Commentary

Melatonin reduces the mortality of severely-infected COVID-19 patients

Dun-Xian Tan, Russel J Reiter

UT Health San Antonio, Long School of Medicine, San Antonio, TX, USA
*Correspondence: tan@uthscsa.edu, Tel: +1 210-331-8816

Received: November 25, 2021; Accepted: December 17, 2021

ABSTRACT

SARS-CoV-2 has ravaged the population of the world for two years. Scientists have not yet identified an effective therapy to reduce the mortality of severe COVID-19 patients. In a single-center, open-label, randomized clinical trial, it was observed that melatonin treatment lowered the mortality rate by 93% in severely-infected COVID-19 patients compared with the control group (see below). This is seemingly the first report to show such a huge mortality reduction in severe COVID-19 infected individuals with a simple treatment. If this observation is confirmed by more rigorous clinical trials, melatonin could become an important weapon to combat this pandemic.

Keywords: melatonin, COVID-9, severe COVID-19 patients, mortality, immune tolerance

---

A wave of SARS-CoV-2 infections has again surged and even after global devastation for almost two years there is still no clear signs of its abatement. In the advanced countries, even with high vaccination rates, this pandemic still lingers and, in some regions, the infected population persists at a relatively high level. This lagging high infection rate may be attributed in part to individuals who have not received vaccination; however, the vaccinated breakthrough cases are also reported with a high frequency (1). Due to the rapid mutation rate of this RNA virus in which the mutations are faster than progress in the development of vaccines, it is not feasible to completely eradicate all the variants of SARS-Co-2 with vaccination alone. Thus, there is a high probability that humans will have to indefinitely acclimate to COVID-19 disease but, hopefully, with lower severity and mortality.

To achieve this goal, vaccination will likely remain the primary weapon for prevention while another important arm of protection will be to identify effective medicines for the treatment of individuals who are afflicted with this disease. Presently, the pharmaceutical companies including Merck and Pfizer have developed several antiviral medications which reportedly reduce the duration of hospitalization or death of the COVID-19 patients by approximately 50 to 89% (2, 3). However, these medicines have only been effective in mild to moderately severe patients. Thus, there is still a lack of effective treatment for severe COVID-19 patients, particularly in terms of reducing their mortality. The mortality rate of COVID-19 infection in hospitalized severe patients is unacceptably high at around 15% or more (4, 5). To reduce the high mortality is a huge challenge for physicians, as well as to researchers.

The results of a newly-released clinical trial have provided some hope on a potential treatment which may indicate "light at the end of the tunnel". Hasan *et al.* (6) reported that conventional treatment plus melatonin significantly reduced mortality of severely-infected COVID-19 patients. This has not been reported previously. In this clinical trial, 158 hospitalized patients, aged 18 to 80, were enrolled who had a confirmed severe COVID-19 infection. All severe patients received standard therapy including oxygen intubation, remdesivir (as an antiviral), levofloxacin (for protection against secondary bacterial infection), dexamethasone (as an anti-inflammatory) and enoxaparin (as an anticoagulant). Among these patients, half received additionally 10 mg melatonin 20-30 minutes before bed time for 14 days following diagnosis. At the end of trial, 13 of 76 patients in the conventional therapy group died. The mortality in this group was 17.1% which is consistent with mortality rate previously reported. In contrast, in conventional plus melatonin treated group only 1 out of 82 patients died with the mortality rate of 1.2%. Thus, the death rate was reduced by 93% with melatonin treatment compared to the conventional treatment. This is a highly significant observation, especially under the current pandemic situation where no effective treatment for severe COVID-19 infections has been identified. The observation also confirmed the results of the previous retrospective study in which the authors claimed that melatonin treatment is associated with increased survival among COVID-19 patients requiring mechanical ventilation after excluding all other interventional factors including age, gender, clinical history and demographics (7).

Many studies have documented the beneficial effects of melatonin on mild to moderate COVID-19 patients (8-11) and the potential mechanisms by which melatonin interferes with a COVID-19 infection have also been widely discussed (12-15). The primary mechanisms of melatonin against SARS-CoV-2 infection are attributed to its antioxidant, anti-inflammatory and immunoregulatory activities. Melatonin mainly targets the host rather than the virus *per se* (16). Hence, melatonin lowers the overreaction of the host to the pathogen, thereby increasing the tolerance of the host to the virus. This tolerance allows the host sufficient time to develop the adaptive immune response and finally eradicate the invading pathogens. The shortcomings of the report by Hasan *et al*. (6), however, are a concern since this was a single-center, open-label, randomized clinical trial. This type of trial cannot completely avoid bias. Thus, more rigorous clinical trials including multi-centers, double-blinding, large scale and randomization should be conducted to confirm this important observation.

Compared to other medicines currently used to treat COVID-19 infections such as Regeneron monoclonal antibody ($2,100 per dose) (17), remdesivir ($3,100 for a course of treatment) (18), the cost of melatonin is negligible (less than $5 for a course of treatment). In addition, melatonin has essentially no serious side effects and can be taken orally. The characteristics of melatonin are especially suitable to the less developed countries and regions in which vaccinations and expensive medicines are not widely available. Collectively, the report of Hasan *et al.* (6) may be of high significance. If this observation is confirmed, melatonin could be an effective and inexpensive way to interrupt the course of the SARS-CoV-2 pandemic.

ACKNOWLEDGMENTS

No funding was available for this study.

AUTHORSHIP

DXT and RJR wrote and edited the paper.

CONFLICT OF INTEREST

The authors report no conflict of interest.

