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Research Article

Have we done Justice to Linus Pauling's Discovery in 1970s with Regards to Utilization of Vitamin C for Prevention of Acute Respiratory Illnesses, Besides Role of Vitamin C in Current COVID19 Epidemic - A Comprehensive Review

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Abstract

At present restricted therapies are existent with regards to COVID-19. The significant antiinflammatory, immunomodulatory, antioxidant, antithrombotic, antiviral characteristics of Vitamin C makes it a promising agent for avoidance in addition to abrogate COVID-19 infection, thus has a role as an adjunctive treatment for the critical care of COVID-19. Here we provide proof with regards to role of Vitamin C deficit in acute respiratory infections, in addition to support of the stress reaction, part of Vitamin C in avoidance as well as therapy of Pneumonia, besides sepsis as well as COVID-19. The proof till date pointed that oral Vitamin C in dosages 2-8g daily might cause reduction of incidence as well as time period of respiratory infections Here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the Me SH terms like Vitamin C; physiological stress; Pneumonia; Sepsis;, COVID-19; mode of action; stress response and Vitamin C; antiinflammatory, immunomodulatory; antioxidant; antithrombotic; antiviral characteristics; oral; intravenous regimens from 1950s till date 2021. We found a total of 1300 articles out of which we selected 50 articles for this review, as per the restrictions of journal. No meta-analysis was done. Proof showed that iv Vitamin C (6-24g daily was demonstrated to cause a reduction in mortality, hospital intensive care unit (ICU) stay besides mechanical ventilation for acute robust respiratory infections. Thus its utilization is warranted in all severe respiratory infections, any viral Pneumonias apart from COVID-19 infection without any side action plus economical.

Keywords: Vitamin C; COVID-19; Sepsis; Pneumonia; Dengue; Sepsis

Introduction

Vitamin C, alias ascorbic acid represents an essential Vitamin that possesses water solubility. In plants its generation occurs from fructose, whereas in case of animals with glucose. It is not generated by primates, in maximum bats, guinea pigs, besides in lesser quantity of birds in addition to fish as the last enzyme gulunolactone oxidase (GULO), whose requirement for ascorbic acid generation is absent secondary to gene mutations which took place before evolution of Homosapiens [1]. Hence they are dependent on Vitamin C that is existent in food. The dependency of primates on enough Vitamin C, whose provision by fruits in addition to vegetables consumption varies from 4.5g daily for gorillas [2]

to 600 mg daily for smaller monkeys (7.5 kg- that is one tenth with regards human size) [3].

The EU mean need of 90 mg daily for males as well as 80mg daily for females is for the sustenance of a normal plasma amount of 50 µmol/l [4], that is the average plasma amount of adults in UK [5]. This is adequate for the avoidance of scurvy, however might not be sufficient on exposure of an individual to viral infection as well as physiological stress. An expert committee, in collaboration with the Swiss Society of Nutrition advocated that each individual gets a supplementation of daily 200mg for taking care of the nutrient gap with regards to the common population in addition to specifically for the elder individuals, that are ≥65 yrs. The objective of this supplementation is for to bolstering the immune system [6]. The recommendations of the Linus Pauling Institute is400mg for adults over 50 yrs [7].

Pharmacokinetics studies that were conducted on healthy volunteers corroborate the daily 200mg dosage utilization of Vitamin C for generation of plasma amount of 70-90 µmol/l [8]. The occurrence of total plasma saturation amongst, 1 g/day in addition to 3g 4 hrly takes place, that is the maximum oral dose tolerated, that provides the anticipated peak plasma amount of 220 µmol/l [9]. Administration of akin dosage intravenous (iv) results in escalation of plasma amount of Vitamin C that is about, 10 times. Probability of greater consumption of Vitamin C appears to be the requirements for viral infection with 2-3g daily needed for sustenance of normal, plasma amount amongst, 60-80 µmol/l [10]. If greater plasma amounts possess any extra advantages has to be found-might be concordant with outcomes of Clinical trial detailed here.

Methods

Here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like Vitamin C; physiological stress; Pneumonia; Sepsis;, COVID-19;mode of action; stress response and Vitamin C; antiinflammatory, immunomodulatory; antioxidant; antithrombotic; antiviral characteristics; oral; intravenous regimens from 1950s till date 2021.

Results

We found a total of 1300 articles out of which we selected 50 articles for this review, as per the restrictions of journal. No meta-analysis was done.

Deficit of vitamin C in pneumonia, sepsis, COVID-19

A reduction of human plasma Vitamin C amounts occurs at fast pace in case situations, existence of physiological stress that is inclusive of infection s, injuries, in addition to surgery in general cause precipitation of observable deficiency in case of hospital admitted patients, that by definition is the plasma amount of Vitamin C<11 µmol/l [11-13]. Two studies that were conducted in Paris documented the existence of plasma amount of Vitamin C<11 µmol/l in 17-44% of patients. In case of a Canadian university hospital, its observation was that 19% of patients possessed a plasma amount of Vitamin C<11 µmol/l [11]. A study that was conducted in Australia in a surgical patients, 21% possessed a plasma amount of Vitamin C<11 µmol/l [12]. In a survey carried out on aged Scottish patients that were hospital admitted, secondary to acute respiratory infections revealed the existence of plasma amount of Vitamin C<11 µmol/l [13]. As per the UK's National Nutritional Survey, that was dependent on a cross section of the UK's population document's that 4% of65 plus people as well as 40% of them that are existent in Institutons in care homes possessed a plasma amount of Vitamin C<11 µmol/l [5], that pointed to how elderly population have a proneness of generation of key infections.

