



Philippine COVID-19 Living Clinical Practice Guidelines

Institute of Clinical Epidemiology, National Institutes of Health, UP Manila

In cooperation with the Philippine Society for Microbiology and Infectious Diseases

Funded by the DOH AHEAD Program through the PCHRD

EVIDENCE SUMMARY

Should melatonin be used in the adjunctive treatment of COVID-19?

Evidence Reviewers: Anna Angelica Macalalad-Josue, MD, FPCP, FPSEDM, Antonio Faltado, Jr, MD, FPCP, FPSEDM and Maria Teresa Sanchez-Tolosa, MD

RECOMMENDATION

There is insufficient evidence to recommend the use of melatonin as adjunct treatment for patients with COVID-19 infection. (*Very low quality of evidence*)

Consensus Issues

There were no consensus issues raised during the panel meeting.

Key Findings

There was only one very low quality RCT that compared melatonin with standard treatment, and it showed significant reduction in cough, dyspnea, and fatigue, and significantly shorter hospital stay and return to baseline health in those given melatonin. There was no significant difference in the proportion of patients discharged on day 14. No adverse events were observed in the use of melatonin among COVID-19 patients.

Introduction

Melatonin, a well-known anti-inflammatory and anti-oxidative molecule, is protective against acute lung injury or acute respiratory distress syndrome caused by viral and other pathogens [1]. Melatonin It is being proposed as an adjunctive therapy for patients with COVID 19 due to its antioxidant, anti-inflammatory, and immunomodulatory effects, as well as its possible antiviral action [2]. Melatonin may restore the optimal circadian rhythm from sleep-wake cycle disruption brought about by social isolation and to control delirium in severely affected patients in the intensive care unit [3].

In a case series of ten COVID-19 patients admitted in a hospital in Manila, the use of high-dose melatonin therapy resulted in clinical stabilization and/or improvement within 4-5 days. No significant adverse events were noted at high doses except for sleepiness which was deemed favorable for patients who had anxiety and symptom-related sleeping problems [4].

Review Methods

We performed a systematic literature search in online databases such as MEDLINE, CENTRAL, and Google Scholar. Additional searches in MedRxiv, WHO ICTRP, and clinicaltrials.gov were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search terms such as “melatonin,” “N-acetyl-5-methoxytryptamine,” and “COVID-19.” References from review articles were also manually searched for additional articles.



Results

The initial search from all the databases retrieved 180 references. We screened the title and abstracts of 14 references. After removing duplicates, letters, commentaries, narrative reviews, and studies not meeting the inclusion criteria, we retrieved one full text article (Appendix 1).

There is one unpublished (preprint) randomized controlled trial [5] that included 74 patients admitted for mild to moderate COVID-19. Patients were randomized to receive melatonin 3mg three times daily for 2 weeks in addition to standard of care versus standard of care alone. Both patients and outcome assessors were blinded to treatment assignment. There was no mention of allocation concealment and there was a significant drop out rate (40%), with only 44 patients included in the final per-protocol analysis. Patients receiving melatonin showed a significant improvement of cough (4.2% vs. 25%; $P = 0.045$) dyspnea (0% vs. 15%; $P = 0.049$), and fatigue (8.3% vs. 30%; $P = 0.020$). No patient died in either of the two groups. Patients in the melatonin group also had a significantly shorter hospital stay (4.65 ± 3.37 vs. 8.15 ± 5.97 ; $P = 0.021$ days). At day 14, more patients showed radiologic improvement of pulmonary involvement (4% vs 25%, RR 0.17 CI [0.21,1.3]), and a higher proportion of patients were discharged on day 14 in the melatonin group (92 vs 85%, RR 0.56 CI [0.1,3]), but both of these were not significant. After four weeks of follow-up, patients given melatonin showed a significantly faster return to baseline health than controls (15.09 ± 8.69 vs. 29.6 ± 21.12 ; $P = 0.004$). No adverse event from melatonin was observed in the trial.

