (F40-F48) or dementia (F01-F03, G31.0) during the visit. Study baseline was defined as the date of hospital admission. The outcome was in-hospital all-cause mortality.

To compare this outcome between patients who received melatonin at baseline (i.e. within the first 24 h from hospital admission) and those who did not, we performed a multivariable logistic regression model adjusted for the aforementioned demographic characteristics and medical risk factors. We also performed three additional analyses. First, to consider potential differences in mortality along time, we reproduced the same analyses while stratifying by hospitalization period. Second, we reproduced the same analyses while stratifying by severity of COVID-19 at baseline. Finally, we studied a potential dose-effect of melatonin by examining the association between the baseline daily dose received (binarized at the median) with mortality among patients who received melatonin at baseline. All statistical assumptions were checked. Statistical significance was fixed a priori at two-sided *P*-value <0.05. All analyses were conducted in R software 3.6.3.

Of 58 562 adult patients, 272 (0.46%) received melatonin at baseline at a mean daily dose of 2.61 mg [standard deviation (SD) = 1.43; range = 1–12 mg] for a mean duration of 15.6 days (SD = 16.6; range = 1–126 days) (Supplementary Figure 1). Over a median follow-up of 13.0 days (SD = 207.0; range = 1–613 days), mortality occurred in 82 patients (30.1%) who used melatonin and 6487 patients (11.1%) who did not. All baseline clinical characteristics were significantly associated with the outcome (Supplementary Table 1), except for any depression, anxiety, dementia or sleep disorders in the multivariable analysis. Melatonin use substantially differed across all demographic and medical risk factors, except for obesity (Supplementary Table 2). Melatonin use was significantly associated with increased mortality in the crude, unadjusted analysis [odds ratio (OR) = 3.45; 95%CI = 2.66–4.47; $P < 0.001$]. However, this association was not significant in the model adjusted for sex and age [adjusted odds ratio (AOR) = 1.26; 95%confidence interval (CI) = 0.96–1.66; $P = 0.100$], nor in the fully adjusted model (AOR = 0.81; 95%CI = 0.61–1.08; $P = 0.149$) (Table 1). Results were similar when stratifying by hospitalization period (Supplementary Table 3) or severity of COVID-19 at baseline (Supplementary Table 4). An additional analysis also showed that exposure to higher vs lower doses of melatonin was not associated with the outcome (Supplementary Table 5).

In this multicenter observational study involving 58 562 adult patients hospitalized for COVID-19, our results suggest that melatonin use at a mean daily dose of 2.61 mg (SD = 1.43) was not associated with reduced mortality in adult patients hospitalized for COVID-19. Limitations of this study include (i) potential unmeasured confounding bias, (ii) unknown generalizability of results to outpatients and (iii) relatively reduced statistical power due to the relatively low number of patients who were prescribed melatonin at baseline ($N = 272$). A *post hoc* statistical power analysis indicates that in order to detect a statistically significant association in our sample with a statistical power of 80%, an OR of either at least 0.54/1.57 would be needed. Therefore, our study is unable to rule out a potential association that would be of lower magnitude.

Further studies are required to examine the potential relationship between melatonin use, especially at higher doses than those used in this study, and the course of COVID-19 symptoms and COVID-19-related outcomes in outpatients and hospitalized patients with COVID-19.

Supplementary data

Supplementary data are available at *JTM* online.

Data Availability Statement

Data can be available upon request from AP-HP Health Data Warehouse (EDS) at https://eds.aphp.fr//.

Author contributions

M.S.R. contributed to the study design, performed statistical analyses and wrote the first draft of the manuscript. P.d.l.M. and J.J.H.M. performed statistical analyses and contributed to the writing of the manuscript. N.H. designed the study and critically revised the manuscript. F.L. and P.A.G. contributed to study design and critically revised the manuscript for scientific content.

Acknowledgments

The authors thank the EDS APHP Covid consortium integrating the APHP Health Data Warehouse team as well as all the APHP staff and volunteers who contributed to the implementation of the EDS-Covid database and operating solutions for this database. Collaborators of the EDS APHP

Covid consortium are: Pierre-Yves ANCEL, Alain BAUCHET, Nathanaël BEEKER, Vincent BENOIT, Mélodie BERNAUX, Ali BELLAMINE, Romain BEY, Aurélie BOURMAUD, Stéphane BREANT, Anita BURGUN, Fabrice CARRAT, Charlotte CAUCHETEUX, Julien CHAMP, Sylvie CORMONT, Christel DANIEL, Julien DUBIEL, Catherine DUCLOAS, Loic ESTEVE, Marie FRANK, Nicolas GARCELON, Alexandre GRAMFORT, Nicolas GRIFFON, Olivier GRISEL, Martin GUILBAUD, Claire HASSEN-KHODJA, François HEMERY, Martin HILKA, Anne Sophie JANNOT, Jerome LAMBERT, Richard LAYESE, Judith LEBLANC, Léo LEBOUTER, Guillaume LEMAITRE, Damien LEPROVOST, Ivan LERNER, Kankoe LEVI SALLAH, Aurélien MAIRE, Marie-France MAMZER, Patricia MARTEL, Arthur MENSCH, Thomas MOREAU, Antoine NEURAZ, Nina ORLOVA, Nicolas PARIS, Bastien RANCE, Hélène RAVERA, Antoine ROZES, Elisa SALAMANCA, Arnaud SANDRIN, Patricia SERRE, Xavier TANNIER, Jean-Marc TRELUYER, Damien VAN GYSEL, Gaël VAROQUAUX, Raphaël VERNET, Jill Jen VIE, Maxime WACK, Perceval WAJSBURT, Demian WASSERMANN, Eric ZAPLETAL.

Sources of funding

This work did not receive any external funding.

Conflict of interest

None declared.

Ethical statement

This observational study using routinely collected data received approval from the Institutional Review Board of the AP-HP Clinical Data Warehouse (decision CSE-20-20_COVID19, IRB00011591, 8 April 2020). AP-HP Clinical Data Warehouse initiatives ensure patient information and informed consent regarding the different approved studies through a transparency portal in accordance with European Regulation on data protection and authorization n°1 980 120 from National Commission for Information Technology and Civil Liberties (CNIL).

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