Scurvy or Vitamin C deficiency has been correlated with Pneumonia for the past decades, that gave the posit that Vitamin C deficiency might be implicated in respiratory infections [14]. In a prospective study comprising of 19,357 with men as well as women that were followed for greater than 20 yrs, the observations were that the people that were existent in the upper quartile of baseline plasma amount of Vitamin C might possess a 30% reduction in the risk of Pneumonia [15]. Moreover, a meta-analysis, pointed that a decrease in chance of pneumonia with the oral supplementation, specifically in persons with lesser dietary consumption [16].

The postmortem evaluation of robust COVID-19 have illustrated a secondary, organizing Pneumonia process [17], thus studies that have been evaluating Vitamin C association with pneumonia might be significant [13,18]. More recently, the study conducted in Newzealand, documented that patients with Pneumonia possessed depletion of amount of Vitamin C (23 µmol/l vs 56 µmol/l, $p < 0.001$). The pneumonia cohort was constituted by62% patients that presented with Vitamin C deficiency along with 22% possessed a plasma amount of Vitamin C<11 µmol/l in contrast to 8% with Vitamin C deficiency besides none with plasma amount of Vi-

tamin C<11 µmol/l in healthy controls [18]. The patients that were critically ill, thus stationed in the ICU possessed average plasma amounts of Vitamin C of 11 µmol/l. Akin observations have got demonstrated in other studies of patients who had been severely ill with Sepsis [19,20]. A study conducted in New Zealand that comprised of patients with sepsis observed that 40% possessed a plasma amount of Vitamin C<11 µmol/l, with maximum of patients had manifestation of Vitamin C deficiency (<23 µmol/l) inspite of receipt of advocated enteral in addition to parenteral consumption of the Vitamin [20].

Till now there have been rare studies that have documented the Vitamin C status of patients with COVID-19. In a study conducted in US comprising of 21 seriously ill of patients with COVID-19 that were stationed in the intensive care unit (ICU) observed that the average amount of Vitamin C 22 µmol/l, that is most had Vitamin C deficiency. The average amount of 11 patients who survived was 29 µmol/l, in contrast to 15 µmol/l in those with mortality, out of which 5 (50%) possessed a plasma amount of Vitamin C<11 µmol/l [21]. Moreover, whereas in a study conducted in Barcelona in 18 patients with COVID-19 admitted in the ICU with ARDS (acute respiratory distress syndrome) criteria their observation was a totally amount of Vitamin C that could not be detected in 17 cases (<9 µmol/l) with a patient possessing low amount of Vitamin C (14 µmol/l)) [22]. Therefore hypo Vitaminosis C is existent in general in severely ill hospital admitted patients with respiratory infections, Pneumonia, Sepsis, COVID-19 with the most probable reason being an escalation of metabolic utilization of Vitamin C [23].

Mode of vitamin C Effects in infections, sepsis, COVID-19

Vitamin C possesses significant anti inflammatory, immunomodulatory, antioxidant, antithrombotic, antiviral characteristic [24,25]. This Vitamin illustrated direct virucidal action besides possessing effector modes in both innate as well as adaptive immune systems [26]. The actions of Vitamin C on immunity at the time of infections are a lot that is inclusive of the generation addition to maturation of T lymphocytes along with the function of phagocytosis in addition to chemotaxis of leukocyte [27]. Additionally, it possesses a key part in the form of an antioxidant by which phagocytes import the oxidized Vitamin C (dehydro ascorbic acid), thus resulting in the re generation back to the reduced Vitamin C (ascorbic acid) [28].

Significantly, in addition to particularly in the context of key phase of COVID-19 aids in downregulation of cytokines, thus confers protection to the endothelium from Oxidative damage besides possessing necessary part in tissue healing [29]. The crosstalk amongst Oxidative stress (OS) as well as induction of genes that are part of the inflammatory response, that is inclusive of Tumor necrosis factor alpha (TNFα) as well as interleukin-1 (IL-1), IL-8, in addition to intercellular cell adhesion molecule [ICAM] has been demonstrated to get modulated via the activation of nuclear factor κB (NFκB) [30]. Reduction of Reactive oxygen species (ROS), as well as inflammation is further caused by Vitamin C vis amelioration of NFκB activation [31]. Significant escalation of SOD, catalase, glutathione along with Reduction of serum TNFα, besides IL-1β amounts in a rat ARDS model [32]. These actions of Vitamin C might be secondary to epigenetic control of several genes, that is up regulation of antioxidant protein in addition to down regulation of proinflammatory cytokines, instead of its direct hunting of oxidants.