Recommendations from Other Groups

Clinical practice guidelines from WHO, IDSA, US NIH, UK NHS, or PSMID made no recommendation on the use of melatonin as adjunctive treatment of COVID-19.

Ongoing Studies

There are currently 15 ongoing randomized clinical trials investigating the effect of melatonin as adjunct in the treatment of COVID-19 patients (Appendix 3).

References

- [1] Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, et al. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci* [Internet]. 2020 Jun;250(January):117583. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0024320520303313>
- [2] Cardinali DP, Brown GM, Pandi-Perumal SR. Can Melatonin Be a Potential “Silver Bullet” in Treating COVID-19 Patients? *Diseases*. 2020;8(4):44.
- [3] Brusco LI, Cruz P, Cangas A V, Rojas CG, Vigo DE, Cardinali DP. Efficacy of melatonin in non-intensive care unit patients with COVID-19 pneumonia and sleep dysregulation. *Melatonin Res*. 2021;4(1):173–88.
- [4] Castillo RR, Quizon GRA, Juco MJM, Roman ADE, De Leon DG, Punzalan FER, et al. Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. *Melatonin Res*. 2020;3(3):297–310.
- [5] Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, Saeedi-Boroujeni A, et al. Efficacy of a Low Dose of Melatonin as an Adjunctive Therapy in Hospitalized Patients with COVID-19: A Randomized, Double-blind Clinical Trial. *Authorea Prepr* [Internet]. 2020; Available from: <https://www.authorea.com/doi/full/10.22541/au.160734344.45295921/v1?commit=5be3e7266256468d59e81ff82a1b125710ba7459>



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Appendix 1: Characteristics of Included Study

Title/Author	Study design	Sample Size	Population	Intervention Group(s)	Control	Outcomes
Farnoosh, 2020	Randomized double blind, controlled trial	N=44	Mild to moderate COVID-19	Melatonin 3mg 3 times a day for 14 days	Standard of care	mortality, radiographic improvement, adverse events, symptomatic improvement



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Appendix 2: GRADE Evidence Profile

Author(s): Josue

Question: Melatonin compared to standard therapy for COVID-19

Setting: hospitalized patients with confirmed mild to moderate COVID-19 at

Bibliography: Farnoosh

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	melatonin	standard therapy	Relative (95% CI)	Absolute (95% CI)		

mortality (follow up: 4 weeks; assessed with: at day 28)

1	randomised trials	very serious	not serious	not serious	serious	none	0/24 (0.0%)	0/20 (0.0%)	not estimable		⊕○○○ VERY LOW ^{a,b}	CRITICAL
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time to clinical recovery (follow up: 4 weeks; assessed with: number of days)

1	randomised trials	very serious	not serious	not serious	serious	none	24	20	-	MD 14.51 days lower (18.86 lower to 10.16 lower)	⊕○○○ VERY LOW	IMPORTANT
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hospital length of stay (follow up: 4 weeks; assessed with: number of days)

1	randomised trials	very serious	not serious	not serious	serious	none	24	20	-	MD 3.5 days lower (6.24 lower to 0.76 lower)	⊕○○○ VERY LOW	IMPORTANT
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pulmonary involvement (radiographic) (follow up: 4 weeks; assessed with: radiographic evaluation at 14 days)



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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	melatonin	standard therapy	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious	not serious	not serious	serious	none	1/24 (4.2%)	5/20 (25.0%)	RR 0.17 (0.02 to 1.31)	208 fewer per 1,000 (from 245 fewer to 78 more)	⊕○○○ VERY LOW	NOT IMPORTANT

adverse outcome (follow up: 4 weeks)

1	randomised trials	very serious	not serious	not serious	serious	none	0/24 (0.0%)	0/20 (0.0%)	not estimable		⊕○○○ VERY LOW	CRITICAL
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CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- Imprecision downgraded due to low event rate, wide confidence interval due to small sample size
- Risk of bias downgraded due to significant drop out rate (40%), not intention-to-treat analysis



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Appendix 3: Characteristics of Ongoing Studies

