D.1.1.1 Entrenas Castillo 2020

Table 1 Entrenas Castillo 2020

Bibliographic reference	-	Entrenas Castillo, Marta; Entrenas Costa, Luis Manuel; Vaquero Barrios, José Manuel; Alcalá Díaz, Juan Francisco; López Miranda, José; Bouillon, Roger; Quesada Gomez, José Manuel; Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study.; J Steroid Biochem Mol Biol; 2020; vol. 203; 105751-105751
Study details	Trial registration number and/or trial name	NCT04366908 in NIH clinical trials database
Study details	Study type	Randomised controlled trial (RCT)
Study details	Study location	Córdoba, Spain.
Study details	Study setting	Hospital, Reina Sofía University Hospital.
Study details	Study dates	Not reported. Paper received by journal 6th July 2020.
Study details	Sources of funding	Clinical Research Program at COVID-19 “Progreso y Salud” Foundation and Foundation for Biomedical Research of Córdoba (FIBICO).
Study details	Inclusion criteria	COVID-19 confirmed by a radiographic pattern of viral pneumonia scored by CURB65 and by a positive SARS-CoV-2 PCR. Clinical samples for SARS-CoV-2 diagnostic testing were obtained according to WHO guidelines. For each patient, a sampling strategy was implemented in which samples were obtained on admission. Upper respiratory tract samples were obtained by nasopharyngeal

		exudate sampling. Procedures for RNA extraction and real-time RT-PCR (rtRT-PCR) were undertaken in the local Central Microbiology Laboratory (Code 202 MagCore® Viral Nucleic Acid Extraction Kit and Allplex™ 2019-nCoV Assay by Seegene or VIASURE SARS-CoV-2 Real Time PCR Detection Kit).Respiratory function was assessed by PaO2/FiO2 index. A chest X-ray was taken in all patients on admission All X-ray tests were evaluated by an expert team of chest radiologist.
Study details	Exclusion criteria	<18 years of age Pregnant women
Study details	Intervention(s)	Eligible patients were allocated at a 2 calcifediol:1 no calcifediol ratio through electronic randomisation performed by hospital statisticians. Participants allocated to the intervention arm took oral Calcifediol in soft capsules (0.532 mg) on the day of admission. They took another 0.266 mg of Calcifediol on days 3 and 7 and then weekly until discharge or intensive care unit (ICU) admission. They also received standard care per hospital protocol: a combination of hydroxychloroquine (400 mg every 12 hours on the first day, and 200 mg every 12 hours for the following 5 days), azithromycin (500 mg orally for 5 days) and for patients with pneumonia and NEWS score≥5, a broad spectrum antibiotic (ceftriaxone 2 g intravenously every 24 hours for 5 days) was added to hydroxychloroquine and azithromycin.
Study details	Comparator	The participants randomised to the comparator arm received standard care per hospital protocol only and no calcifediol: a combination of hydroxychloroquine (400 mg every 12 hours on the first day, and 200 mg every 12 hours for the following 5 days), azithromycin (500 mg orally for 5 days) and for patients with pneumonia and NEWS score ≥ 5, a broad spectrum antibiotic (ceftriaxone 2 g intravenously every 24 hours for 5 days) was added to hydroxychloroquine and azithromycin.
Study details	Outcome measures	COVID-19 mortality
Study details	Number of participants	N=76 n=50 randomised to intervention arm n=26 randomised to comparator arm
Study details	Duration of follow-up	Until ICU admission, death or discharge from hospital.
Study details	Loss to follow-up	No loss to follow-up.
Study details	Methods of analysis	Descriptive statistics were used for demographic, laboratory, and clinical prognostic factors related to COVID-19 for each treatment arm. The comparison between groups of quantitative

