Short Communication

Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial

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Abstract

Background: We aimed to investigate the efficacy of high-dose vitamin C, melatonin, and zinc in patients with severe Covid-19.

Materials and Methods: Twenty-one adult patients were randomized 1:1 to standard care alone or standard care plus IV vitamin C (2 g, q6hr), oral melatonin (6 mg, q6hr), and oral zinc sulfate (50 mg, q6hr) for 10 days. Patients were monitored for changes in hypoxemia and inflammatory markers.

Results: Both treatment modalities were effective to improve PaO2/FiO2 and oxygen saturation. However, there were no significant differences between the 2 study groups (P>0.05). There were reductions in CRP, ESR, and LDH levels in both study groups, although were not significant. No significant difference was noted in the length of ICU stay between the 2 study groups (P=0.3).

Conclusion: Our study suggests that the addition of vitamin C, melatonin, and zinc to standard care is not associated with considerable improvement in patients with severe Covid-19.

Keywords: Covid-19, Vitamin C, Melatonin, ICU, Hypoxemia

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Introduction

Coronavirus disease 2019 (Covid-19) a global pandemic is defined as an illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). At present, there is no data in the literature about the combination of vitamin C, melatonin, and zinc for treating Covid-19 (3, 4). This was our purpose. We hypothesized that combined administration of high-dose vitamin C, melatonin, and zinc can improve clinical outcomes of hospitalized patients with severe Covid-19.

Methods

Study design: This randomized, single-center, active-controlled, open-label, parallel-group, compassionate use study was performed in Kowsar Hospital, Semnan, Iran. The Institutional Ethics Committee, Semnan University of Medical Sciences approved the study coded IR.SEMUMS.REC.1399.005 while the study was registered in the Iranian Clinical Trial registry coded IRCT20151228025732N52. Diagnosis of Covid-19 was done using real-time PCR (ABI, USA) in a respiratory tract sample. Subjects with a positive Covid-19 who aged between 18 and 65 years were included. They had confirmed pneumonia, oxygen saturation (SaO2) less than 94%, and partial pressure of oxygen (PaO2) to the fraction inspired oxygen (FiO2) below 200 mmHg. Patients with severe infection who admitted to intensive care unit (ICU) were randomized 1:1 to standard care alone or standard care plus IV vitamin C (2g, q6hr), oral melatonin (6 mg, q6hr), and oral zinc sulfate (220 mg containing 50 mg elemental zinc, q6hr) for 10 days (5-7).

Our standard cares were azithromycin (250 mg/day), lopinavir/ritonavir (100mg/25mg/day), glucocorticoids, and necessary oxygen. Patients did not receive either remdesivir or tocilizumab and were excluded if they had a history of nephrolithiasis, allergy to study drugs, pregnancy, hepatic diseases with aminotransferase exceeding 5 times the upper limit of the normal range, use of fluvoxamine, sodium oxybate and alcohol, history of copper deficiency, and renal failure (estimated glomerular filtration rate of less than 30 ml/min). Also, the patients were excluded from the study for these reasons: safety, loss of follow-up, and voluntary reluctance. Informed consent forms were taken from patients or their legal representatives before trial.

Assessment of response: Changes in severity of hypoxemia (PaO2/FiO2 ratio) were the primary exploratory outcomes. In addition, inflammatory markers including lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), ferritin, and C-reactive protein (CRP) were measured at baseline, day 5, and day 10 after treatment initiation.

Data analysis: This study was a pilot study to define a sample size. Data are shown as Mean ± SD. Shapiro-Wilk was used to test the normality of data. We used x^2 and Fisher's exact test to study the associations

Table 1: Effects of treatments on PaO2/FiO2, SaO2, inflammatory markers, and WBC count.

