ROLE OF HDIVC IN CRITICALLY ILL PATIENTS

Dissertation Submitted to

The IIHMR University, Jaipur

For the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

In

Hospital And Health Management

By

Diksha Pawar

Under the Supervision and guidance of
Dr. Anoop Khanna

2021

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DECLARATION BY STUDENT

I hereby declare that this dissertation titled **'Role of HDIVC in Critically ill patients.'** is the bonafide record of my original researchwork. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished workof others has been duly acknowledged in the text.

Diksha
Pawar

30.06.21

CERTIFICATE

This is to certify that **Diksha Pawar** in partial fulfillment of the requirements for the award of the degree of MBA (Hospital and Health Management) from the IIHMR University, Jaipur has been working with **Figmd, Pune in CDA department** from **April 1, 2021, till date** and has completed her internship as a part of her on-job training. Her internship report has been reviewed and the details mentioned therein are found to be accurate.

Place: Pune

Date: 28 June 2021

Preceptor/Head of the Department: Narendra Shaligram

Name of the organization: Figmd Pvt. Ltd., Pune

CERTIFICATE

This is to certify that dissertation titled **'Role of HDIVC in Critically ill patients.'** is record of the research Work undertaken by **Diksha Pawar** in partial fulfillment of the requirements for the awardof the degree of MBA (Hospital and Health Management from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

Faculty Guide
IIHMR University, Jaipur
Date: 31.06.21

School Dean
IIHMR University, Jaipur
Date: 31.06.21

ABSTRACT:

Introduction: Ascorbic acid popularly known as Vitamin C is a water-soluble vitamin which provides plethora of benefits and advantages to human body. From being vital for body growth to providing shelter against immune system. There are several randomized control trials going on to weigh the benefits of Ascorbic acid in critical care. Taking for instance the example of corona virus pandemic, a lot of studies has been going to test its treatment variants. One of the possible properties of vitamin C in using it for corona virus treatment and prevention is its antioxidant power. In one of the randomized controls trial, it was noted that in the cases of surgical sepsis, vitamin C was able to revert the effects of shock and shortened the stay of patients in ICU. Different clinical studies have shown to use combination of therapies in conjugation with Vitamin C supplementation.

Objectives: there are three objectives for this review: first is to study the benefits of Ascorbic Acid as a dietary supplementation, second is to study the role of Vitamin C in human body during moderate to severe disease pathogenesis and third is to probe the effects of High dose of vitamin C in patients undergoing critical care management.

Methodology: Narrative Literature review is done in this study where articles published from 2012 -2021 were taken and compilation of 11 such articles were done in summarized form, both published and unpublished data was studied for this research.

Findings: In different Randomized control trials and clinical trials for HDIVC in critical patients "AA intravenous decreased the need of vasopressor support (standardized mean difference −0.71; 95% confidence interval (−1.16 to −0.26); p = 0.002) also decreased duration of mechanical ventilation (standardized mean difference −0.5; 95% confidence interval (−0.93 to −0.06); p = 0.03)."

Conclusion: Based on randomized control trials, clinical trials, case studies run around the world on Vitamin C in critical care., it is concluded from recent studies that there exists a positive correlation between including Vitamin C as Critical care treatment to patients under high oxidative stress which shortens the stay in ICU as we as reduce the support of mechanical ventilation.

Keywords searched: Antioxidants, Ascorbic acid, Vitamin C, Biological Availability, Critical illness therapy, Nutritional requirements, Dose-response Relationship, oxidative stress, Biological Availability, Oxidation-Reduction

ACKNOWLEDGMENT

I would like to take this opportunity to show my gratitude to everyone who supported me on my journey. I am grateful to my Institute, Indian Institute of Health Management Research for providing me with the foundation of knowledge and skills. I would like to extend my gratitude towards my Guide, Dr. Anoop Khanna for his constant guidance throughout this journey and for pushing me to do better. I will try my best to use this knowledge and skills for the goodwill of the society and people. I will continue to work on my future endeavours with the same zeal and hard work.

Sincerely,
Diksha Pawar.

