EFFECTIVENESS OF VITAMIN D3 IN THE FORM OF CALCIFEDIOL AS ADDITION TO STANDARD THERAPY IN INPATIENT COVID-19 PATIENTS

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ABSTRACT

Background: COVID-19 is caused by the SARS-CoV-2 virus and was declared a pandemic in early 2020. Moderate degree COVID-19 patients are generally hospitalized and receive several treatment regimens. Vitamin D3 is one of the additions to the standard therapy of COVID-19. Calcifediol is a more potent vitamin D3, able to increase serum 25OHD levels rapidly. However, it is not yet known the effectiveness of calcifediol in reducing mortality and worsening of COVID-19. **Objective:** Figure out the effectiveness of calcifediol and standard therapies in reducing mortality or clinical worsening of COVID-19 hospitalization patients.
Methods: The literature search was conducted through five databases: Pubmed, Cochrane, EBSCO, ProQuest, and Scopus. Three literatures that matched clinical questions and eligibility criteria were then critically examined using Oxford's Center for Evidence-Based Medicine (CEBM) and Critical Appraisal Skills Program (CASP) forms.
Result: The three selected studies include one RCT and two cohort studies. All studies used calcifediol at doses of 0.266 mg/capsule and standard therapy according to hospital protocol. All three studies suggest that calcifediol and standard therapy can lower the risk of mortality compared to standard therapy use alone, two studies suggest it can reduce clinical worsening in the form of ICU admission.
Conclusion: Administration of calcifediol in addition to standard therapy of COVID-19 inpatients results in a better decrease in mortality and clinical worsening than standard therapy alone.
Keywords: Calcifediol, COVID-19, standard therapy, hospitalization

ABSTRAK

Latar Belakang: COVID-19 disebabkan oleh virus SARS-CoV-2 dan dinyatakan sebagai pandemi pada awal tahun 2020. Pasien COVID-19 derajat sedang umumnya dirawat di rumah sakit dan mendapat beberapa regimen pengobatan. Vitamin D3 merupakan salah satu tambahan terapi standar COVID-19. Kalsifediol merupakan vitamin D3 yang lebih poten, mampu meningkatkan kadar 25OHD serum lebih cepat. Namun belum diketahui efektivitas kalsifediol dalam menurunkan mortalitas dan perburukan COVID-19.
Tujuan: Mengetahui efektivitas kalsifediol dan terapi standar dalam menurunkan mortalitas atau perburukan klinis pasien COVID-19 rawat inap
Metode: Pencarian literatur dilakukan melalui lima basis data: Pubmed, Cochrane, EBSCO, ProQuest, dan Scopus. Ditemukan tiga literatur yang sesuai pertanyaan klinis dan kriteria eligibilitas kemudian ditelaah secara kritis menggunakan formulir CEBM dan CASP.
Hasil: Tiga studi yang terpilih meliputi satu RCT dan dua penelitian kohort. Semua studi menggunakan kalsifediol dengan dosis 0,266 mg/kapsul dan terapi standar sesuai protokol rumah sakit. Ketiga studi menyatakan kalsifediol dan terapi standar dapat menurunkan risiko mortalitas lebih rendah dibandingkan dengan penggunaan terapi standar saja, dua studi menyatakan dapat menurunkan perburukan klinis berupa admisi ICU.
Kesimpulan: Pemberian kalsifediol sebagai tambahan terapi standar pasien rawat inap COVID-19 menghasilkan penurunan mortalitas dan perburukan klinis lebih baik dibandingkan terapi standar saja
Kata Kunci: Kalsifediol, COVID-19, terapi standar, rawat inap

