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Applied nutritional investigation

Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19)

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ABSTRACT

Objectives: The aim of this study was to determine clinical outcomes of older patients with coronavirus (COVID-19) who received a combination of vitamin D, magnesium, and vitamin B12 (DMB) compared with those who did not. We hypothesized that fewer patients administered this combination would require oxygen therapy, intensive care support, or a combination of both than those who did not.

Methods: This was a cohort observational study of all consecutive hospitalized patients ≥50 y of age with COVID-19 in a tertiary academic hospital. Before April 6, 2020, no patients received the (DMB) combination. After this date, patients were administered 1000 IU/d oral vitamin D3, 150 mg/d oral magnesium, and 500 mcg/d oral vitamin B12 upon admission if they did not require oxygen therapy. Primary outcome was deterioration leading to any form of oxygen therapy, intensive care support, or both.

Results: Between January 15 and April 15, 2020, we identified 43 consecutive patients ≥50 y of age with COVID-19 in a tertiary academic hospital. Before April 6, 2020, no patients received the (DMB) combination. After this date, patients were administered 1000 IU/d oral vitamin D3, 150 mg/d oral magnesium, and 500 mcg/d oral vitamin B12 upon admission if they did not require oxygen therapy. Primary outcome was deterioration leading to any form of oxygen therapy, intensive care support, or both.

Conclusions: A vitamin D / magnesium / vitamin B12 combination in older COVID-19 patients was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen therapy.
support, intensive care support, or both. This study supports further larger randomized controlled trials to ascertain the full benefit of this combination in ameliorating the severity of COVID-19.

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Introduction

The coronavirus (COVID)-19 pandemic, which began in late 2019, has raged across the globe with >20 million infections and 700 000 deaths recorded to date. A broad theme of immune hyperinflammation has emerged as a key determinant of patient outcome with uncontrolled immune response postulated as a pathophysiologic factor in disease severity. Intuitively, immunomodulation becomes an attractive potential treatment strategy. In addition to lung involvement, gastrointestinal symptoms are frequent and carry a worse prognosis [1]. Therefore, COVID-19 is a multorgan phenomenon and it is becoming evident that appropriate systemic inflammatory control is necessary for overall survival benefit. Age > 50 y, hypertension, diabetes, and coronary artery disease, are also known patient factors associated with increased severity and death [2].

Much of the current therapeutic effort is targeted at viral elimination instead of pre-emptively modulating hyperinflammation. A number of immunomodulatory agents may serve the latter role. Vitamin D, for instance, has a protective effect against respiratory tract infection [3]. Magnesium enhances vitamin D function in addition to being an antihypertensive, antithrombotic, and bronchodilator [4,5]. Vitamin B12 is an important modulator of gut microbiota [6]. Importantly, these compounds are generally safe and well tolerated by patients. A short course of vitamin D/magnesium/vitamin B12 supplements (DMB) upon diagnosis of COVID-19 could potentially exert synergistic effects to modulate host immune response, ameliorate COVID-19 severity, and reduce adverse outcomes. This study was conducted to evaluate the potential efficacy of DMB on progression of COVID-19 to severe disease.

Methods

Study design

This study was approved by the Institutional Ethics Committee of Singapore General Hospital with waiver of consent granted. We included all consecutive COVID-19 patients >50 y of age admitted to Singapore General Hospital, a tertiary academic hospital, between January 15 and April 15, 2020. Diagnosis required a positive severe acute respiratory syndrome coronavirus (SARS-CoV)-2 polymerase chain reaction (PCR) from nasopharyngeal or throat swab. Primary outcome was defined as the requirement of oxygen therapy when oxygen saturation fell <95% detected by pulse oximetry, intensive care unit (ICU) support, or both. As the COVID-19 situation evolved, we decided to start DMB beginning April 6, 2020 on COVID-19 patients >50 y of age if they did not require oxygen therapy when oxygen saturation fell <95% detected by pulse oximetry, intensive care unit (ICU) support, or both. This study supports further larger randomized controlled trials to ascertain the full benefit of this combination in ameliorating the severity of COVID-19.

Forty-three consecutive patients were identified, with 17 patients in the DMB arm and 26 in the control arm. Baseline demographic and clinical characteristics were significantly different for age between the two groups (Table 1). In the treatment arm, most patients received DMB within the first day of hospitalization with a median duration of therapy of 5 d (IQR = 4 to 7 d). Significantly fewer patients receiving DMB required subsequent oxygen therapy compared with controls (3 of 17 vs 16 of 26; P = 0.006; Table 1). On univariate analysis, increasing age and hypertension demonstrated significantly higher OR for oxygen therapy, whereas exposure to DMB therapy was associated with a significantly improved OR (Table 2). Multivariate analysis showed that DMB remained a significant protective factor against clinical deterioration after adjusting for age or hypertension separately. Eight of the 16 patients who needed supplemental oxygen therapy in the control group also required further ICU support. Of the three