TABLE OF CONTENTS

ABBREVIATIONS:

1.ICU – Intensive Care Unit

2. ROS – Reactive oxygen species

3. HDIVC – High-dose intravenous vitamin C

4. ARDS – acute respiratory distress syndrome

5. GMP – Guanosine monophosphate

6. SARS – severe acute respiratory syndrome

7. AA – Ascorbic Acid

8. LOS – Length of Stay

9. SOFA – Sequential organ failure assessment

TABLE OF FIGURES

1. INTRODUCTION:

Ascorbic acid popularly known as Vitamin C is a soluble in water, that provides plethora of benefits and advantages to human body. From being vital for body growth to providing shelter against immune degrading diseases and dysfunction , coronary artery diseases, pre and post natal health issues, cancers, stroke, eye diseases, and skin diseases, it has efficiently demonstrated repairment of connective tissue of our body which is indispensable to the needs of the body when it been subjected to various infections and diseases which has caused long-standing damage to the tissues and in turn to the organs. A study published in *Seminars in Preventive and Alternative Medicine* looks at 100 studies over 10 years and examines budding gains of Vitamin C. Ascorbic acid is one amongst many antioxidants that shields against destruction due to dangerous free radicals, toxins, and pollutants. C Vitamin is the key to a rock-solid and well-functioning immunity.

TABLE 1.1 shows ways Vitamin C contributes to the immune mechanism of the body.

Vitamin C helps interferons in generating cellular defence mechanism against disease pathogens
Vitamin C backs up the functioning of phagocytes
Vitamin C supports both cellular and antibody immunity
Vitamin C increases the production of cytokines which is integral part of immune response
Vitamin C helps in survival of T lymphocytes for cell mediated immune response
Vitamin C backs up circular GMP levels in lymphocytes
Vitamin C in WBC is 80 times higher as compared to its levels in plasma

Several studies with a few randomized controlled trials suggested HDIVC can play a major role in counteracting the oxidative stress during sepsis or multiorgan failure. From the onset of COVID-19 pandemic, various therapies and treatment modalities have been proposed for its control as well as for treatment. Vitamin C has been one of them and due to its antioxidant properties, it has been taken through as an essential food supplement. The absorption of Vitamin C is limited i.e.., about 70–85 µmol/L for a daily intake of 300 mg. suggesting that everyday oral supplementation can only preserve its reservoir to a certain degree only.

It has been observed that low level of Vitamin C in plasma is in relation to poor end results and expanded fatality among critically ill patients. It has been suggested by several trials that intravenous administration of Vitamin C can be beneficial in managing the incidences of organ failure and can improve the mortality rate. However, the studies comprised of combination therapies of Vitamin C with other antioxidants which can act as a confounder for the effects of AA alone. the study looks into the role of AA in critical management of diseases and Hospice care.

TABLE 1.2 few established benefits of Vitamin C are as summarized below:

Supports immune system
Induces collagen formation, muscles, and tendons strength
Antihistamine and Antioxidative properties
Prevents iron deficiency and Anaemia

RESEARCH QUESTION: What role does HDIVC plays in treatment of Critically ill patients?

1.1 OBJECTIVES

1.To study the benefits of Ascorbic Acid as a dietary supplementation.

2.To study the Role of HDIVC in Critically Ill patients.

1. LITERATURE REVIEW:

TABLE 2.1 Summarizes literature review.

Sno	Title	Author/Year	Methodology	Outcome
1.	"Influences on Vitamin C Status and ubiquity of its Deficiency".	"Carr AC, Rowe S. (2020)"	Systematic review	"Deficiency is governed by cultural factors like traditional cooking practices, income strata of countries, Environmental factors, demographic factors such as sex, age and health conditions like weight and pregnancy"
2.	"Effects of oral vitamin C supplementation on oxidative stress and inflammation status in haemodialysis patients"	"Fumeron C, Nguyen-Khoa T"	randomized, open-label trial	"Short-acting oral vitamin C supplements did not affect oxidative stress and inflammatory markers in Haemodialysis patients. Still a higher oral dose could change markers still needs to be studied."
3.	"Rationale and impact of vitamin C in clinical nutrition"	"McGregor GP, Biesalski HK."	Randomized control trial	"In critical patients especially with 3rd degree burns and more, the quick replenishing of low ascorbate levels with high-dose ascorbic acid can reduce circulatory shock, fluid intakes and swelling."
4.	"Vitamin C: should we supplement?"	"Spoelstra-de Man AME, Elbers PWG (2018)"	Case study	"clinical studies related to trauma, ischemia/reperfusion, and sepsis depicts that vitamin C administered reduces oxidative stress & inflammatory markers"
5.	"Functional and physiological role of vitamin C transporters."	"Bürzle M, Hediger MA. (2012)"	Systematic review	"Ascorbic acid is made use for the synthesis of collagen, carnitine, catecholamine"
6.	"Vitamin C and acute respiratory infections."	"Hemilä H, Douglas RM. (2021)"	Conceptual framework of Literature review	"Three controlled trials showed lowering of minimum 80% in the occurrence of pneumonia, and one randomised trial suggested benefits from vitamin C in patients under critical care with pneumonia and bronchitis."
7.	"Application of methylene blue -vitamin C -N-acetyl cysteine in management of critical illness"	"Alamdari DH, Moghaddam AB (2020)"	Randomized control trial	"Methaemoglobin and oxidative stress play a pivot role in the critical care of COVID-19 patients"

