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Use of ascorbic acid in patients with covid-19 pneumonia

Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione
ARNAS Civico-Di Cristina-Benfratelli di Palermo

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Title	**Use of ascorbic acid in patients with covid-19 pneumonia**
Rationale for the Study	Different studies showed that ascorbic acid (vitaminC) positively affects the development and maturation of T-lymphocytes, in particular NK (natural Killer) cells involved in the immune response to viral agents. It also contributes to the inhibition of ROS production and to the remodulation of the cytokine network typical of systemic inflammatory syndrome. Recent studies have also demonstrated the effectiveness of vitamin C administration in terms of reducing mortality, in patients with sepsis hospitalized in intensive care wards. Given this background, in the light of the current COVID-19 emergency, since the investigators cannot carry out a randomized controlled trial, it is their intention to conduct a study in the cohort of hospitalized patients with covid-19 pneumonia, administering 10 gr of vitamin C intravenously in addition to conventional therapy.
Main end-point	In-hospital mortality
Surrogate end-points	• Reduction of PCR levels > 50% in comparison with PCR levels at the admission, within 72 hours after the administration • Lactate Clearance • Hospital stay • Resolution of symptoms • Duration of positive swab • Resolution of tomography imaging
Study design	Uncontrolled open label longitudinal study
Setting	Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione ARNAS Civico-Di Cristina-Benfratelli di Palermo
Duration of the study	Undefined
Sample size	Consecutive patients with COVID-19 pneumonia admitted to ARNAS Civico-Di Cristina-Benfratelli, Palermo

Data Collection	For each patient will be considered: • Sex • Age • Origin • Comorbidities • Drugs • PAO • Sp02 • BUN • Creatinine • Electrolytes • Glicaemia • Blood count • PCR • PCT • SOFA score at the admission • Liver function • Coaugulation • Hemogasanalysis • Thorax tomography • Lactate Clearance • Lenght of hospital stay
Inclusion criteria	• In case of doubt of interstitial pneumonia with indications for intubation • Positive swab test of SARS-CoV-2 • Interstitial pneumonia • Signature of informed consent
Exclusion criteria	• Unsigned informed consent • Negative swab test of SARS-CoV-2
Statistical analysis	Stata Statistical Software: Release 14.1. College Station, TX: StataCorp LP) was used for database management and analysis.
Ethics	The data will be collected in accordance to art. 13 and 23 of D. L.gs. n. 196/2003 and current regulations. The study will be conducted according to the rules established by the standards of Good Clinical Practice and according to the "Helsinki Declaration". Medical practices are carried out according to the most recent recommendations of the World Medical Assembly (Helsinki Declaration, 1964, and subsequent amendments).

Rationale for the Study

The Sars-COV-2, has spread all over the world, in two months after its discovery in China. Outbreaks have been reported in more than 50 countries with more than 118,223 confirmed cases and 4,291 deaths worldwide. In Italy, the scenario is progressively worsening with 8514 confirmed cases and 631 deaths at 10/3/2020.

Along with the spread of this new virus there has been an increase in the number of pneumonia identified with the term novel coronavirus (2019-nCoV)-infected pneumonia (NCIP), which are characterized by fever, asthenia, dry cough, lymphopenia, prolonged prothrombin time, elevated lactic dehydrogenase, and a tomographic imaging indicative of interstitial pneumonia (ground glass and patchy shadows).

Recent studies have shown the efficacy of vitamin C and thiamine administration in patients hospitalized for sepsis in the setting of intensive wards in terms of mortality reduction. The use of intravenously vitamin C arises from the experimental evidence of its anti-inflammatory and antioxidant properties. Vitamin C causes a greater proliferation of natural killers without affecting their functionality. Moreover, the vitamin C reduces the production of ROS (reactive oxygen species) that contribute to the activation of the inflammosomi and, in particular, the NLRP3 that affetcs the maturation and secretion of cytokines such as IL1beta and IL-18 that are involved in the inflammatory systemic syndrome that characterized sepsis. Vitamin C blocks the expression of ICAM-1 and activation of NFKappaB that are involved in inflammatory, neoplastic, and apoptotic processes by the inhibition of TNFalfa.

