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Role of supramaximal dosing of vitamin C in sepsis patients

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Introduction

Sepsis remains a life-threatening medical condition of unregulated immune response with a mortality rate exceeding 50% in septic shock. More than 5 million deaths globally could be attributed to sepsis.[1] Given the high burden of sepsis all over the world, the search continues for effective targeted therapies in improving sepsis outcomes, especially in developing and third-world countries with the aim of finding inexpensive, safe, and accessible interventions.[2]

Vitamin C is an essential water-soluble vitamin that humans are not able to store or synthesize in-vivo. It plays an extensive role as an antioxidant, electron donor, and cofactor for many enzymes and proteins[3]. When depleted, the inter-endothelial electrical coupling of nitric oxide synthase is reduced, and this in turn accelerates the inflammatory cascade, leading to an increase in microvascular dysfunction and endothelial permeability[4].

Sepsis is the amalgamation of a complex interaction between the host response and infecting organism which results in severe organ dysfunction.[5] Widespread distribution of pro-inflammatory mediators plays an important role in the pathogenesis and high morbidity and mortality associated with sepsis. High cellular production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays an active role and contributes to oxidative stress which reults in tissue and organdamage. Since the beginning of the last century, it has been established through a number of studies that protective antioxidants and Vitamin C levels are low in critically ill patients[6]. As oxidative stress is high there is

increased consumption of vitamin C in sepsis, supplementing Vitamin C and other antioxidants has been suggested as a possible complementary treatment in patients of sepsis.

Vitamin C plays a vital role in the immune response via several pathways and is known to increase endothelial function and microcirculatory flow [7]. Several studies have been carrying out to study the therapeutic effects of vitamin C in septic patients.

Despite some promising results, the effects of these vitamins against sepsis remain to be established [8]. Hence the present study will be conducted to analyze the role of Vitamin C in sepsis patients.

Material and methods

The study was undertaken at surgery department of Chattrapati Shivaji Subharti Hospital, Meerut on all patients during study period whom were diagnosed with sepsis were shortlisted according to inclusion and exclusion.

- current hospitalization of more than 30 days.
- chronic hypoxemia requiring supplemental non-invasive oxygen via nasal cannula or NIPPV (i.e., continuous positive airway pressure and bi-level positive airway pressure) or home mechanical ventilation
- chronic cardiovascular failure requiring home mechanical hemodynamic support (e.g., ventricular assist device) or home chemical hemodynamic support (e.g., milrinone)
- known allergy or known contraindication to vitamin C (including previous history or active diagnosis of primary hyperoxaluria or oxalate nephropathy or both, known/suspected ethylene glycol ingestion, or known glucose-6- phosphate dehydrogenase deficiency).
- use of vitamin C at a dose of greater than 1 g daily (oral of intravenous) within the 24 h preceding first episode of qualifying organ dysfunction.
- pregnancy or known active breastfeeding.
- inability or unwillingness of subject or legal surrogate/representative to give written informed consent.
- Patients with known coagulopathies both with under and over coagulation.

Data analysis

Risk of mortality in patients was assessed using APACHE-2 scoring system.

Various additional parameters were taken into account like ESR, LFT, KFT,ionotropes, etc;

Data was analyzed using APACHE-2 according to which a score was provided to all

patients on day 1, 3, 5 and 7.

This scale provided an idea about the patients' vulnerability at fixed intervals.

Results

A total of 108 patients with sepsis satisfying inclusion criteria were included in the study.

The analysis of the results were done after cleaning of the excel sheet using SPSS software. The categorical data was expressed in form of percentage while continuous data was represented in form of mean ± standard deviation. The difference of mean among the three groups A, B and C was calculated using ANOVA and results were represented in form of F value and p value. The specific difference among the three groups was analysed used Tukey's post hoc test and any significant difference was reported in form of p value <0.5.

In our study, out of the 36 patients in group A, 5 were under the age of 20, 15 were in theage group of 20-40,

7 were in the age group 41-60 and 9 were in the age group 61-80. Out of the 34 patients in group B, 3 were under the age of 20, 12 were in the age group of 20-40, 13 were in the age group 41-60, 5 were in the age group 61-80 and 1 patient was >80 years of age.