8.	"Intravenous Vitamin C Administered as Adjunctive Therapy for Recurrent Acute Respiratory Distress Syndrome"	"Bharara A, Grossman C, (2016)"	Systematic review	"Vitamin C in high dose used via parenteral route improved alveolar fluid clearance."
9	"AA as concurrent treatment for ARDS"	"Fowler Iii AA, Kim C, (2017)"	Systematic review	"On giving HDIVC patient's recovery was fast, and ventilators discontinued in 1 week and patient recovered with no long-term ARDS side effects."
10.	"AA and cortisol in viral pneumonia."	"Anstey MH, Luu J (2021)"	Randomized control trial	"It is possible that a HDIVC can provide more profits, or it may work only when combined with corticosteroids"

2. RESEARCH METHODOLOGY:

2.1 Secondary Research based on Narrative literature review.

TABLE 3.1 Data sources used for the Narrative literature are summarized below:

"PUBMED"	"https://www.ncbi.nlm.nih.gov/pmc/articles/"
"RESEARCH GATE"	"https://www.researchgate.net/"
"GOOGLE SCOLAR"	"https://scholar.google.com/"
"SCIENCE DIRECT"	"https://www.sciencedirect.com/"
"JAMA NETWORK"	"https://jamanetwork.com/"
"BIOMEDCENTRAL"	"https://www.biomedcentral.com/"
"ANNALS OF INTENSIVE CARE"	"https://annalsofintensivecare.springeropen.com/"
"ACCJOURNAL"	"https://www.accjournal.org/"

All the figures used in research are collected from primary research from unpublished sources. (All listed in references)

TABLE 3.2 Few Sources of unpublished data:

THE PRINT
INDIAN EXPRESS
TIMES OF INDIA

3.3 The **keywords** used to search the publications that are relevant to the aim and the objective of this review were:

Antioxidants, Ascorbic acid, Vitamin C, Biological Availability, Critical illness therapy, Nutritional requirements, Dose-response Relationship, oxidative stress, Biological Availability, Oxidation-Reduction.

3.4 Articles published from 2012 -2021 were taken in study and compilation of 10 such articles were done in summarized form for literature review.

4. FINDINGS:

1. **Figure 4.1** four Randomized control trails and one retrospective study summarized below:

1. Five studies (four randomized controlled trials and one retrospective review) enrolling a total of 142 patients compared with controls, the administration of intravenous vitamin C was associated with a decreased need for vasopressor support (standardized mean difference −0.71; 95% confidence interval (−1.16 to −0.26); p = 0.002) and decreased duration of mechanical ventilation (standardized mean difference −0.5; 95% confidence interval (−0.93 to −0.06); p = 0.03), but no difference was found in mortality (odds ratio 0.76; 95% confidence interval (0.27 to 2.16); p = 0.6). Trends were also noted toward decreased fluid requirements and increased urine output.
2. In another study the included trials enrolled a total of 1210 patients. Intravenous (IV) AA doses of 3-10 g/d reduced the mortality of critically ill patients (OR 0.25; 95% CI (0.14-0.46); p < 0.001; I^2 = 0.0%), while low (< 3 g/d) and high AA doses (≥ 10 g/d) had no effect (OR 1.44; 95% CI (0.79-2.61); p = 0.234; I^2 = 0.0% versus OR 1.12; 95% CI (0.62-2.03); p = 0.700; I^2 = 0.0%). AA was associated with a decreased duration of vasopressor support and mechanical ventilation but did not influence fluid requirement or urine output during the first 24 h of admission. The number of patients suffering from acute kidney injury and the length of intensive care unit or hospital stays were also unaffected by the AA.