For this reason, the use of vitamin C could be effective in terms of mortality and secondary outcomes in the cohort of patients with covid-19 pneumonia.

In view of the emergency of SARS-VOC-2 and the impossibility of carrying out a randomized controlled study, it is their intention to conduct an intervention protocol (administration of 10 grams of vitamin C intravenously in addition to conventional therapy) involving the cohort of hospitalized patients with covid-19 pneumonia.

Methods

An uncontrolled longitudinal study will be conducted at the Arnas Civico-di Cristina-Benfratelli National Relevance Hospital in Palermo. This study will include all patients consecutively hospitalized with positive swab test of SARS-CoV-2 and interstitial pneumonia or with interstitial pneumonia with indication of intubation. At the admission, data will be collected: personal and anamnestic information, clinical and laboratory findings such as Gender, Age, Ethnicity, Comorbidities, Drugs, blood urea nitrogen, Creatinine, Electrolytes, Blood cell count, Clearance of the lactates, PCR, PCT, SOFA score, liver function, Coagulation, Blood gas analysis, Systolic and Diastolic Blood Pressure, Sp02, Glycaemia, Body Mass Index (BMI). Length of hospital stay will be recorded. After written informed consent, 10 grams of vitamin C in 250 ml of saline to infuse at a rate of 60 drops / minute will be administered. In-hospital mortality, reduction of PCR levels > 50% in comparison with PCR levels at the admission within 72 hours after the administration, lactate clearance, length of hospital stay, resolution of symptoms, duration of positive swab (days). Resolution of the CT imaging will be analysed. Stata Statistical Software: Release 14.1. College Station, TX: StataCorp LP) was used for database management and analysis.

Ethics

The data will be collected in accordance to art. 13 and 23 of D. L.gs. n. 196/2003 and current regulations. The study will be conducted according to the rules established by the standards of Good Clinical Practice and according to the "Helsinki Declaration". Medical practices are carried out according to the most recent recommendations of the World Medical Assembly (Helsinki Declaration, 1964, and subsequent amendments).

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ATTACHMENT 1

Method for administration of Ascorbic Acid (Vitamin C).

1. Introduce yourself to the patient;

2. Check personal data;

3. Verify that the patient is suitable for treatment. Inform the patient before signing the consent. Ask for the presence of allergies to vitamin C or its excipients (methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium hydroxide);

4. Make sure that informed consent is signed in all its parts;

5. Prepare the patient by cannulating a vein with a cannula-over-needle device, preferably green (18G) or pink (20G);

6. Dilute, according to sterile procedure, 10 grams of vitamin C in 250 cc of physiological solution;

7. Administer the solution by infusing at a rate of 60 drops / minute.

8. In the absence of incompatibility studies, this medicine should not be mixed with other products;

9. Monitor the patient for at least half an hour after the infusion;

10. Observe patient-reported signs and symptoms.

Attachment 2

INFORMED CONSENT FORM FOR VITAMIN TREATMENT C

Dear Madam / Dear Sir,

This document, which we invite you to read carefully, is intended to inform you about the benefits and possible negative effects associated with the administration of Vitamin C, a water-soluble antioxidant vitamin, intravenously.

To facilitate its understanding, we report some definitions and information regarding the aforementioned therapy.

Possible side effects related to prolonged administration of vitamin C
- gastric acidity with heartburn and reflux;
-a ument excretion urine of oxalates

We therefore invite you, during the day of administration, to take at least 1.5 liters of water per day by drinking little and often.

The undersigned: Surname _____ Name _____

Clinical record n ° _____
declares to have been informed in detail about the benefits and potential negative effects associated with the intravenous infusion therapeutic treatment with Vitamin C at high doses and to have understood that this treatment may lead to the onset of undesirable effects.
On the basis of the information received, I grant my free and voluntary consent to the treatment with vitamin C.

Date: _____

Doctor’s signature Patient's signature