Out of the 38 patients in group C, 13 were under the age of 20, 45 were in the age group of 20-40, 30 were in the age group 41-60, 19 were in the age group 61-80 and 1 patient was >80 years of age. (Table 1)

Age group	Group A		Group B		Group C		Total	
	N	%	N	%	N	%	N	%
≥20	5	13.9	3	8.8	5	13.2	13	12.0
21- 40	15	41.7	12	35.3	18	47.4	45	41.7
41- 60	7	19.4	13	38.2	10	26.3	30	27.8
61- 80	9	25.0	5	14.7	5	13.2	19	17.6
>80	0	0.0	1	2.9	0	0.0	1	0.9
Total	36	100.0	34	100.0	38	100.0	108	100.0

Table 1: Descriptive analysis of age in study population (N=108)

Out of the 36 patients in group A, 12 were male and 24 were female. Out of the 34patients in group B, 16 were male and 18 were female. Out of the 108 patients in group C, 42 were male and 66 were female.

Out of the 36 patients in group A, 8 had diabetes, 9 had hypertension, 2 were obese and 1 had tuberculosis. Out of the 34 patients in group B, 12 had diabetes, 11 had hypertension, 4 were obese and 2 had tuberculosis. Out of the 108 patients in group C,27 had diabetes, 28 had hypertension, 10 were obese, 3 had tuberculosis and 1 had COPD. (Table 2)

Co-Morbidities	Group A		Group B		Group C		Total	
	N	%	N	%	N	%	N	%
Diabetes Mellitus	8	29.6	12	44.4	7	25.9	27	100.0
Hypertension	9	32.1	11	39.3	8	28.6	28	100.0
Obesity	2	20.0	4	40.0	4	40.0	10	100.0
Tuberculosis	1	33.3	2	66.7	0	0.0	3	100.0
COPD	0	0.0	0	0.0	1	100.0	1	100.0

Table 2: Descriptive analysis of risk factors in study population (N=108)

Primary diagnosis	Group A	Group B	Group C
Perforation	13	8	14
Soft tissueinfection	3	6	7
Burn	2	0	1
Polytrauma	7	9	8
Others	11	11	16
Total	36	34	38

Table 3: Descriptive analysis of primary diagnosis in study population

Isolated organism	Group A		Group B		Group C		Total	
	N	%	N	%	N	%	N	%
Acid fast bacilli	0	0.0	1	50.0	1	50.0	2	100.0
Acinetobacter baumannii	2	25.0	3	37.5	3	37.5	8	100.0
Aciteobacter colcoacetius- A. baumannii complex	0	0.0	1	50.0	1	50.0	2	100.0
Candida glabrata	1	100.0	0	0.0	0	0.0	1	100.0
Candida tropicalis	1	33.3	1	33.3	1	33.3	3	100.0
Citrobacter koseri	1	33.3	1	33.3	1	33.3	3	100.0
Coagulase negativeStaphylococcus	1	25.0	1	25.0	2	50.0	4	100.0
Commensal flora	0	0.0	0	0.0	1	100.0	1	100.0
E.coli	9	40.9	6	27.3	7	31.8	22	100.0
Enterobacter cloacae	0	0.0	0	0.0	1	100.0	1	100.0
Enterococcus spp	2	33.3	0	0.0	4	66.7	6	100.0
Klebsiella pnemonia	7	30.4	10	43.5	6	26.1	23	100.0
Klesbsiella oxytoca	5	38.5	3	23.1	5	38.5	13	100.0
No bacteria seen (pus)	0	0.0	1	100.0	0	0.0	1	100.0
Pseudomonas aueroginosa	2	25.0	2	25.0	4	50.0	8	100.0
Staph. epidermidis	1	100.0	0	0.0	0	0.0	1	100.0
Staph.Aureus	4	44.4	4	44.4	1	11.1	9	100.0

Table 4 : Descriptive analysis of organisms isolated in study population (N=108)

Descriptive analysis of CBC in study population:

No significant difference was observed in hemoglobin levels among the three groupson day 1, 3 and 7 however, a statistically significant difference was observed on day 5 as the mean hemoglobin level of 11.716 ± 1.666 observed in Group C which was higher when compared with Group A.