2. **Figure** 4.2 summarizes two Randomized control trials and its findings.

3. Totally, twelve patients were enrolled including six severe [age of mean, 56; interquartile range (IQR), 32-65 years, 3 men] and six critical (age of mean, 63; IQR, 60-82 years, 4 men) patients. The dosage of vitamin C [median (IQR), mg/kg (body weight)/day] were [162.7 (71.1-328.6)] for severe and [178.6 (133.3-350.6)] for critical patients. By Generalized estimating equation model, C-reactive protein was found to decrease significantly from day 0 to 3 and 7 (severe: 59.01±37.9, 12.36±22.12, 8.95±20.4; critical: 92.5±41.21, 33.9±30.2, 59.56±41.4 mg/L). Lymphocyte and CD4+ T cell counts in severe patients reached to normal level since day 3. Similar improving trends were observed for PaO2/FiO2 (severe: 209.3±111.7, 313.4±146, 423.3±140.8; critical: 119.9±52.7, 201.8±86.64, 190.5±51.99) and sequential organ failure assessment score (severe: 2.83±1.72, 1.33±1.63, 0.67±1.03; critical: 6.67±2.34, 4.17±2.32, 3.83±2.56). Better improving effect was observed in severe than critical patients after HDIVC.
4. In a Randomized control trial, the HDIVC and control groups each comprised 55 patients. For the primary outcomes, there was a significant difference in the number of patients that evolved from moderate to severe type between the two groups (HDIVC: 4/55 vs. control: 12/55, relative risk [RR] = 0.28 [0.08, 0.93], P = 0.03). Compared to the control group, there was a shorter duration of systemic inflammatory response syndrome (P = 0.0004) during the first week and lower systemic inflammatory response syndrome occurrence (2/21 vs 10/22, P = 0.0086) on Day 7 (6-7 days after admission). In addition, HDIVC group had lower C-reactive protein levels (P = 0.005) and higher number of $CD4^+$ T cells from Day 0 (on admission) to Day 7 (P = 0.04)." The levels of coagulation indicators, including activated partial thromboplastin time and D-dimer were also improved in the HDIVC compared to the control group on Day 7.

2. A longitudinal cohort study in ICU patients depicting circulatory septic shock were collated, sufferers were ministered HDIVC, thiamine, and hydrocortisone (treatment group) compared to those given cortisol alone (control group). Data was equated to guarantee similitude at reference line. The Sequential Organ Failure Assessment score when computed on day 0 (diagnosis day) and every day for 3 consecutive days, showed the finding: "ICU length of stay was significantly lowered in the treatment group compared to control (7.1 compared to 15.6 days, respectively, p=0.04)"

TABLE 4.1 shows comparison of disease illness between control and treatment.

Disease Severity Markers	Control (N=38)	Treatment (N=38)
Vasopressors need (%)	76	79
Mean SOFA score ± SD	6 ± 3	6.9 ± 4
Need for Mechanical ventilation (%)	45	50

Figure 4.3 Shows Mortality in ICU is 2% more when compared to in treatment group, mortality is 6% more in Hospitals for control group, 3% and 8% more within 28 days and 66 days respectively in control group as compared to treatment group.