REFERENCES

1. Christensen PA, Olsen RJ, Long SW, Subedi S, Davis JJ, Hodjat P, Walley DR, Kinskey JC, Ojeda Saavedra M, Pruitt L, *et al*. (2021) Delta variants of SARS-CoV-2 cause significantly increased vaccine breakthrough COVID-19 cases in Houston, Texas. *Am. J. Pathol.*: S0002-9440(21)00480-6. doi:10.1016/J.AJPATH.2021.10.019.
2. Mahase E (2021) Covid-19: UK becomes first country to authorise antiviral molnupiravir. *BMJ* **375**: n2697, doi:10.1136/BMJ.N2697.
3. Pfizer's Novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in interim analysis of phase 2/3 EPIC-HR study | Pfizer Available online: https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate (accessed on Nov 24, 2021).
4. Mughal MS, Kaur IP, Jaffery AR, Dalmacion DL, Wang C, Koyoda S, Kramer VE, Patton CD, Weiner S, Eng MH, *et al.* (2020) COVID-19 patients in a tertiary US hospital: Assessment of clinical course and predictors of the disease severity. *Respir. Med.* **172**: 106130. doi:10.1016/J.RMED.2020.106130.
5. Mughal MS, Kaur IP, Wang C, Alhashemi R, Buemio A, Patton CD, Granet KM (2021) Variation in clinical characteristics, outcomes, and mortality of hospitalized patients with COVID-19 during the second wave of the pandemic: a single-center experience. *J. Investig. Med.* **69** (8): 1479-1482, jim-2021-001876, doi:10.1136/JIM-2021-001876.
6. Hasan ZT, Atrakji DMQYMAA, Mehuaiden DAK (2021) The Effect of melatonin on thrombosis, sepsis and mortality rate in COVID-19 patients. *Int. J. Infect. Dis.* **114**: 79-84. doi:10.1016/J.IJID.2021.10.012.
7. Ramlall V, Zucker J, Tatonetti N (2020) Melatonin is significantly associated with survival of intubated COVID-19 patients. *medRxiv. Prepr. Serv. Heal. Sci.* doi:10.1101/2020.10.15.20213546.
8. Castillo RR, Quizon GRA, Juco MJM, Roman ADE, Leon D.G, Punzalan FER, Guingon RBL, Morales DD, Tan D-X, Reiter RJ, Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. *Melatonin Res.* **3**: 297–310, doi:10.32794/MR11250063.
9. Alizadeh Z, Keyhanian N, Ghaderkhani S, Dashti-Khavidaki S, Shoormasti RS, Pourpak Z (2021) A pilot study on controlling coronavirus disease 2019 (COVID-19) inflammation using melatonin supplement. *Iran (remove .) J. Allergy Asthma Immunol.* **20**: 494–499, doi:10.18502/ijaai.v20i4.6959.
10. Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, Saeedi-Boroujeni A, Rezaie E, Ghaleh HEG, Aghamollaei H, Fasihi-ramandi M, *et al*. (2021**)** Efficacy of a low dose of melatonin as an adjunctive therapy in hospitalized patients with COVID-19: A randomized,

double-blind clinical trial. *Arch. Med. Res.* **S0188-4409** (21): 00141-7. doi: 10.1016/j.arcmed.2021.06.006 doi:10.1016/J.ARCMED.2021.06.006.
11. Mousavi SA, Heydari K, Mehravaran H, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Shamshirian A (2022) Melatonin effects on sleep quality and outcomes of COVID-19 patients: An open-label, randomized, controlled trial. *J. Med. Virol.* **94**: 263–271. doi:10.1002/JMV.27312.
12. Reiter RJ, Sharma R, Ma Q, Dominquez-Rodriguez A, Marik PE, Abreu-Gonzalez P (2020) Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: A mechanistic analysis. *Med. drug Discov.*, **6**: 100044, doi:10.1016/j.medidd.2020.100044.
13. Tan DX, Hardeland R (2020) Potential utility of melatonin in deadly infectious diseases related to the overreaction of innate immune response and destructive inflammation: focus on COVID-19. *Melatonin Res.* **3**: 120–143, doi:10.32794/mr11250052.
14. Cardinali DP, Brown GM, Pandi-Perumal SR (2020) Can melatonin be a potential "silver bullet" in treating COVID-19 patients? *Dis. (Basel, Switzerland)*, **8:** 44, doi:10.3390/DISEASES8040044.
15. Reiter RJ, Abreu-Gonzalez P, Marik PE, Dominguez-Rodriguez A (2020) Therapeutic Algorithm for Use of Melatonin in Patients With COVID-19. *Front. Med.* **7**: doi:10.3389/FMED.2020.00226.
16. Tan DX, Hardeland R (2020) Targeting host defense system and rescuing compromised mitochondria to increase tolerance against pathogens by melatonin may impact outcome of deadly virus infection pertinent to COVID-19. *Molecules* **25**: (19): 4410doi:10.3390/MOLECULES25194410.
17. Regeneron Announces New U.S. Government Agreement to Purchase Additional Doses of REGEN-COV™ (casirivimab and imdevimab) Antibody Cocktail Regeneron Pharmaceuticals Inc. Available online: https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-new-us-government-agreement-purchase (accessed on Nov 24, 2021).
18. Gilead's coronavirus treatment remdesivir to cost $3,120 for U.S. insured patients Available online: https://www.cnbc.com/2020/06/29/gileads-coronavirus-treatment-remdesivir-to-cost-3120-for-us-insured-patients.html (accessed on Nov 24, 2021).

This work is licensed under a Creative Commons Attribution 4.0 International License

Please cite this paper as:
Tan, D.-X. and Reiter, R.J. 2021. Melatonin reduces the mortality of severely-infected COVID-19 patients. Melatonin Research. 4, 4 (Dec. 2021), 613-616. DOI:https://doi.org/https://doi.org/10.32794/mr112500115.