Moreover, whereas, SARS CoV2 causes down regulation of the expression of type1 interferon (host's, primary antiviral defense mode) [33]. Vitamin C results in up regulation of crucial host defense protein [25]. In case of GULO knockout, mice, Vitamin C demonstrated *in vivo* anti viral immune responses in addition to a decrease in viral titres in the lung, at the time of early stages of infection, in particular against influenza virus, via escalation of generation of interferon [34]. Animal studies have documented a reduction in the incidence, in addition to robustness of bacterial as well as viral infections [35], that is inclusive of escalation of, resistance (of chick embryotracheal organ cultures to corona virus infection, beside protection of broiler chicks against avian corona virus [36].

Dependent on the isolation of angiotensin converting enzyme (ACE2) in the form of a receptor with regards to SARS CoV2 entry, a posit is that the escalation of risk of robust COVID-19 is a function of up regulation of ACE2, the way its observation is in comorbidities of diabetes mellitus (DM). cardiovascular disease (CVD) as well as hypertension [37]. The SARS CoV2 spike protein possess the capacity of binding to ACE2 [38]. Noticeably, in human, arterial endothelial cells, Vitamin C ameliorated the up regulation of ACE2 that got stimulated via IL-7 [39].

Despite, the existence of a lot of probable targets with regards to Vitamin C, at the time of infection event, replication of virus, besides pathology in COVID-19, notably, a crucial protease in the virus, Mpro, that works for the activation of various viral non structural protein, has been posited to be a target. During a modeling study with the utilization of the crystal structure of Mpro, the active region of this enzyme was seen to bind magnesium ascorbate, that has the maximum robust binding of the 16 nutaceuticals. Kumar V, Jenna M [40] pointed that ascorbate might be causing a robust hampering agent for this enzyme [40].

The key besides the usually fatal phase of COVID-19, gets initially stimulated by the response of the host to the dead virus particles in the generation of failure of a lot of organs, that takes place with the generation of proinflammatory cytokines as well as chemokines, that causes the generation of failure of a lot of organs. This might cause neutrophils migration along with collection in the lung interstitium along with bronchoalveolar space that is the crucial determining the propagation of ARDS [41]. Neutrophils extracellular traps generation (NETosis) represents a cell death pathway separate from apoptosis along with necrosis which traps besides resulting in inactivation of the pathogens [42]. This, represents a maladaptive reaction that might aid in tissue in addition to organ injury that resulted in organ failure. In case of GULO knockout, mice Vitamin C deficiency documented escalation of NETosis in the lungs of septic animals in addition to escalation of circulating cell free DNA (ccf DNA) that pointed that Vitamin C is an innovative controller of NETos is [43]. Furthermore, Vitamin C causes escalation of lung epithelial barrier working in an animal model of sepsis by facilitation of epigenetic in addition to transcriptional expression of protein channels at the alveolar capillary membrane which-control alveolar fluid clearance that is inclusive of cystic fibrosis trans membrane conductance regulator, aquaporin-5, the Na^+ K^+ -ATPase pump besides epithelial sodium channel.

Moreover, there is escalation of proof that Vitamin C, that possesses actions other than its effect as a Vitamin, in the form of a stress hormone, might be playing key part in the modulation of adrenocortical stress response, specifically in sepsis [24]. Vitamin C amounts are3-10 fold greater in the adrenal gland in contrast to any other organs [44]. Under situations, of physiological stress it is liberated from the adrenal cortex (ACTH stimulation) that is inclusive of exposures to viruses, that results in escalation of plasma Vitamin C amounts 5 times. Vitamin C causes escalation of cortisol generation in addition to causing potentiation of anti inflammatory along with endotheliocyte protection actions of glucocorticoids [45]. External glucocorticoid steroids are the ones that have been evidenced to be the single disease- modulating treatment for COVID-19 [45] (see figure 1 for modes of Vitamin C in mitigation of COVID-19).

Figure 1: Courtesy ref 45-Postulated mechanisms for vitamin C's amelioration of COVID-19 pathology. ↓—decreased; ↑—increased; ALI—acute lung injury; ARDS—acute respiratory distress syndrome; NF-κB—nuclear factor kappa B

Clinical proof for the part of Vitamin C in cold

Linus Pauling, who received a nobel prize, made up the conclusions, subsequent to randomized controlled trial (RCT), with re-

gards to Vitamin C causing avoidance, besides ameliorated colds, by which this became very favorite treatment by utilization of Vitamin C for this purpose in1970s [46]. A Cochrane review of placebo controlled trials with administration of Vitamin C for avoidance in addition to treatment of colds observed no reduction in the general population with the addition of 200mg supplements [47]. Nevertheless, in 5 trials that had 598 marathon runners, skiers as well as soldiers on subarctic exercises as participants, resulted in reduction in the incidence of colds by 54% ($p < 0.0001$) [47]. Dependent on these observations Vitamin C seemed to have an impact on resistance to infections with viruses by particular situations, like in short time spans of robust physical exercises.