| Table 1 |
|-----------------|
| **Baseline characteristics** |
| **DMB (n = 17)** | **Control (n = 26)** | **P-value** |
| **Demographic characteristics** | | |
| Age, y, mean (SD) | 58.4 (7) | 64.1 (7.9) | 0.021 |
| Male, n (%) | 11 (64.7) | 15 (57.7) | 0.755 |
| Female, n (%) | 6 (35.3) | 11 (42.3) | 0.755 |
| Comorbidities, n (%) | | | |
| Diabetes | 6 (35.3) | 18 (69.2) | 0.066 |
| Hypertension | 0 (0) | 6 (23.1) | 0.006 |
| Hyperlipidemia | 5 (29.4) | 15 (57.7) | 0.118 |
| CVD | 1 (6) | 6 (23) | 0.376 |
| Asthma/COPD | 2 (11.7) | 2 (7.7) | 1.000 |
| Stroke | 0 (0) | 2 (7.7) | 0.511 |
| **Clinical features** | | | |
| Normal CXR on admission, n (%) | 7 (41.2) | 7 (26.9) | 0.507 |
| Time from onset of symptoms to admission, d, median (IQR) | 7 (1–9) | 5 (3–8) | 0.455 |
| Time from onset of symptom to initiation of therapy, d, median (IQR) | 7 (4–10) | 1 (0–1) | |
| Duration of therapy, d, median (IQR) | 5 (4–7) | 3 (1/2/0), 17.6 | |
| Treatment with Kaletra/remdesivir/hydroxychloroquine, n (respective numbers), % | 3 (17.6) | 16 (61.5) | 0.006 |
| **Outcome** | | | |
| - Requiring oxygen therapy (including ICU support), n (%) | 3 (17.6) | 16 (61.5) | |
| - Requiring oxygen therapy but no ICU support, n (%) | 2 (11.8) | 8 (30.8) | |
| - Requiring ICU support, n (%) | 1 (5.9) | 8 (30.8) | |
| - Mortality, n (%) | 0 (0) | 0 (0) | |

CVD, cardiovascular disease; CXR, chest x-ray; DM, diabetes mellitus; DMB, vitamin D, magnesium, vitamin B12; ICU, intensive care unit; IQR, interquartile range. P-values < 0.05 are highlighted in bold.

primary demographic and clinical characteristics and outcomes of the patients given DMB therapy and control patients
patients who required oxygen therapy in the DMB group, two were started on oxygen therapy within 24 h from initiation of DMB. The third patient required supplemental oxygen therapy after 3 d of DMB supplementation, but did not require ICU support. Among the nine patients given DMB within the first week of onset of symptoms, only one patient required oxygen therapy. This patient was one of the two cases who deteriorated within 24 h of DMB initiation. Of note, there were no side effects or adverse events directly attributable to DMB. There was no death in either group during the follow-up period.

Subgroup analysis was performed by removing patients with diabetes and <60 y of age, in order to better match the DMB and control groups (Table 3). Thirteen patients were excluded and the baseline characteristics did not differ between the two groups. One-fourth of the patients in the DMB group required oxygen therapy or ICU support compared with more than half (58%) of the controls.

Discussion

COVID-19 is now understood to be potentially life-threatening in ≤20% of patients. As the world awaits an effective vaccine, the effectiveness of various antivirals are largely muted by lack of survival benefit. Targeted therapies against cytokines and antithrombotic agents may only address the terminal events in severe cases with limited benefits. At the point of giving DMB to older patients, it became obvious that preemptive downregulation of hyperinflammation with relatively safe agents was an attractive alternate strategy. This combination was chosen based on substantial, albeit indirect evidence of their role in tempering the inflammatory response to viral infections. Vitamin D, through its effect on nuclear factor-κB and other pathways, can attenuate various proinflammatory cytokines mediating the uncontrolled cytokine storm seen in severe COVID-19 with deficiency associated with severe COVID-19 [7]. Magnesium is critical in the synthesis and activation of vitamin D, acting as a cofactor in many of the enzymes involved in vitamin D metabolism. Vitamin B₁₂ is essential in supporting a healthy gut microbiome, which has an important role in the development and function of both innate and adaptive immune systems [8]. This could be pivotal in preventing excessive immune reaction [9], especially in COVID-19 patients with microbiota dysbiosis, which has been associated with severe disease [10].

Our results provide early positive evidence of an immunomodulatory approach to ameliorating severe outcomes in COVID-19. DMB-treated patients were significantly less likely to require oxygen therapy than controls. Among three DMB-treated patients with clinical deterioration, two likely deteriorated within 24 h from their underlying infection but were included in an intention-to-treat analysis. Had they been excluded on the basis of inadequate time of DMB exposure, the demonstrated benefits would have been more profound. The last patient who deteriorated was started on DMB 7 d after onset of symptoms. To benefit from its preemptive effects, patients may need to be started earlier in the infective course. The ease of administration of DMB should allow for early initiation in the primary care setting at first onset of symptoms, or as prophylaxis among high-risk contacts during outbreaks in identified clusters.
As all agents in this combination are readily available, safe, and inexpensive, DMB can benefit a large swath of the world population, especially in economically challenged countries with limited or late access to vaccines and other therapies. DMB may also exhibit a generic efficacy against other viral infections with similar pathologic mechanism.

The limitations of this study included its retrospective cohort design with the control arm being older and showing a trend of having more comorbidities, especially diabetes. However, subgroup analysis excluding these factors still demonstrated a lower proportion of the DMB group requiring oxygen therapy or ICU support than the controls (25 versus 58%, respectively). The benefits of DMB were retained, although statistical significance could not be demonstrated, considering the small number of patients in this subgroup analysis. Post hoc estimation of necessary sample size was performed using two-sided Fisher’s exact test with assumed proportion of primary outcomes of requirement of oxygen therapy, ICU support, or both in the DMB and control groups to be 40% and 80%, respectively and the significance level of the test set as 5%. The necessary sample size was estimated to be 28 patients for both the DMB and control groups, requiring 56 patients. This study was conducted under difficult dynamic circumstances and is thus limited by the small sample size, which was smaller than our post hoc estimation. Additionally, we were not able to include systematic biological measures to support our findings.

Nonetheless, this proof-of-principle effort has yielded promising results supporting the benefit of the vitamin D / magnesium / vitamin B12 combination in preventing clinical deterioration in patients at high risk. Our findings will need to be further validated in a well-designed randomized controlled trial.

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