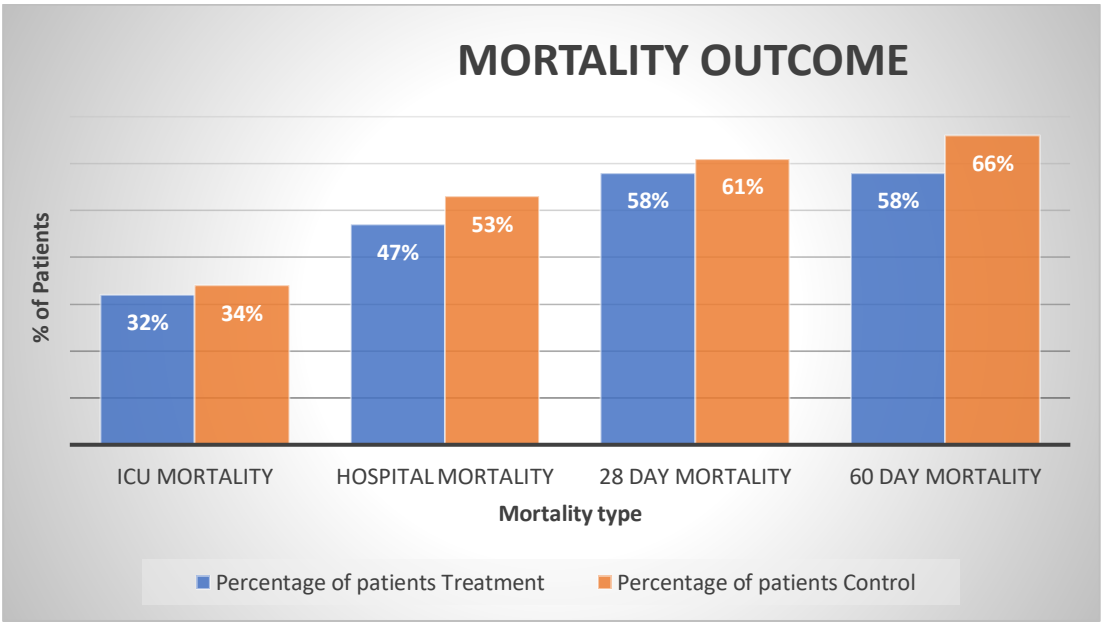


FIGURE 4.4 shows the Comparison between the treatment and control in terms of hospital stay, vasopresser duration and ICU stay, LOS in treatment group is visibly reduced to 2.5 days for vasopresser duration, 7.1 days for ICU stay as compared to 15.6 days in control and 20 days for hospital stay as compared to 32.6 days in control

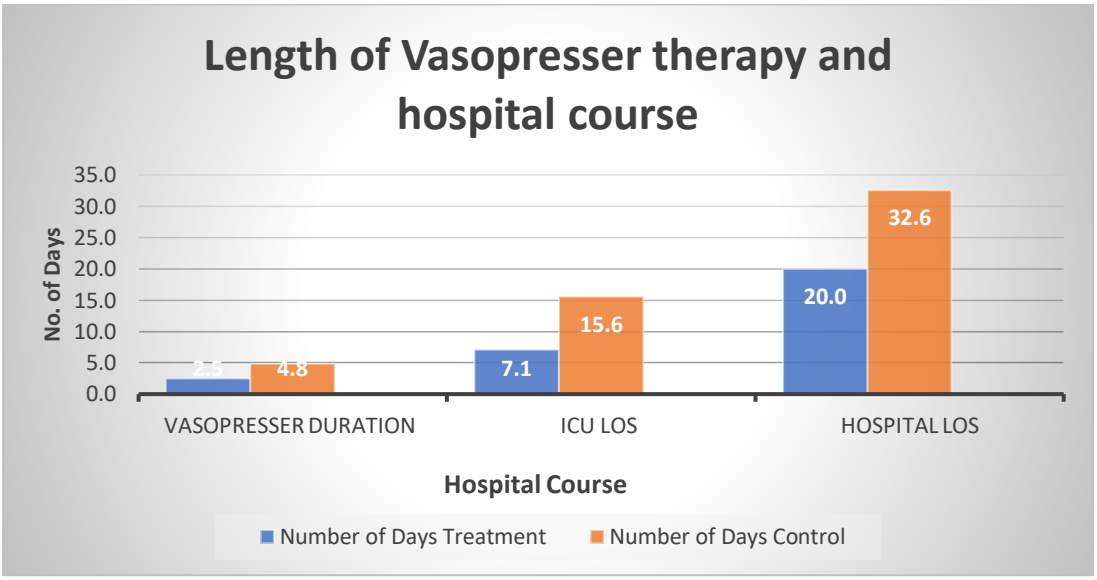
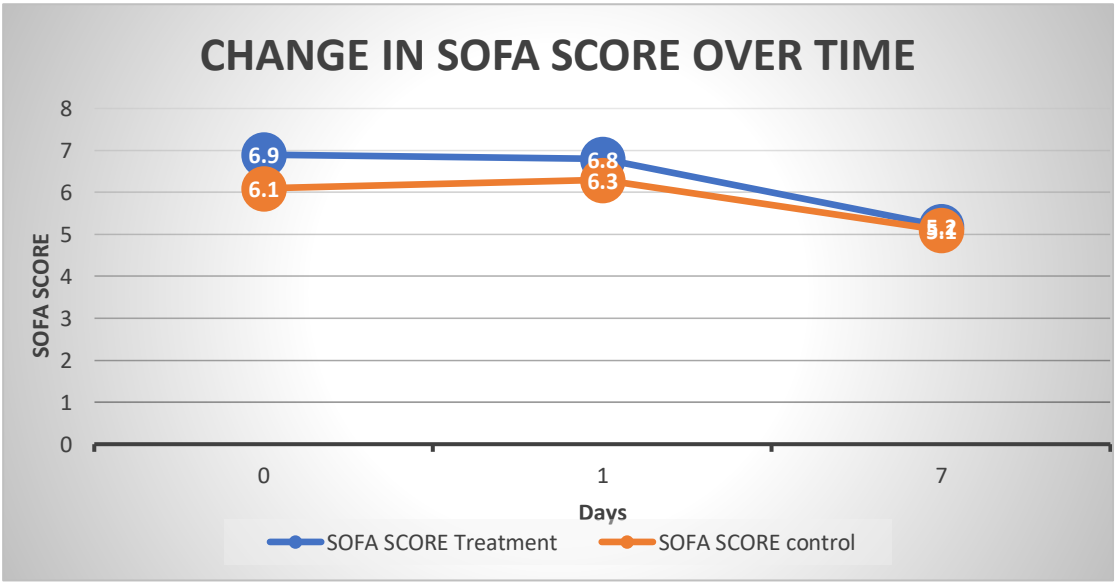