While trials in which administration of Vitamin C occurred subsequent to the initiation of symptoms did not demonstrate concordant advantages, trials that continuously delivered Vitamin C led to reduction in the time period of infections in adults by 8%, along with 14% in children with a dose dependency that is apparent up to 6-8 g/d [35,47]. In case of children, 1-2 g/day Vitamin C resulted in reduction in time period of cold by 18%, besides the reduction in the robustness of cold by continuous delivery [47].

More recently, in a UK placebo controlled trial pointed that a in significant clinical variation amongst the amount of cold, robustness of cold as well as time period of cold [45]. In this trial 168 volunteers that got randomized for receipt of placebo or Vitamin C (500 mg bd daily) over a time span of 60 days in winter. The Vitamin C group experienced lesser colds (37 vs 50, $p = 0.05$), in addition to lesser viral stimulated 'cold' days (85 vs 178, $p = 0.03$). The amount of enrolled, resulting in2 colds was significantly decreased (2/84 on Vitamin Cvs 16/84 in placebo group; $p = 0.04$) [45].

Summary

Cold symptoms have got demonstrated to be of lesser, robustness besides more rapid resolution subsequent to oral supplementation of Vitamin C in a dose -based manner. Colds that posses >100 viruses strains, as etiology certain of which are corona viruses, get definition any group of symptoms akin to most of who get generation of SARS-CoV2 infection without transformation, into acute illness. The akin nature of symptoms in addition to the disease modification action of Vitamin C in the reduction in time period, along with robustness of cold in a wide groups of viruses is the basis for thinking of utilization of Vitamin C in the reduction in time period, along with robustness of cold is not virus particular, that possesses probably the capacity of amelioration of SARS-CoV2 correlated symptoms. Every one of these i.e. reduction in time period, robustness of cold in addition to number of colds - could get posited with regards to SARS-CoV2 for reduction in transformation from mild infection to the critical phase of COVID-19. Having the knowledge that concordant actions of continuous Vitamin C delivery of the reduction in time period, along with robustness of cold as well as lesser cost besides safety one can rightly use Vitamin C it for patients with respiratory virus infections, for obtaining the advantages of Vitamin C in therapeutic dosages to get evaluated.

In view of the disease secondary to novel corona viruses might be of greater robustness in contrast to usual viruses it might be justified for utilization of continuously delivered Vitamin C escalation of dose with earlier high Prevalence, when patients present with virus infection as well as, acute cold symptoms In those who have tested PCR positive to SARS-CoV2 as well as in COVID-19 hospital intensive care unit/or simple admissions, an oral dose of 6-8g daily might be thought of Pauling 's originally advocated dose of 1g each 4 hr of oral Vitamin C at the time of active infection still requires evaluation, in a RCT, thus maximum efficacious dose still not clear.

Clinical proof for the part of vitamin C in Pneumonia

Klener evaluated the actions of high amts Vitamin C that was intravenous delivery for virus disease that was inclusive of Pneumonia [45]. A Cochrane review on Pneumonia as well as Vitamin C observed 3 prophylactic RCTs revealing the no of Pneumonias patients, in enrolled patients getting oral Vitamin C [22]. The observation of every one was a ≥80% reduction in Pneumonias incidence in Vitamin C group [45]. Of these one comprised of a RCT where 2g of Vitamin C vs placebo to US Marines participants at the time of 2 mth of training time duration of recruitment that documented 1/331 patients of Pneumonia in the Vitamin C group vs 7/343 cases in placebo group (p0.044) [45].

Two therapeutic trials were performed. Of these 1 was a RCT where elderly subjects in the UK (average age 81 yrs) got admitted in hospital with acute bronchitis or Pneumonias. The observation of this study was that plasma Vitamin C amount at baseline was 23 µmol/l (Hypovitaminosis C) with a third of patients, possessing Vitamin C amount of (<11 µmol/l [13]. 0,2g daily Vitamin C resulted in reduction in the respiratory symptoms score in the

patients that were having disease with greater robustness of illness however not in the patients with lesser robustness of illness. Six demises were documented at the time of this study, all in the disease with greater robustness of illness of which 5 occurred in the placebo group, however just 1 in the Vitamin C group. The other RCT was in the erstwhile Soviet Union, delivered 2 separate dosages, a different high or low dosages that were associated with the dosages of antibiotic administered [27]. At the time of the hospital stay from the control group was 23.7 days. 19% lesser hospital stay was the observation in the lower Vitamin C group (0.25-0.8g daily) along with 36% lesser hospital stay in the greater dosage Vitamin C group (-.5-1. 6g daily). Advantages were further documented in association with ESR, besides achieving normal, Chest X-ray along with temperature.

Clinical proof for the part of Vitamin C in critically ill septic patients

The major reason for botheration is the high chances of hospital intensive care unit (ICU) stay in COVID-19 patients required for treatment. Meta-analysis of intravenous delivery of Vitamin C in critically ill septic patients (sepsis, burns, septic shock) pointed that it might result in vasopressor sparing action reduction in time duration of ICU stay in addition to requirements of mechanical ventilation. In 6 trials reduction in orally delivered Vitamin C in dosage of 1-3g daily resulting in reduction In total quantity of ICU) stay by 8.6% ($p = 0.003$). In case of 5 trials that was inclusive of, patients having requirement of ventilation >10h. 1-6g Vitamin C daily resulted in reduction of ventilation time duration by 25% ($p < 0.0001$).