Variable	Control group (n=10)			Treatment group (n=10)			P-value
	day 0	day 5	day 10	day 0	`day 5	day 10	
PaO2/FiO2	189 ± 40	204.1 ± 31.9	222.2 ± 65	178 ± 57	211.0 ± 29.3	230.1 ± 59.1*	0.2
SaO2 (%)	90 ± 1	93.3 ± 1	95.1 ± 2	90 ± 3	94.2 ± 1	95 ± 1.1	0.6
LDH (U/L)	665.7 ± 224	774 ± 222.1	788 ± 241.3	667.9 ± 233.7	761 ± 219.3	796 ± 231.9	0.9
ESR (mm/hr)	46.3 ± 28.6	35 ± 22.1	36 ± 24.1*	47.3 ± 28.3	39.1 ± 24.1	37.1 ± 26.8	0.08
CRP (mg/L)	10.4 ± 5.3	6.1 ± 3.6	4.4 ± 3.1*	10.3 ± 5.1	5.9 ± 3.3	4.8 ± 3.6*	0.06
Ferritin (ng/mL)	422.3 ± 187.1	523.5 ± 219.1	512.4 ± 227.5	410.7 ± 196.1	601.7 ± 228	588.3 ± 235.6	0.2
WBC count, 10^9/L	10.7 ± 4.3	9.7 ± 4.3	9.9 ± 4.3	10.9 ± 4.1	10 ± 3.9	9.1 ± 3.3	0.2
Lymphocyte (%)	18.8 ± 8.4	16.8 ± 9.4	17.1 ± 9	18.8 ± 7.9	16.1 ± 6.9	18.8 ± 9.9	0.1
Neutrophil/lymphocyte	7.8 ± 6.5	7.5 ± 6.6	7.2 ± 4.8	7.9 ± 6.9	7.9 ± 4.5	8 ± 4.6	0.5

Data are shown as mean ± SD or number (%). Analyzed by Friedman test. fraction inspired oxygen to inspired fraction of oxygen ratio (PaO2/FiO2) ratio; SaO2: arterial saturation of oxygen, LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. * $P < 0.05$ vs day 0 (baseline).

between variables. Friedman's test was used to study mean differences. $P < 0.05$ was considered as statistical significance. Analysis was carried out using SPSS software (version 14; SPSS Inc, Chicago, IL, USA).

Results

Baseline characteristics: No patient was lost to follow up and all 20 participants were observed over the course of 10 days. The range of age was about 20-65 years in both groups. The mean age was 59 ± 19 years with an excess of males (65 % vs 35 %). No significant between-group differences in patients 'characteristics were seen at enrollment.

Efficacy: As shown in Table 1, both treatment modalities improved PaO2/FiO2 and SaO2. The between-group difference was not statistically significant at day 10 ($P = 0.1$). Furthermore, no significant difference was noted in the length of ICU stay between the 2 groups (15 ± 3.3 days vs 14.1 ± 4.2 days, $P = 0.3$). There were no significant differences in deterioration of the disease (30% in the control group vs 20 % in the treatment group). After 10 days of treatment, 2 individuals (20%) did not respond to standard care. The study was stopped before the completion of treatment in 1 patient due to hypersensitivity to treatments.

Discussion

In this randomized trial, we observed for the first time that the addition of high-dose vitamin C, high-dose melatonin, and zinc to standard care was not associated with considerable improvement in patients with severe Covid-19. Overall, improvement was not different from that associated with usual care alone. Both treatment modalities had equal effects on gas exchange, LDH, ESR, CRP, ferritin, and lymphocytes. Of note, this was a hypothesis-generating study on compassionate use of drugs and confirmatory investigations are needed.

Another study indicated that high-dose vitamin C (6g/day) could not improve outcomes in patients hospitalized due to severe Covid-19 (8). Another pilot study by Zhang showed that treatment with 24 g/day vitamins for 7 days had no beneficial effects on the clinical status of patients with severe Covid-19 (9). Finally, a trial with more than 200 patients admitted to the general ward reported no significant benefit for vitamin C and zinc. Included patients received daily 8-gram vitamin C with or without 50 mg of zinc for 10 days (10).

Though vitamin C has been used in perioperative care (11), taken together, the current study did fail to open an avenue for vitamin C and other supplementary agents like zinc and melatonin in the Covid-19 era.

The most important limitation of the present study was the small sample size. We had no power-based sample size calculation.

Conclusion

Adding high-dose vitamin C, high-dose melatonin, and zinc to standard care is not associated with considerable improvement in the clinical status of patients with severe Covid-19.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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