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INTRODUCTION

In late December 2019, an unknown cause of pneumonia was reported in Wuhan, China. On February 11, 2020, the disease was named *coronavirus disease 2019* (COVID-19), a highly contagious disease caused by SARS-CoV- 2.[1,2] The World Health Organization (WHO) declared that COVID-19 is a pandemic on March 11, 2020. The first confirmed case of COVID-19 in Indonesia was found four months after the first case in Wuhan, as many as two cases.[1] Limiting the spread of this virus and its variants has become an increasingly worrying issue, as many countries experience a second or third wave and the emergence of mutant virus variants. Based on WHO epidemiological updates As of June 22, 2021, four SARS-SoV-2 *variants of concern* (VOC) have been identified since the start of the pandemic: alpha (B. 1.1.7), beta (B.1.351), gamma (P.1), and delta (B.1.617.2).[3] On March 1, 2021, two cases of COVID-19 variant B.1.1.7 were found in Indonesia.[4] The vaccine is a form of effort to deal with COVID-19, the types of vaccines circulating in Indonesia include Sinovac, Sinopharm, AstraZeneca, and Moderna.[5]

In addition to reducing the severity of the disease when infected with SARS-CoV-2 with the vaccine, the management of COVID-19 itself is divided based on the severity of symptoms, divided into asymptomatic, mild, moderate, severe/severe pneumonia, and critical. In moderate-grade patients, there are clinical signs of pneumonia but with oxygen saturation 93% with room air. Patients with moderate-grade COVID-19 need to be hospitalized and given standard therapy in the form of oxygen, fluid therapy, complete rest, adequate calorie intake, and taking certain drugs. Drugs given to patients with moderate COVID-19 include vitamin C, azithromycin, and antivirals in the form of favipiravir or remdesivir, symptomatic treatment, treatment of comorbid diseases, and prophylactic anticoagulants according to the doctor's evaluation.[1]

In addition, vitamin D is also given as a supplement or drug, at a dose of 400-1000 IU/day or 1000-5000 IU/day, respectively.[6] It has been suggested that activation of vitamin D receptor signalling may benefit ARDS by reducing cytokine storm, modulating neutrophil activity, regulating the renin-angiotensin system, and maintaining the integrity *barrier* of the pulmonary epithelial.[7] Another form of vitamin D, calcifediol, is the result of the hydroxylation of cholecalciferol to 25-hydroxy-vitamin D3 (25OHD) in the liver. Calcifediol has several advantages over cholecalciferol, namely by increasing serum 25OHD more quickly, being more potent so that it requires a smaller dose and is absorbed more quickly in the intestine.[8,9]

CASE ILLUSTRATION

A man, 61 years old, had a fever that went up and down with the highest temperature of 38,5^{o}C since 5 days before hospitalization. Fever could be reduced with febrifuge, but fever returns, and the patient feels weak when fever occurs. The patient felt short of breath, especially when doing strenuous activities and had a cough without phlegm. The patient was declared a positive confirmed patient for COVID-19, moderate grade with pneumonia, type II diabetes mellitus receiving insulin therapy, and hypertension with controlled blood pressure. The patient received therapy in the form of remdesivir, vitamin C, paracetamol, levofloxacin, zinc, as well as drugs for comorbid diseases such as T2DM and hypertension. In addition, the patient received vitamin D3 therapy 2x1000 Units during the treatment, written with the active ingredient calcifediol. The patient asked the doctor whether taking calcifediol as an adjunct to the therapy he is receiving can be beneficial for his disease. Therefore, a literature search was carried out to compile evidence-based case reports.

Clinical Question

The clinical question formulated in this report is "Does the combination of calcifediol and standard therapy in COVID-19 patients result in a better reduction in mortality or clinical deterioration than standard therapy alone?". The PICO component in this report consists of: Confirmed COVID-19 patients (Patient/Problem), administration of calcifediol and standard therapy (Intervention), standard therapy alone (Comparison), clinical worsening or mortality (Outcome). The clinical question type is intervention.

STUDY METHOD

Searching Strategy

Literature searches were carried out through various electronic databases using Pubmed, Cochrane, EBSCO (MEDLINE), ProQuest, and Scopus from 14th to 15th of August 2021. Literature search strategy using the keywords "Calcifediol" or "Calcidiol" or "25 hydroxyvitamin D3" and "COVID-19" with Boolean operators AND and OR. The search strategy, the number of articles from the search results, and the number of articles selected for critical review are listed in Table 1.