Definitive proof is existent, with regards to precipitous fall of Vitamin C in critically ill patients besides septic patients [36]. Despite, Vitamin C 0. 1g daily of Vitamin C is sufficient in sustenance of normal plasma Vitamin C amount in a healthy individual, significantly greater Vitamin C amounts (3-3g daily are the requirements of critically ill patients with in normal value [11]. Its water solubility besides excretion with in hrs as well as lot of doses are significant for sustenance sufficient blood amounts at the time of active infection. Restriction amongst bioavailability has resulted in the development of posit with regards to the requirement of plasma Vitamin C amount in therapeutic plasma amount for reduction In Oxidative stress as well as have an impact on anti inflammatory actions that, get attained with greater effectiveness with intravenous delivery in contrast to oral delivery by itself only [29].

Those physicians that have employed utilization of intravenous delivery in robustly ill COVID-19 patients have documented Clinical actions with 3g delivery 6 hrly in addition to steroids besides anti coagulants. Nevertheless, Definitive proof of the dosage in possession of maximum effectiveness along with frequency has got to be estimated. A 4 group randomized Pharmacokinetics trial evaluating 20r 10g either as bd bolus infusions or continuous supplementation, 2g was correlated with normal plasma Vitamin C amounts, whereas, 10g was correlated with supra normal plasma Vitamin C amounts, escalation of oxalate excretion along with metabolic alkalosis. De-Grooth HJ., *et al*. conclusions stated that continuous treatment is required for protection from Hypovitaminosis C [11]. Reduction in mortality was documented with Vitamin C in case of septic patients whose need was vasopressor therapy, randomly allocated 25 mg/kg body wt intravenous delivery Vitamin C 5 hrly vs placebo group (14% vs 64%; $p = 0.009$) [48].

In the biggest trial on Vitamin C, in sepsis correlated ARDS the CITRIS ALI trial patients were recipient of placebo or Vitamin C 50 mg 6 hrly x 4 days, thus yielding 15g daily for 75 kg individual. Significantly enhancement of inflammation markers, vascular injury organ function impairment were not seen –the primary results [19]. Nevertheless, there was existence of statistically significant advantages in ¾ Clinically important results namely lesser mortality ($p = 0.03$), at the time of ICU free days ($p = 0.03$), along with hospital free days ($p = 0.04$) Reevaluation of the results pointed that at the time of Vitamin C delivery, mortality was 81% lesser, however no variation was seen amongst the 2 trial group. Subsequent to the finishing of 4 days of Vitamin C delivery, the rate of mortality was 23% (19/83) in the placebo group as well as 5% (4/84) in the Vitamin C group ($p = 0.0007$). This variation of 18% correlated with the numbers required for the treatment. Moreover, the authors of that study acknowledging the exclusion of sequential organ failure assessment (SOFA) scores in the patients who died, documented in the post hoc evaluation allotting the dead patients a score of 20, discharged patients SOFA) score of 0, that a 60% possibility of any random patient that belonged to the placebo group possessed a greater SOFA) score in contrast to any random patient that belonged to the Vitamin C group ($p = 0.03$) at 96h.

One more trial randomized 216 patients to low dosage Vitamin C group (1.5g 6 hrly, giving 7.5g daily), thiamine as well as hydrocortisone for till 10 days or till septic shock resolution occurred with an average of 3.4 days vs only hydrocortisone, with observation of no discernible action on primary outcomes of vasopressor free time to 7 days or on 90 day mortality. 2 short comings of this study are the postponement of Vitamin C, probably v late in the disease event as well as for a v short time to hydrocortisone therapy addition offered no benefit to therapy.

Clinical proof for the part of vitamin C in COVID-19

Having the knowledge of probable advantages of oral as well as intravenous delivery Vitamin C at dosage of 2-8g daily for the reduction of robustness of time period in addition to robustness of common cold, Pneumonia, sepsis as well as ARDS it asks for evaluation, with regards to if oral delivery might be of advantage in avoidance of transformation from mild infections towards those with greater critically ill symptoms with regards to COVID-19 patients in reduction of mortality besides stay in ICU, hence escalation of recovery rate.

Intriguingly, a lot of risk factors that correlated with COVID-19 are overlapping with the ones with Vitamin C deficiency [45]. Some sub groups (male, African, American, elder, ones suffering from comorbidities of hypertension diabetes mellitus (DM, COPD), all at greater risk for robust COVID-19 infections, have further been illustrated to possess lesser Vitamin C amount [49]. Mean plasma Vitamin C amounts are usually lesser in men in contrast to women, despite with comparative consumption of Vitamin C, that has got correlated with their greater body weight [45]. A posit of changed sodium –based Vitamin C transporter (SVCT 1 and 2) expression in these sub groups has been posited [49]. In case of old vs young rat hepatocytes, Vitamin C amounts occurred by66%that is mainly associated with reduction of absorption in view of a 45% reduction of SVCT1 with age. Noticeably inflammatory cytokines are further existent in comorbidities, cause a down regulation SVCT2 that causes deletion of intra cellular Vitamin C [45].