TrialID	Scientific title	Population	Intervention	Outcome
	Melatonin as Adjuvant treatment for COVID-19 in Patients Requiring hospitalization (MAC19 PRO): A Randomized, Double-Blind, Placebo-Controlled Trial (RCT)	Hospitalized COVID-19	High dose melatonin	Observable clinical outcomes and tolerability
IRCT 20200411047030N 1	Evaluation of adding melatonin to routine treatment on outcomes and quality of sleep in COVID-19 patients	COVID-19	Melatonin 3mg/night (in addition to hydroxychloroquine and azithromycin)	Time to stop the fever
IRCT 20200408046988N 1	Evaluation of the efficacy of melatonin tablets as auxiliary medication in accelerating the improvement of the COVID-19 symptoms and clinical findings: A double-blind randomized and placebo controlled trial	COVID-19	Melatonin 3mg/night (in addition to HCQ)	No mention
IRCT 20151228025732N 52	A study on melatonin and Vitamin C and zinc efficacy in patients with COVID19 hospitalized in intensive care unit of Semnan Kowsar Hopsital	COVID-19	Melatonin 40mg/day	Respiratory rate
EUCTR 2020-001808-42- ES	Phase ii clinical trial, single-blind, randomized, placebo controlled to explore the effectiveness and safety of melatonin i.v. in patients with covid-19 entered into the icu (melcovid study) - melcovid	Severe COVID-19 (ICU)	Melatonin 6mg/IV	mortality
IRCT 20200506047323N 5	Evaluation of the efficacy and safety of Melatonin in patients with COVID-19: a randomized clinical trial	Moderate COVID-19	Melatonin 50mg once a day	Body temperature
IRCT 20200922048804N 1	Inflammation control in patients with COVID-19 using melatonin supplement compare to controls referred to Imam Khomani Hospital	Mild to moderate COVID-19	Melatonin 6mg x 2 weeks	headache
IRCT 20200426047206N 4	Evaluating the effect of Melatonin in prognosis and clinical improvement in patients with COVID-19: A Randomized Clinical Trial	Mild to moderate COVID-19	Melatonin 18mg 2x a day x 7 days	Need for oxygen therapy
NCT04409522	Evaluation of Therapeutic Effects of Melatonin by Inhibition of NLRP3 Inflammasome in COVID19 Patients	Moderate to severe COVID-19	Melatonin 9mg/day for 7-10 nights	No mention
NCT04474483	Safety and Efficacy of Melatonin in Outpatients Infected With COVID-19 (COVID-19)	COVID-19 (outpatient)	Melatonin 10mg 3x a day for 14 days	Cumulative Incidence of Treatment-Emergent Adverse Events
NCT04530539	The Effect of Melatonin and Vitamin C on COVID-19	Symptomatic COVID-19 (outpatient)	Melatonin 10mg at bedtime, Vitamin C 1000 mg/day, vs placebo	Symptom severity
NCT04531748	Selective Estrogen Modulation and Melatonin in Early COVID-19	COVID-19	Toremifene 60mg + Melatonin 100mg vs	Peak increase in COVID-19



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TrialID	Scientific title	Population	Intervention	Outcome
			Melatonin 100mg; vs placebo	Sign and Symptom score
NCT04568863	A Phase II, Single-center, Double-blind, Randomized Placebo-controlled Trial to Explore the Efficacy and Safety of Intravenous Melatonin in Patients With COVID-19 Admitted to the Intensive Care Unit (MelCOVID Study)	Severe COVID-19 (ICU)	Melatonin 7 days of 5 mg per Kg of actual body weight per day of intravenous melatonin every 6 hours	mortality
NCT04570254	Open Clinical Trial of the Use of Antioxidants and Pentoxifylline as Adjuvant Therapy to Standard Therapy in Patients With and Without Septic Shock Secondary to COVID-19 Severe Pneumonia	Severe COVID-19	Vitamin C vs Vitamin E vs Melatonin 50mg/day vs N-acetyl cysteine, in addition to Pentoxifylline	Death from any cause; Percentage of patients who required orotracheal intubation