FIGURE 4.5 "compares sequential organ failure assessment in both control and treatment from day of diagnosis(day 0) to day 3"



3. A Randomized Control trial in Wuhan studied the role of HDIVC in ICU COVID 19 patients and computed their LOS for Hospital and ICU.

Results : "HDIVC administration showed a significant depletion in 28-day mortality (P=0.05) in more severe patients where SOFA score was more than 3 under univariate survival analysis"

TABLE 4.2 shows SOFA Score comparison between placebo and control, where in treatment SOFA score reduced to 3 from 3.5.

DAYS IN HOSPITAL	**SOFA SCORE IN PLACEBO**	**SOFA SCORE IN TREATMENT GROUP**
Day 1	2	3.5
Day 7	6	3

Analysis :

The analysis of 8 vitamin C control trials suggested that HDIVC cuts off the use of supported ventilators in critically ill patients The outcome was congruous with antecedent clinical trials depicting that HDIVC shortened the expanse of multiple organ failure and ameliorated the momentary results of circulatory septic shocks. Also, AA levels in blood were indirectly proportional to the incidence of multiple organ failure and death**.** patients having severe organ failure had a severe hypovitaminosis, for which HDIVC treated the deficiency and improved the organ status. Therefore, the survival was better expected in severely ill patients with a higher SOFA score. The vitamin C administration did not negatively affected patient health and there was decreased ICU stay. Still more data is required to study the treatment benefits in moderate to severe disease prognosis.

5. DISCUSSION:

Several studies shows that premature recuperation from shock and multiorgan failure can be realized on repeating Vitamin C in dosage of 2 to 3 g given intravenous in conjugation with thiamine in dosage of 100 mg per day, also death can be avoided when pharmacological dose of 2g given intravenous and thiamine in dose of 200-400 mg per day monitored, although these studies are less in number and variates with respect to dosage, time span, pathogenesis and prognosis of disease. Still a lot of biological evidence is required to conform the results.

Observational research also shows the synergistic effect of Vitamin C and corticosteroids which is used against septic shock. The use of Vitamin C as oral dose and as i.v. dose in Covid 19 patients has shown to reduce the inflammatory markers and helped in active recovery as well prevention of the viral function, still the research is still active for the viral infection and the role Vitamin C plays in backing up Immunity response to such viruses.

5.1 LIMITATIONS:

1.varying degrees of statistical significance between different trials and studies on Vitamin C and use in critical care management.

2.The prognosis is highly dependent on the disease in question, the stage of the pathogenesis of the disease, dose, and immunity response of the patient.