Currently 45 trials are registered on Clinical trials. gov that are causing evaluation of Vitamin C with/without other treatments for COVID-19. In the first RCT with regards to evaluation of role of Vitamin C in patients with robust illness of COVID-19 patients, 54 patients in China were in receipt of ventilation were administered placebo (sterile water)/iv Vitamin C at dosage of 24g daily x 7 days. Subsequent to 7 days ratio of PaO_2/FiO_2 in the Vitamin C group was 229 mmHg vs 151 mmHg in the control group (p = 0.01), besides there was an enhancement over time in Vitamin C group.

On day 7, the IL-6 amounts were lesser in the Vitamin C group in contrast to the placebo group; 19 pg/ml vs 158 pg/ml (p = 0.04) The patients with, greater robust illness with SOFA scores ≥3 in the Vitamin C group demonstrated, a decrease in the 28 day mortality; 18% vs 50% (p = 0.05) in univariate survival evaluation (Figure 2). No study correlated side actions were documented. The actions of treatment on PaO_2/FiO_2 along with IL-6 were Clinically significant, however further studies are required for the estimation whether lower mortality pattern can be validated. To start with the trial was fashioned with 140 patients, thus was underpowered, with just 54 patients secondary to absence of new admissions.

Figure 2: Courtesy ref 45 - The 28-day mortality from randomization (day 1) to day 28 in a trial of high-dose intravenous vitamin C (HDIVC) in patients with COVID-19. Kaplan–Meier analysis was used to estimate the 28-day mortality and survival curves were compared with the Wilcoxon test (p = 0.05) among severe COVID-19 patients (baseline SOFA score ≥ 3). Cox regression was used as multiple comparisons (HR, 0.32 (95%CI, 0.10–1.06); p = 0.06). HDIVC—high-dose intravenous vitamin C.

The Biggest trial with regards to Lessening Organ Dysfunction with Vitamin C - COVID- (LOVIT-COVID) trial conducted in Canada, that has enrolled 800 patients randomly allocated to Vitamin C (intravenous 50 mg/kg 6 hrly) or placebo x 96h that is equivalent, to 15g daily for a 75 kg individual (NCT04401150). This protocol has further been an addition in the form of Vitamin C arm in the randomized embedded, multifactorial Adaptive Platform trial for community acquired Pneumonia (REMAP-CAP; NCT02735707). The study design further gives the basis for the utilization of Vitamin C in COVID-19 patients [50]. Moreover, a High dose (10g daily) Vitamin C intervention study in 500 adults is going on in Palermo Italy (NCT04323514).

Botheration exists, nevertheless, that these study designs restrict the utilization of Vitamin C to greatest of 4 days, that might not be advised in acutely ill patients in view of probability of symptoms return back once Inflammation resolution does not occur. As was demonstrated in CITRIS ALI trial, that documented greatest decline in mortality in contrast to placebo on day 4, that is the last day of Vitamin C delivery, however a reduction in variation amongst the group subsequent to 28 days.

In the UK Chelsea and Westminster hospital ICU, where adult ICU patients were given 1g intravenous Vitamin C 12 hrly in addition to anticoagulants [51], revealing 29% mortality [45], in contrast to mean 41% documented by the intensive care National Audit and Research Center (ICNARC) For all UK ICU. Whereas the authors have said that Anti Oxidant addition as Vitamin C might have aided in reduction of mortality rate, it is noticeable that other Clinical parameters along with procedures might further have attributed to the enhancement of mortality along with Chelsea and Westminster hospital ICU works as a greater affluent population sector in possession of lesser deprivation dependent, on the index of multiple deprivation (IMD) e. Deprivation, whereas a risk factor for COVID-19 mortality is further an anticipator of low Vitamin C status. In the UK, calculated 25% of men along with 16% women in low income/material deprivation population possess Vitamin C deficiency in Vitamin C amount >11 µmol/l [45].

The Frontline COVID-19 Critical Care Expert Group (FLCCC), a group of emergency medicine experts have documented that a combination of6gdaily intravenous Vitamin C (1.5g 6 hrly) +steroids along with anticoagulants resulted in 5% mortality in two ICUs in US (United Memorial hospital in Houston, Texas, as well as Norfolk General hospital in Norfolk, Virginia) the least mortality in their respective countries [45].

A case report of 17 COVID-19 patients, 1g Vitamin C 8 hrly x 3d documented mortality rate 12% as well as 18% rates of intubation, mechanical ventilation along with significant reduction in inflammation biomarkers, that was inclusive of ferritin, D-dimer along with tendency for reduction in FiO_2 needs [45].

Safety of oral and intravenous Vitamin C

See ref 45 for details.