Table 1. Literature Searching Strategy

Database	Searching Strategy	Hits	Selected
Pubmed	((calcifediol[MeSH Terms]) OR (calcidiol[MeSH Terms])) AND ("covid 19"[MeSH Terms]) Filters: Meta-Analysis, Randomized Controlled Trial	1	1
Cochrane	"calcifediol" in Keyword OR "calcidiol" in Keyword OR 25 Hydroxycholecalciferol in Title Abstract Keyword OR 25 hydroxyvitamin D3 in Title Abstract Keyword AND "SARS-CoV" in Keyword - (Word variations have been searched)	6	0
EBSCO - MEDLINE	((MM "COVID-19") OR (MM "SARS-CoV-2")) AND TI calcifediol	1	1
ProQuest	ti(calcifediol) OR ti(calcidiol) AND ti(COVID 19)	55	1
Scopus	(TITLE-ABS-KEY (calcifediol) OR TITLE-ABS-KEY (calcidiol) OR TITLE-ABS-KEY (25-hydroxycholecalciferol) OR TITLE-ABS-KEY (25-hydroxyvitamin AND d3) AND TITLE-ABS-KEY (covid-19) OR TITLE-ABS-KEY (sars- cov- 2)) AND (LIMIT-TO (PUBSTAGE , "final")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English"))	51	0

Eligibility Criteria

The inclusion criteria in this report include that the study population in the literature is adult patients (over 18 years of age) diagnosed with COVID-19 and currently hospitalized due to COVID-19. Meanwhile, the exclusion criteria set by the authors included the use of additional therapy other than calcifediol, articles that were not

available in full text, and articles that were not in English or Indonesian.

Article Selection

Article selection was carried out in stages by excluding articles that did not fit into this evidence-based case review as shown in Figure 1. The last stage was reading the full text to evaluate the eligibility criteria, resulting in 3 articles that qualify for this report.