Descriptive analysis of platelet count in study population:

No significant difference was observed in platelet levels among the three groups on day 3 and 7 however, a statistically significant difference was observed on day 1 and 3. On day 1, the mean platelets levels were higher in group A (322.25 ± 234.95) as compared to group B (216.00 ± 78.20) and similar finding was observed on day 3 where the mean platelet levels were found to be significantly higher in group A as compared to group B.

Descriptive analysis of serum urea and serum creatinine in study population:

No significant difference was observed in the serum urea levels among the three groups on day 1,3, 5 and 7. No significant difference was observed in creatinine levels among the three groups on day 1,3 and 5 however, a significant difference was observed on day 7 as the

creatinine levels in group A (0.85 ± 0.42) were found to be significantly lower when compared with group B (1.75 ± 1.23).

Descriptive analysis of serum electrolytes in study population:

A significant difference was observed in serum sodium levels on day 3 as the mean sodium levels were significantly higher for group B (142 ± 7.31) as compared to group A (136.97 ± 6.94).

A significant difference was observed in serum potassium levels on day 3 as the mean potassium levels were significantly higher for group A (4.35 ± 0.95) as compared to group B (3.75 ± 0.60). Potassium levels were significantly higher on day 1 when compared with day 3 ingroup B.

The difference between the serum chloride levels of group A, B and C on day 1, day 3, day 5 and day 7 was not statistically significant.

Descriptive analysis of LFT in study population

The difference between the total bilirubin levels of group A, B and C on day 1, day 3, day 5 and day 7 was not statistically significant.

The difference between the total protein of group A, B and C on day 1, day 3, day 5 and day 7 was not statistically significant.

The difference between the serum albumin of group A, B and C on day 1, day 3, day 5 and day 7 was not statistically significant.

The difference between the SGOT , SGPT , ALP , GGT and serum lactate of group A, B and Con day 1, day 3, day 5 and day 7 was not statistically significant.

Descriptive analysis of APACHE-II scores in study population

Table 5

APACHE-II		Day 1 (n=108)		Day 3 (n=92)		Day 5 (n=59)		Day 7 (n=32)	
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Group A		15.11	7.40	13.32	6.43	13.76	6.90	14.93	8.44
Group B		13.47	5.56	12.46	5.04	11.71	7.06	15.67	8.14
Group C		14.71	6.16	13.21	6.42	10.52	4.87	12.42	5.71
F		0.615		0.174		1.412		0.514	
P value		0.542		0.841		0.252		0.603	
Post hoc (p value)	A & B	0.537		0.849		0.581		0.978	
	A & C	0.961		0.997		0.228		0.677	
	B & C	0.694		0.880		0.834		0.667	

Group A- 0.5g/ day of Vit. C **Group B**- 6 g of Vit. C
Group C- 12 g of Vit. C

The difference between the APACHE-II scores of group A, B and C on day 1, day 3, day 5 and day 7 was not statistically significant. There was also no statistical difference in the APACHE-II scores (table 5)

Descriptive analysis of need for and weaning off of ionotropic support instudy population:

Out of the 36 patients in group A, 25 patients (37.3%) needed ionotropic support out of which 20 (37,0%) were weaned off. Among the 34 patients in group B, 17 (25.4%) needed ionotropic support out of which 15 (27.8%) were weaned off. Among the 38 patients in group C, 25 (37.3%) needed ionotropic support out of which 19 (35.2%) were weaned off.

Out of the 36 patients in group A, 23 patients (63.8%) needed ionotropic support out of which 10 (43.5%) were weaned off. Among the 34 patients in group B, 21 (61.8%) needed ionotropic support out of which 15 (34.8%) were weaned off. Among the 38 patients in group C, 23 (60.5%) needed ionotropic support out of which 19 (50%) were weaned off.