Conclusions

With the low cost, safer nature, lot of disease modulating actions Vitamin C possessesthat are inlusive of significant antiinflammatory, immunomodulatory, antioxidant, antithrombotic, antiviral characteristic, makes it a promising agent with regards to reduction in viral load with oral delivery with doses varying from 2-8gdailyfor aiding in the amelioration of transformation towards the critical phase of COVID-19. Akin to that Vitamin C possesses probable advantages with regards to acute respiratory infections along with amelioration of inflammation in critical COVID-19 patients with the utilization of intravenous Vitamin C infusion varying from 6-24 g/day for the rectification of the disease stimulated deficiency, reduction of inflammation, escalation of generation of interferon, besides supporting anti-inflammatory effects of glucocorticoids, in particular having the knowledge of high mortality rates for patients with robustCOVID-19 infection in addition to exhaustive proof of probable advantages with regards to Vitamin C, the present therapy is justified on compassionate basis till greater COVID-19 trials are attained, besides intravenous, oral Vitamin C supplementation in ICU in 2-8g dosage in hospitalized patients in view of escalation of requirements for fight against a viral infections, as has been the conclusions of a lot reviews [45]. Choice of oral/iv clinically cn be decided by criteria akin to that of oral/iv antibiotics, keeping robustness of illness besides possession of capacity of swallowing by patients at a minimum of 4 times daily.

Subjects in high risk groups of COVID-19 mortality need to be stimulated to have higher oral Vitamin C supplementation for making sure no Vitamin C deficit at all times, in addition to escalation of dosage once viral infections occurs to 6-8g daily [45]. If or not it avoids transfer to critical phase needs to be seen.

Bibliography

1. DrouinG., *et al*. "The genetics of Vitamin C". *Current Genomics* 12 (2011): 371-378.
2. Milton K. "Micronutrient intake of wild primates: are humans different?" *Comparative Biochemistry and Physiology Part A: Physiology* 136 (2003): 47-59.
3. Milton K. "Nutritional characteristics of wild primate foods: Do the diets of our closest living relatives have lessons for us?" *Nutrition* 15 (1999): 488-498.
4. "European Food Safety Authority Panel on dietetic products, Nutrition and Alergies. Scientific opinion on dietary reference vales for Vitamin C". *EFSA Journal* 11 (2013): 3418.
5. Bates B., *et al*. "National diet and Nutrition Survey Years 1 to 9 of the Rolling Programme (2008/2009-2016/2017)". Time Trend and Income Analysis; Public Health England: London, UK (2019).
6. Berger MM., *et al*. "White Paper on Nutritional Status in Supporting a Well Functioning immune system for optimal Health with a recommendation for Switzerland". SGE: Bern, Switzerland (2020).
7. "Linus Pauling Institute, Micronutrient Information Center". Micronutrient s for Older Adults Oregon State University (2020).
8. Levine M., *et al*. "Vitamin C Pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance". *Proceedings of the National Academy of Sciences of the United States of America* 97 (1996): 3704-709.
9. Padayatty SJ., *et al*. "Vitamin C Pharmacokinetics: implications for oral and intravenous use". *Annals of Internal Medicine* 140 (2004): 533-537.
10. De-Grooth HJ., *et al*. "Vitamin C Pharmacokinetics in critically ill patients: a randomized trial of four intravenous regimens". *Chest* 153 (2018): 1368-1377.
11. Gan R., *et al*. "Vitamin C deficiency in a University teaching hospital". *Journal of the American College of Nutrition* 27 (2008): 428-433.
12. Ravindran P., *et al*. "Vitamin C deficiency in an Australian cohort of metropolitan surgical patients". *Pathology* 50 (2018): 654-658.
13. Hunt C., *et al*. "The Clinical effects of Vitamin C supplementation, in elderly hospitalized patients with acute respiratory infections". *International Journal for Vitamin and Nutrition Research* 64 (1994): 212-219.
14. Hemila H and Louhiala P. "Vitamin C may affect lung infections". *Journal of the Royal Society of Medicine* 100 (2007): 495-498.
15. Milton K., *et al*. "Plasma Vitamin C Concentrations and risk of incident respiratory and mortality in the European prospective investigations into Cancer-Norfolk population based cohort study". *European Journal of Clinical Nutrition* 73 (2019): 1492-1500.
16. Hemila H and Louhiala P. "Vitamin C for preventing and treating Pneumonia". *Cochrane Database System Review* (2013).
17. Kory P and Kanne JP. "SARS CoV2 organizing Pneumonia :has there been a widespread failure to identify and treat COVID-19". *BMC Open Respiratory* 7 (2020): e000724.
18. Carr AC., *et al*. "Patients with community acquired Pneumonia exhibit depleted Vitamin C status and elevated Oxidative stress". *Nutrients* 12 (2020): 1318.
19. Fowler AA., *et al*. "Effect of Vitamin C organ failure and biomarkers of inflammation and Vascular injury in patients with sepsis and severe acute respiratory failure :the CITRIS ALI randomized Clinical trial". *JAMA* 322 (2019): 1261-1270.
20. Carr AC., *et al*. "Hypovitaminosis C and deficiency in critically ill patients despite recommended Ther enteral and parenteral intake". *Critical Care* 21 (2018): 300.
21. Arvirite C., *et al*. "Serum levels of Vitamin C and Vitamin D in a cohort of critically ill in patients of a north American community hospital intensive care unit In May 2020: a pilot study". *Medical Drug Discovery* 8 (2020).
22. Chis Cano-CamonL., *et al*. "Vitamin C levels in patients with SARS CoV2 associated ion acute respiratory distress syndrome". *Critical Care* 24 (2020): 522.