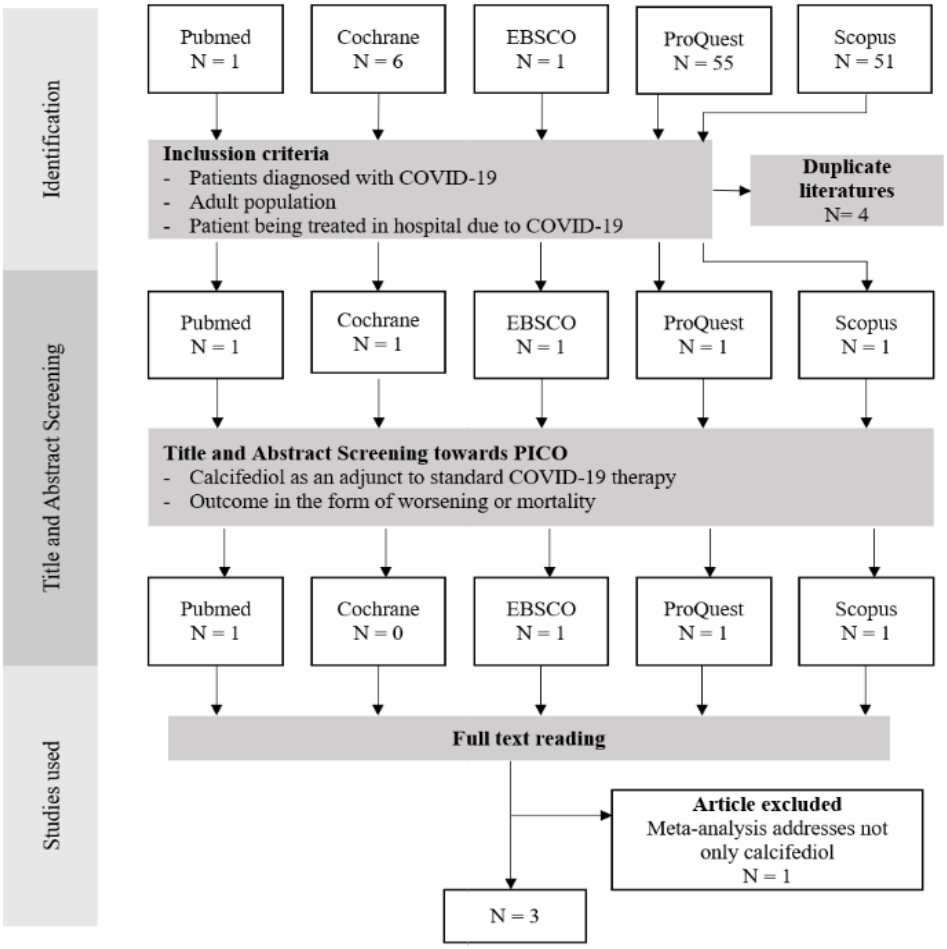

Figure 1. Search Strategy Flowchart

RESULT

Study Characteristic

One article is an RCT written by Castillo et al. published in 2020. Two articles are cohort studies written by Alcala-Diaz et al. and Nogues et al. published in 2021. The characteristics of each study are described in Table 2.

Table 2. Study Characteristic

Author (Year)	Study Design	Population	Intervention	Comparison	Outcome
Castillo et al. (2020)	Parallel pilot randomized open label, double-masked clinical trial.	Hospitalized COVID-19 patient, age 18 years, not pregnant	Calcifediol and standard therapy	Standard therapy (hydroxychloroquine, azithromycin, and antibiotics)	ICU admission and mortality
Alcala-Diaz et al. (2021)	Retrospective, multicenter, open, non-randomized cohort study.	COVID-19 patients admitted between 5 February and 5 May 2020 at 5 hospitals in Southern Spain	1st, 3rd, 7th and weekly oral calcifediol and the best available standard therapy	Best standard therapy available	Hospital mortality during the first 30 days after admission
Nogues et al. (2021)	Observational cohort	Patients with SARS-CoV-2 infection with chronic conditions and/or severe COVID-19 symptoms enrolled at admission, age 18 years	Calcifediol and standard therapy	Standard therapy (hydroxychloroquine, azithromycin, and ceftriaxone)	ICU admission and mortality

Critical Appraisal

The critical appraisal refers to the Oxford's Center for Evidence-Based Medicine (CEBM) form for RCT review and meta-analysis. Meanwhile, the cohort study design uses the CEBM and the Critical Appraisal Skills Program (CASP) form. The results of the critical appraisal are described in Table 3.

Tabel 3. Critical Appraisal Result

Author (Study design), Year	*Validity*					*Importance*	*Applicability*		
	Randomization	*Baseline*	*Allocation*	*Maintenance*	*Blinding*	*Effect size*	*Difference*	*Feasible*	*Benefits*
Castillo, *et al.* (RCT), 2020[7]	✓	✓	✓	✓	✓	Absolute risk reduction (ARR) 0,48 Number needed to treat (NNT) 2,08 Univariate risk estimate odds ratio for ICU admission in patients with Calcifediol treatment vs Without Calcifediol treatment: 0,02 (95%CI 0.002-0.17) Multivariate risk estimate odds ratio for ICU admission in patients with Calcifediol treatment vs Without Calcifediol treatment (adjusting by Hypertension and T2DM): 0.03 (95 %CI: 0.003-0.25).	✕	✓	✓
Alcala-Diaz, et al. (Retrospective cohort), 2021[10]	✕	✓	✓	✓	✕	Absolute risk reduction (ARR) 0,15 Number needed to treat (NNT) 6,67 The OR of death among patients treated with calcifediol (mortality rate of 5%) was 0.22 (95% CI, 0.08 to 0.61) compared to patients who only receive standard therapy (mortality rate of 20%; $p < 0.01$).	✕	✓	✓
Nogues, *et al.* (Observational cohort), 2021[11]	✓	✓	✓	✓	✕	Of the 447 patients treated with calcidiol on admission, 20 (4.5%) required an ICU, while 82 of the 391 untreated patients (21%) (p-value <0.0001). Logistic regression of calcidiol treatment when admitted to the ICU, adjusted for age, gender, linear 25OHD level at baseline, and comorbidities, showing that the patients receiving treatment have a reduced risk of requiring ICU (OR 0.13 [95 CI %: 0.07, 0.23]) The overall mortality rate is 10%. In the Intention to Treat analysis, 21 of the 447 patients treated with calcidiol at admission died (4.7%), while 62 (15.9%) of the 391 untreated patients died (P = 0.0001). The adjusted results showed a reduced mortality risk, with an OR of 0.21 [95% CI: 0.10; 0.43]). In the second analysis, the OR obtained was 0.52 [95% CI: 0.27; 0.99].	✕	✓	✓