Descriptive analysis of outcome in study population

Table 6

OUTCOME	DEATH (N=25)		DISCHARGE (N=54)		LAMA (N=54)	
	n	%	n	%	n	%
Group A	11	44.0	19	35.2	6	20.7
Group B	5	20.0	15	27.8	14	48.28
Group C	9	36.0	20	37.0	9	31.03
X^2	7.193					
P value	0.303					

Group A- 0.5g/ day of Vit. C **Group B**- 6 g of Vit. C
Group C- 12 g of Vit. C

Among the 36 patients in group A, 11 patients died, 19 patients recovered and 6 patients were lost to follow-up. Among the 34 patients in group B, 5 patients died, 15 patients recovered and 14 patients were lost to follow-up. Among the38 patients in group C, 9 patients died, 20 patients recovered, 9 patients were lost to follow-up. (Table 6)

Discussion

In this prospective randomized study, 108 patients with sepsis satisfying inclusion criteria were included. The final group was segregated into three groups based on the amount of intravenous vitamin C administered. Group A (n=36), B (n=34), and C (n=38) patients were administered 0.5 g/day, 6 g (100 mg/kg/day) and 12 g (200 mg/kg/day) of vitamin C, respectively. In all three groups, most patients were under 20, followed by the age group of 20-40 and females; in contrast to our findings, Jung et al. And Shawver et al. Observed that the mean (SD) age was 69.0 (15.4) years and 65 years (SD 17.3), and 57% were male.[9]

Medical comorbidities, including diabetes mellitus, hypertension, congestive heart failure, ischemic heart disease, malignancy, end-stage renal disease (ESRD), and COPD, are known to influence the body's immune response to infection. In the current study, in group A, the most had hypertension (n=9), followed by diabetes mellitus (n=8), obese (n=2), and tuberculosis (n=1). In group B, the majority had diabetes mellitus (n=12), followed by hypertension (n=11), obese (n=4), and tuberculosis (n=2). In group C, the majority had hypertension (n=8), followed by diabetes mellitus (n=7), obese (n=4), and COPD (n=1). Whiles et al. Reported the mostcommon comorbidity was hypertension (56.2% of encounters), and the least common was peptic ulcer disease (0.04%).[10]

In our study, no significant difference was observed in hemoglobin levels among the three groups on day 1, 3, and 7; however, a statistically significant difference (<0.05) was observed on day 5 as the mean hemoglobin level of 11.716 ± 1.666 was observed in Group C which was higher when compared with Group A. This statistically significant result might show a correlation between high doses of Vitamin C and hemoglobin levels. Later studies have also shown that vitamin C treatment increased blood hemoglobin level, thereby reducing the ESA dose requirement. Hypochromic red blood cells (HRC) reflect iron adequacy for erythropoiesis. A higher HRC percentage is known to be associated with a better response to vitamin C.[11] Further definitive clinical studies are required to confirm this correlation.

A significant difference was observed in serum sodium levels on day 3 as the mean sodium levels were significantly higher for group B (142 ± 7.31) as compared to group A (136.97 ± 6.94) in the present study.

Our data showed a significant difference was observed in serum potassium levels on day 3 as the mean potassium levels were significantly higher for group A (4.35 ± 0.95) as compared to group B (3.75 ± 0.60).

Potassium levels were significantly higher on day 1 when compared with day 3 in group B.

Here, it is a possible that a hospital bias may have prevailed where the sicker patients were retained in the hospital whereas the patients who were improving were leaving the hospital against medical advice.

Blinding was not possible as the ampules of Vitamin C were procured by the patients' attendants. Therefore, neither the nursing officer, the patient nor the analyzing doctor were blinded.

Conclusion

Sepsis remains as a life-threatening medical condition of dysregulated immune response with a mortality rate exceeding 50% in septic shock. In critically ill patients, several investigations have demonstrated low circulating levels of vitamin C, particularly in sepsis. Additionally, laboratory research suggests that vitamin C reduces platelet aggregation of surface P-selectin expression, attenuates hypothalamic neuronal damage, may prevent cellular immunosuppression, impedes phagocyte adhesion to endothelial cells preventing phagocyte oxidative damage and improves endogenous vasopressor synthesis. Despite some promising results, the effects of these vitamins against sepsis remain to be established. Hence the present study was conducted to analyze the role of Vitamin C in sepsis patients.

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