Vitamin C and corticosteroids in viral pneumonia: a prospective cohort study

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Brief report

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Abstract

16 patients were admitted to a tertiary intensive care in 2019 for viral pneumonia. 11 were prescribed corticosteroids for vasopressor resistant shock, and 9 received intravenous vitamin C (1.5 g QID) at the discretion of the treating clinician. Data was collected prospectively to examine the change in PaO₂/FiO₂ ratios after administration of Vitamin C, and the association with mortality. Vitamin C did not change oxygenation, but combined with corticosteroids there was trend towards a beneficial separation in the P/F ratio over time. The use of corticosteroids was associated with a mortality benefit. These findings need confirmation in a larger study.

Wordcount 99

Background

The current COVID-19 pandemic has re-ignited the controversy surrounding corticosteroids for ARDS and viral pneumonia. (1–3) At the start of the pandemic, World Health Organisation and Surviving Sepsis guidelines gave different recommendations about the use of corticosteroids in COVID 19, based on interpretations of prior ARDS trials(4–6). Furthermore, in the search for other agents that attenuate the severity of ARDS, Vitamin C has been suggested as a potential agent.(7–9) Animals models have suggested it reduces lung injury.(10)

We describe a prospective observational cohort of patients admitted to Sir Charles Gairdner Hospital Intensive Care Unit (ICU) between June and August 2019 with presumed viral pneumonia, who required mechanical ventilation. We hypothesised that high dose intravenous Vitamin C (6g/day) could improve oxygenation in these patients.

Methods

Sir Charles Gairdner Hospital is a tertiary teaching hospital in Western Australia, with 23 ICU beds. The 2019 winter season was expected to have a significant outbreak of viral/influenza pneumonia, and in expectation of this, the treating intensive care clinicians at the hospital decided that based on the favourable safety profile of Vitamin C, and its potential benefit, could be provided to any patient with presumed viral pneumonia requiring intensive care. Viral pneumonia was determined at admission to ICU based on the combination of the prodrome (viral upper respiratory tract symptoms), acute onset, and/or radiological features (bilateral infiltrates). Data was collected on all consecutive patients admitted to the ICU for presumed viral pneumonia in winter. Patients received Vitamin C at the discretion of the treating clinician, meaning some patients received Vitamin C and others didn't (control group). Vitamin C (Rotexmedica, 1.5g QID for 3 days) was provided within 12 hours of admission to ICU, and prescribed according to the Special Access Scheme for off-label medications, with the hypothesis that it would improve oxygenation (PaO₂/FiO₂ ratio). Oxygenation change was assessed at 6 and 24 hours following administration of Vitamin C. A subgroup of patients received corticosteroids (hydrocortisone 50mg QID for up to 7 days or until clinical improvement) for vasopressor dependent shock (usually provided when noradrenaline infusion dose exceeds 10 mcg/min). Hypothesising that, if it was to have an effect on oxygenation, it would occur within 24 hours, the primary outcome assessed was the change in PaO₂/FiO₂ ratio in the 24 hours following administration of Vitamin C (measured at 6 and 24 hours). Since not all patients received either vitamin C or corticosteroids, we collected the same data in this comparator group. Secondary outcomes included mortality, length of mechanical ventilation and intensive care stay.

Descriptive summaries consisted of frequency distributions for categorical data and medians and interquartile ranges (IQRs) for continuous data. Categorical and non-normally distributed variables were analysed by Chi-squared and Mann-Whitney U tests, respectively. To analyse change in P/F ratio over time, repeated measures of two way ANOVA was used. As a sensitivity analysis to reduce the risk of type I error with our small sample size, multiple permutations (repeated for 10,000 times) were used to adjust for the p value generated for any predictors that were predictive of mortality. Statistical analysis was conducted using Stata 15.0 (StataCorp LLC, College Station, Texas).

Approval for the study was granted as a quality improvement project for monitoring of outcomes of patients with presumed viral pneumonia admitted to the Intensive Care (SCGH # 32985), with a waiver for ethics approval.

Results

Table 1 outlines the demographic and clinical characteristics of the 16 patients. There was no significant difference in illness severity (APACHE II) between the steroid or Vitamin C groups. 7/16 patients had bacterial or fungal pathogens detected in their sputum samples, and were treated according to the sensitivity results.

Table 1. Characteristics of the patients (n=16)