		variables were performed by using t-test for qualitative variables, Chi squared tests and Fisher's exact tests (with frequencies < 5) were used. Univariate and multivariable logistic regressions were used to estimate odds ratio and 95 % CIs for the probability of admission to ICU. Significant p-value was considered when $p < 0.05$. All the analysis has been done using IBM SPSS. The pilot trial was reported according to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.
Study details	Study limitations (reviewer)	There is a possible interaction between vitamin D and azithromycin. The standard care given to participants is not standard for the UK, limiting study applicability. Follow-up length was not noted in the study. This study was conducted during the first wave of infections. There is a difference in people being admitted to ICU between the first wave population and the second wave population. For example, in this study during the first wave patients were well enough to take capsules on admission. Blinding was incomplete and participants may have been put into ICU earlier in the comparator group than in the intervention group.
Study arms	Calcifediol (N = 50)	Participants who were randomised to receive calcifediol, the intervention.
Study arms	No calcifediol (N = 26)	Participants who were randomised to receive no calcifediol, the comparator.
Study-level characteristics	Ethnicity	(N = 76) Custom value N/A
Study-level characteristics	Body mass index	(N = 76) Custom value N/A
Study-level characteristics	Socioeconomic status	(N = 76) Custom value N/A
Study-level characteristics	Previous history of COVID-19	(N = 76) Custom value N/A
Study-level characteristics	Other supplement use	(N = 76) Custom value N/A

Study-level characteristics	Timing of vitamin D measurements	(N = 76) Custom value N/A
Study-level characteristics	Shielding status	(N = 76) Custom value N/A
Study-level characteristics	Living in care homes	(N = 76) Custom value N/A
Arm-level characteristics	Age	Calcifediol (N = 50) Mean/SD 53.14 (10.77) No calcifediol (N = 26) Mean/SD 52.77 (9.35)
Arm-level characteristics	Males	Calcifediol (N = 50) Mean/SD 56.3 (8.29) No calcifediol (N = 26) Mean/SD 52.13 (10.05)
Arm-level characteristics	Females	Calcifediol (N = 50) Mean/SD 49.43 (12.28) No calcifediol (N = 26) Mean/SD 54.13 (7.99)
Arm-level characteristics	% Female	Calcifediol (N = 50) Sample Size n = 23; % = 46 No calcifediol (N = 26) Sample Size n = 8; % = 31
Arm-level characteristics	Comorbidities	Calcifediol (N = 50) No calcifediol (N = 26)
Arm-level characteristics	≥60 years	Calcifediol (N = 50) Sample Size n = 14; % = 28 No calcifediol (N = 26) Sample Size n = 5; % = 19.23
Arm-level characteristics	Previous lung disease	Calcifediol (N = 50) Sample Size n = 4; % = 28 No calcifediol (N = 26) Sample Size n = 2; % = 7.69
Arm-level characteristics	Previous chronic kidney disease	Calcifediol (N = 50) Sample Size n = 0; % = 0 No calcifediol (N = 26) Sample Size n = 0; % = 0
Arm-level characteristics	Previous diabetes	Calcifediol (N = 50) Sample Size n = 3; % = 6 No calcifediol (N = 26) Sample Size n = 5; % = 19.23
Arm-level characteristics	Previous high blood pressure	Calcifediol (N = 50) Sample Size n = 11; % = 24.19 No calcifediol (N = 26) Sample Size n = 15; % = 57.69
Arm-level characteristics	Previous cardiovascular disease	Calcifediol (N = 50) Sample Size n = 2; % = 4 No calcifediol (N = 26) Sample Size n = 1; % = 3.85