23. Marik PE and Hooper MH. "Doctor-your septic patients have Scurvy". *Critical Care* 22 (2018): 23.

24. Marik PE. "Vitamin C: An essential ''stress hormone'' during sepsis". *Journal of Thoracic Disease* 12 (2020): S84-S88.

25. Colunga Biancatelli RML., *et al*. "The antiviral properties of Vitamin C". *Expert Review of Anti-Infective Therapy* 18 (2020): 99-101.

26. Dahl H and Degree M. "The effect of ascorbic acid on production of human interferon and the antiviral activity in vitro". *Acta pathologica et microbiologica Scandinavica. Section B* 84 (1976): 280-284.

27. Carr AC and Maggini C. "Vitamin C and immune function". *Nutrients* 9 (2017): 1211.

28. Nualart FJ., *et al*. "Recycling of Vitamin C by a bystander effect". *Journal of Biological Chemistry* 278 (2003): 10128-10133.

29. May JM and Harrison EE. "Role of Vitamin C in the function of Vascular endothelium". *Antioxidants and Redox Signaling* 19 (2013): 2068-2083.

30. Sen CK and Packer L. "Anti Oxidant and Redox regulation of gene transcription". *FASEB Journal* 10 (1996): 709-720.

31. Chen Y., *et al*. "Vitamin C mitigates Oxidative stress and Tumor necrosis factor alpha in severe community acquired Pneumonia and LPS induced macrophages". *Mediators Inflammatory* 2014 (2014): 426740.

32. Erol N., *et al*. "The protection potential of antioxidant Vitamins against acute respiratory distress syndrome: a rat trial". *Inflammation* 42 (2019): 1585-1594.

33. Blanco- Melo D., *et al*. "Imbalanced host response to SARS CoV2 drives the development of COVID-19". *Cell* 181 (2020): 1036-1045.

34. Kim Y., *et al*. "Vitamin C is an essential factor on the antiviral immune through the production of interferon-a/b at theinitial stages of influenza virus A virus (H3N2) influenza". *Immune Network* 13 (2013): 70-74.

35. Hemila H. "Vitamin C and infections". *Nutrients* 9 (2017): 339.

36. Atherton JG., *et al*. "The effect of ascorbic acid on infection chick embryo ciliated tracheal organ cultures by corona virus". *Archives of Virology* 56 (1978): 195-199.

37. Gan R., *et al*. "COVID-19 as a viral functional ACE deficiency in disorder with ACE-related multi organ disease". *Medical Hypothesis* 144 (2020): 11024.

38. Ni W., *et al*. "Role of angiotensin converting enzyme (ACE2) in COVID-19". *Critical Care* 24.1 (2020): 422.

39. Ma S., *et al*. "Single cell transcriptomic atlas of primate cardiomyopulmonary aging". *Cell Research* 31.4 (2020): 415-432.

40. Kumar V and Jenna M. "In silico virtual screening –based study of nutaceuticals predict the therapeutic potential of folic acid and its derivatives against COVID-19". *Virus Disease* 32.1 (2021): 1-9.

41. Grommes J and Schonlein O. "Contribution of Neutrophils in acute lung injury". *Molecular Medicine* 17 (2011): 293-307.

42. Brinkmann V., *et al*. "Neutrophils extracellular traps kill bacteria". *Science* 303 (2004): 1532-1535.

43. Mohammed BM., *et al*. "Vitamin C: A novel regulator of Neutrophils extracellular traps generation". *Nutrients* 5 (2013): 3131-3151.

44. Padayatty SJ., *et al*. "Human adrenal gland secrete Vitamin C in responses to adrenocortical hormone". *The American Journal of Clinical Nutrition* 86 (2007): 145-149.

45. Holford P., *et al*. "Vitamin C –an adjunctive therapy for respiratory infections, Sepsis and COVID-19". *Nutrients* 12 (2020): 3760.

46. Pauling L. "The significance of the evidence about ascorbic acid and the common cold". *Proceedings of the National Academy of Sciences of the United States of America* 68 (1971): 2678-2681.

47. Hemila H and Chalker C. "Vitamin C for preventing and treating cold". *Cochrane Library: Cochrane Reviews* (2013).

48. Zabet MH., *et al*. "Effect of High dose ascorbic acid on vasopressor requirements in Septic shock". *Journal of Research in Pharmacy Practice* 5 (2016): 94-100.

49. Patterson G., *et al*. "Low levels of Vitamin C and dysregulation of Vitamin C transporter might be involved in the severity of COVID-19 infection". *Aging and Disease* (2020): 12.

50. Domain specific Appendix: VITAMINC. REMAP-CAP: randomized embedded, multifactorial Adaptive Platform trial for community acquired Pneumonia (2020).

51. Vizcay chipi MP., *et al*. "Development and implementation of a COVID-19 near –time traffic light system in an acute hospital setting". *Emergency Medicine Journal* 37 (2020): 630-636.

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