Variable	Mean (interquartile range) unless stated otherwise
Age, years	67 (58-80)
Female, no. (%)	7 (44)
APACHE II score	18.5 (13.3-22.8)
Number of quadrants with infiltrates on chest X-ray	2 (0-3)
Inspired oxygen concentration (FiO ₂) before initiation of vitamin C, %	50 (43-60)
Arterial oxygen tension (PaO ₂) before initiation of vitamin C, mmHg	86 (73-115)
PaO ₂ / FiO ₂ ratio before initiation of vitamin C, mmHg	173 (135-251)
Length of invasive mechanical ventilation, hours*	216 (96-444)
Requiring vasopressors, no. (%)	11 (69)
Requiring renal replacement therapy, no. (%)	4 (25)
Treated with systemic corticosteroids, no. (%)	11 (69)
Treated with high-dose vitamin C, no. (%)	9 (56)
Treated with both corticosteroids and vitamin C, no. (%)^	7 (44)
Treated with oseltamivir, no. (%)	14 (88)
Viral organism confirmed on nasal polymerase chain reaction, no. (%):	7 (44)
- <i>Influenza A</i>	1 (6)
- <i>Influenza B</i>	4 (25)
- <i>Respiratory syncytial virus</i>	3 (19)
- <i>Negative</i>	1 (6)
- <i>Not obtained (before death)</i>	
Coexisting non-viral organisms in sputum or blood, no. (%):#	1 (6)
- <i>Gram positive bacteria (enterococcus)</i>	4 (25)
- <i>Gram negative bacteria (haemophilus, pseudomonas, klebsiella, e.coli)</i>	5 (31)
- <i>Non-bacterial including fungal (such as Candida species & Aspergillus)</i>	9 (56)
- <i>Not identified</i>	
Co-morbidity, no. (%)	4 (25)
- <i>Chronic obstructive airway disease / asthma</i>	2 (13)
- <i>Immunosuppressed (with active cancer or chemotherapy)</i>	
Hospital mortality, no. (%)	5 (31)

*Only data from 9 patients who were invasively ventilated were included; 6 patients treated with only non-invasive ventilation and also one treated only with high flow nasal oxygen were not included.

#Some patients had more than one type of coexisting organisms isolated.

APACHE, Acute Physiology and Chronic Health Evaluation, illness severity score.

^ 3 patients received neither Vitamin C nor corticosteroids.

Table 2 outlines the mortality for patients receiving either corticosteroids, Vitamin C or the combination. The association between corticosteroids and mortality in our cohort remained unchanged after adjustment for multiple permutations (Chi Square = 8.045, $p = 0.0118$).

	Survived	Died	p
Received corticosteroids	10/11	1/11	0.001
Received Vitamin C	6/9	3/9	0.84
Received both Vitamin C and corticosteroids	6/7	1/7	0.21

Length of mechanical ventilation or duration of ICU stay was not statistically different between the groups receiving both Vitamin C and corticosteroids, or either agent alone.

Discussion

The administration of Vitamin C did not change oxygenation in these patients with presumed viral pneumonia. This is consistent with previous studies, although while the CITRIS-ALI study did not show any change in sequential organ failure (SOFA) scores, the unadjusted mortality was much lower in the Vitamin C group.(8,11) It may be that a higher dose of Vitamin C may have more effects than the dose that we used.(12) Combined with corticosteroids, there did start to be a non-statistically significant beneficial separation in the P/F ratio over time. It is important to note that the administration of Vitamin C to critically ill patients has not been associated with any significant adverse effect.(8,13)

This small study also suggests a mortality benefit for corticosteroids in patients with viral pneumonia and ARDS. The recently published RECOVERY Trial in COVID showed a reduced mortality in COVID-19 patients requiring oxygen from 6mg of dexamethasone daily (14,15). The dose of corticosteroids used here was 50mg QID, which is approximately equivalent to 7.5mg of dexamethasone daily. In this cohort, 10/11 patients who received corticosteroids survived, as compared to the 5 patients who died, only one of the five received corticosteroids. Prior studies for corticosteroids in ARDS are controversial, but perhaps low dose steroids do reduce duration of mechanical ventilation.(16,17) Current recommendations advise against corticosteroids for influenza pneumonia, but in critically ill patients on vasopressors, there is a contrary recommendation to suggest steroids for vasopressor refractory shock.(18,19) Vitamin C has been already used in COVID 19 patients requiring mechanical ventilation and studies are underway looking at the combination of Vitamin C and corticosteroids in COVID-19. (20)

There are several limitations to this study. It was not randomised study, and while the illness severity did not vary between groups, it is possible that the results reflect bias from unaccounted variables. Indeed, while all patients received non-invasive ventilation as a minimum, only 9 of the 16 patients were mechanically ventilated. Second, the viral pathogen was not the same for all patients, and it may be that ARDS from influenza (which has a treatment in oseltamivir) is not the same process as ARDS from RSV. Finally, as a single centre study, these questions require testing in a larger, multi-centre study.

Conclusion

In patients with viral pneumonia admitted to ICU, corticosteroids were associated with a mortality benefit, and when combined with Vitamin C, they may improve oxygenation. These findings need confirmation in a larger study.

Declarations

Ethics approval

Approval for the study was granted as a quality improvement project for monitoring of outcomes of patients with presumed viral pneumonia admitted to the Intensive Care (SCGH # 32985), with a waiver for ethics approval.

Consent for publication

Not applicable.

Availability of data

The data that support the findings of this study are available on reasonable request from the corresponding author MA. The data are not publicly available due to the current approvals, but this could be re-considered on application.

Competing interests

The authors declare that they have no competing interests.

Funding

This was an unfunded study.

Author contributions

MA, BW conceived of the study. JL, EM, RP collected the data. MA, KH were responsible for the data analysis. All authors contributed to and approved the final paper.

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Figures

Figure 1

Figure 1. a) P/F ratio over time in patients who received Vitamin C

Figure 2

Figure 1. b) P/F ratio over time in patients who received Vitamin C and corticosteroids