3. Limited data availability on role of vitamin C in other chronic conditions like Cancer and autoimmune diseases.

5.2 STRENGTHS:

1.Enough biological evidence available for the use of ascorbic acid in septic shock and multiorgan failure suggesting positive outcome for other diseases as well resulting in sepsis and multiorgan failure

2.Oral supplementation is of value in maintaining the health of an individual as a very small amount of vitamin C is stored in body and is not actively maintained naturally in the body, an in-depth research on vitamin C and oral supplementation can prevent array of diseases at an early stage.

6.CONCLUSION:

Although there is varying degree of statistical variations in significance between different studies, it is concluded from recent studies that there exists a positive correlation between including Vitamin C as Critical care treatment to patients under high oxidative stress which shortens the stay in ICU as we as reduce the support of mechanical ventilation, although more data is required to prove a causal relationship existing. Vitamin C has great potential to improve the critical care management of the diseases (focusing on sepsis, burns, respiratory infections like ARDS, pneumonia etc) which will in turn reduce the mortality rate in patients.

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43. **https://indianexpress.com/**

44. **Dr. Rath Health Foundation (dr-rath-foundation.org)**

45. **https://clinicaltrials.gov/**

46. **https://pubmed.ncbi.nlm.nih.gov/**

47. **http://dspace.sctimst.ac.in/jspui/**

48. **Acute and Critical Care (accjournal.org)**

49. **National Center for Biotechnology Information (nih.gov)**

50. **SAGE Journals: Your gateway to world-class research journals (sagepub.com)**

51. **Committees - UK Parliament**

52. **MDPI - Publisher of Open Access Journals**

53. **Medwave**

54. **Preprints - The Multidisciplinary Preprint Platform**

55. **Frontiers | Peer Reviewed Articles - Open Access Journals (frontiersin.org)**

56. **Nutrition Evidence (nutrition-evidence.com)**

57. **Share and Discover Knowledge on SlideShare**

58. **SciELO - Scientific Electronic Library Online**

59. **Research Square**

60. **Home | Cambridge University Press**

8. ANNEXURE

Figure 8.1 Indicates Ascorbic Acid benefits in COVID -19

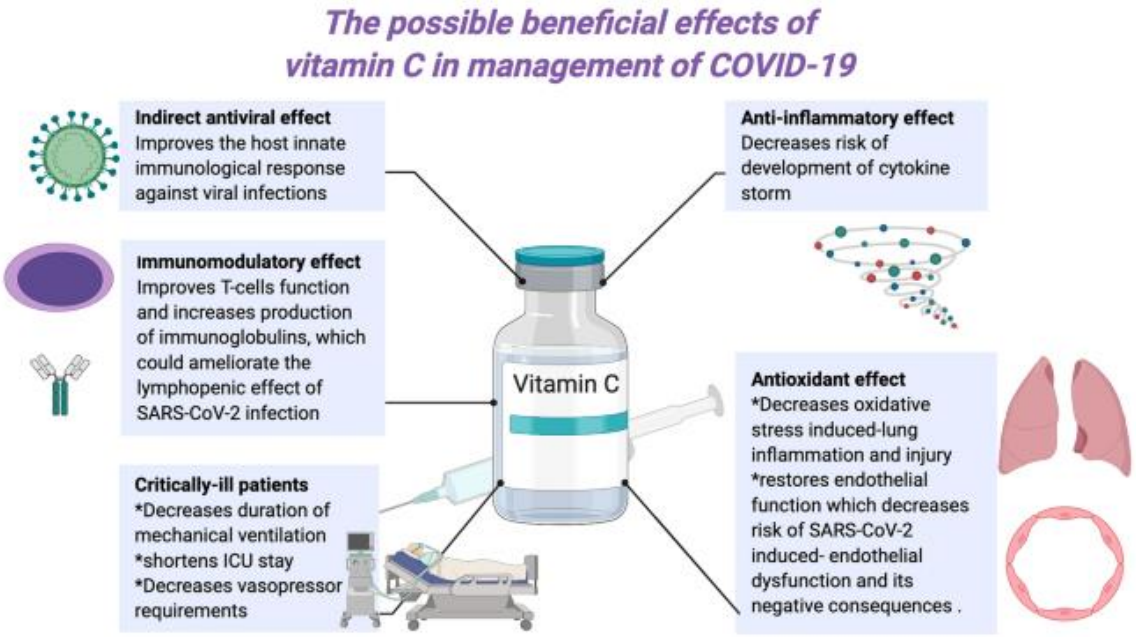

Figure 8.2 Indicates the Vitamin C effects in Critical illness