DISCUSSION

The three selected articles were discussing the effectiveness of vitamin D3 in the form of calcifediol as an adjunct to standard therapy for COVID-19 patients in reducing clinical deterioration or mortality. The literature by Castillo et al. is a parallel pilot randomized open label, double-masked clinical trial that discusses the effects of calcifediol and the best available standard therapy versus standard therapy alone on ICU admission rates and mortality in COVID-19 patients. Limitations of this study include that it was not conducted in a double-blind placebo-controlled design and that it is still a pilot study so that larger trials with matched groups are needed to provide a definitive answer.[7]

A retrospective cohort study conducted by Alcala-diaz et al. was discussing calcifediol therapy and hospitalization mortality due to COVID-19. In a multivariable logistic regression analysis, adjusted for confounding factors, there was a significant difference in 30-day hospitalization mortality in patients receiving calcifediol and standard therapy compared with patients not receiving calcifediol. However, the observational design and sample size may limit the interpretation of these findings.[10]

The observational cohort study by Nogues et al. described the effect of calcifediol treatment on COVID-19-related outcomes, the outcomes being ICU admission and mortality. A total of 832 participants were included in the intention to treat analysis (ITT analysis), 447 patients received calcifediol therapy (intervention group) during admission and 391 others did not (only received standard therapy). There are 53 patients in the standard therapy-only group received calcifediol when admitted to the ICU. The strength of this literature is the administration of calcifediol since the beginning of hospital admission and upon admission to the ICU, so that it can also be observed whether calcifediol can reduce the risk of mortality in ICU patients. In addition, this study had 25OHD serum data for each patient and was adjusted for statistical analysis. However, this study was not placebo-controlled and did not perform electronic/statistical randomization.[11]

Three studies discussed used calcifediol at the same dose of 0.266 mg/capsule and were given 2 capsules on the day of hospital admission and given on days 1, 3, 7, and so on. The studies of Castillo et al. and Nogues et al. used the same standard therapy, namely hydroxychloroquine, azithromycin, and antibiotics. However, the study by Alcala-Diaz et al. only said that all patients received the best care and standard care for co-morbidities of COVID-19 patients. The standard therapy used should be updated in line with the development of treatment for COVID-19, such as the drug hydroxychloroquine which is no longer used for the treatment of COVID-19 according to WHO since June 2020.[12] Standard therapy those used should refer to the latest guidelines for the management of COVID-19 in their respective countries. In the study of Nogues et al, it was found that patients with an adequate baseline serum 25OHD level (≥ 20 ng/mL) had a lower risk of ICU admission (OR 0.30 [95% CI 0.14;0.65) and in patients who died they were found to have lower serum 25OHD levels than the living.[11]

CONCLUSION

Based on the three selected literatures, it can be concluded that the administration of calcifediol as an adjunct to standard therapy for adult COVID-19 hospitalized patients resulted in a better reduction in mortality and clinical deterioration compared to standard therapy alone. The author recommends that adult COVID-19 patients can consume calcifediol as an adjunct to standard therapy when hospitalized. Moreover, it is necessary to update the standard COVID-19 therapy used in intervention studies according to the latest guidelines for the management of COVID-19, and research on calcifediol as an adjunct to standard therapy in hospitalization of COVID-19 patients' needs to be conduct in

clinical trials with a larger scale and clearer randomization.

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