Arm-level characteristics	At least one prognostic risk factor	Calcifediol (N = 50) Sample Size n = 24; % = 48 No calcifediol (N = 26) Sample Size n = 16; % = 61.54
Arm-level characteristics	PaO2/FiO2	Calcifediol (N = 50) Mean/SD 346.57 (73.38) No calcifediol (N = 26) Mean/SD 334.62 (66.33)
Arm-level characteristics	C-reactive protein	Calcifediol (N = 50) mg/L Mean/SD 82.93 (62.74) No calcifediol (N = 26) mg/L Mean/SD 94.71 (63.64)
Arm-level characteristics	LDH (U/L)	Calcifediol (N = 50) Mean/SD 308.12 (83.83) No calcifediol (N = 26) Mean/SD 345.81 (108.57)
Arm-level characteristics	D-dimer (ng/mL)	Calcifediol (N = 50) Mean/SD 650.92 (405.61) No calcifediol (N = 26) Mean/SD 1333.54 (2570.5)
Arm-level characteristics	Ferritin (ng/mL)	Calcifediol (N = 50) Mean/SD 691.04 (603.54) No calcifediol (N = 26) Mean/SD 825.16 (19.54)
Arm-level characteristics	IL-6 (22/48) pg/mL	Calcifediol (N = 50) Mean/SD 28.88 (75.05) No calcifediol (N = 26) Mean/SD 19.54 (19.45)
Arm-level characteristics	Use of immune suppressing treatments Immunosuppressed and transplanted	Calcifediol (N = 50) Sample size n = 6; % = 12 No calcifediol (N = 26) Sample size n = 1; % = 3.85
Outcomes	ICU admission Polarity: Lower values are better	Calcifediol (N = 50) Sample size n = 1; % = 2 No calcifediol (N = 26) Sample size n = 13; % = 50
Outcomes	Mortality Polarity: Lower values are better	Calcifediol (N = 50) Sample size n = 0; % = 0 No calcifediol (N = 26) Sample size n = 2; % = 7.69

Risk of ICU admission depending on treatment

Comparison of calcifediol vs no calcifediol on ICU admission. A statistically significant difference was identified for the variable hypertension (26 had a history of hypertension of which 11 (42 %) received Calcifediol and 15 (58 %) not (CI: - 0.58 to - 0.13; p: 0.002) and close to statistical significance for diabetes 3 (6%)

versus 5 (19 %). Therefore, a multivariable logistic regression analysis was performed to adjust the model by possible confounding variables such as hypertension and type 2 diabetes mellitus for the probability of the admission to the Intensive Care Unit.

	Calcifediol vs No calcifediol
	N1 = 50, N2 = 26
ICU admission *Polarity: Lower values are better*	
Unadjusted Univariate analysis without taking into account other variables	
Odds ratio/95% CI	0.02 (0.002 to 0.17)
Adjusted Multivariable analysis taking into account other variables	
Odds ratio/95% CI	0.03 (0.003 to 0.25)

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes

Section	Question	Answer
	Risk of bias judgement for the randomisation process	High *(2:1 [intervention:comparator] ratio not justified. Two comorbidities were unbalanced and were found to be more prevalent in the comparator group*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable

Section	Question	Answer
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Difficult or impossible for participants in the comparator group to receive vitamin D, but missing doses could have occurred for the intervention group. ITT analysis conducted.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Difficult or impossible for participants in the comparator group to receive vitamin D, but missing doses could have occurred for the intervention group.)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes

Section	Question	Answer
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low *(No missing data.)*
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably no
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Not applicable
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Low *(Objective measures of outcome conducted at one site.)*
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Yes/Probably yes
	Risk-of-bias judgement for selection of the reported result	High *(Baseline characteristics suggest problem with randomisation; Reported outcome, mortality, not analysed in multivariable analysis. Only ICU was reported in this way, even though they are both listed on the clinical trials register as outcomes. Adjustment for multivariable analysis not fully explored or reported, only hypertension and diabetes are reported as definitively included in the model but does include "others".)*
Overall bias and Directness	Risk of bias judgement	High *(Randomisation; Selection of the reported result.)*

Section	Question	Answer
	Overall Directness	Directly applicable (*There could be differences in the clinical decisions made before hospitalisation and ICU admission due to this study not being in the UK and changes over the course of the pandemic)*