ORIGINAL RESEARCH PAPER

Anaesthesiology

THERAPEUTIC ROLE OF ASCORBIC ACID AS AN ADJUNCT IN SEPSIS: A PROSPECTIVE RANDOMIZED CLINICAL STUDY

KEY WORDS: Ascorbic Acid, Sepsis, Sofa Score, Red Cell Distribution Width

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ABSTRACT

Introduction- Vitamin C is focus of intense interest with respect to its role in treatment of critically ill patients. It has vast beneficial effects including the attenuation of lipid peroxidation, reduced vascular permeability, preservation of endothelial function and microcirculatory flow. **Aim-** To assess the role of ascorbic acid as an adjunct by comparing the three different doses of ascorbic acid in terms of Sequential Organ Failure Assessment (SOFA)Score, acute inflammatory markers- C-reactive protein (CRP), serum lactate levels, Red Cell Distribution width, dose and duration of norepinephrine administration. **Methods-** Total of 233 patients having sepsis admitted to ICU of Rajindra hospital were enrolled in study. Of these, 23 patients died before completing the study duration of 96 hours. Hence, data of 210 patients (70 in each of the three groups) was analyzed using SPSS software and Microsoft excel. Patients received intravenous ascorbic acid 50mg/kg/24hours, 100mg/kg/24 hours, 200 mg/kg/24 hours for 96 hours in group A, group B and group C respectively. **Results-** there was significant reduction in SOFA scores, CRP levels, red cell distribution width, serum lactate levels in all the three groups However, maximum reduction in SOFA scores, CRP levels and red cell distribution width was in group C There was significant reduction in mean dose of noradrenaline in all the three groups and statistically significant difference in mean duration of noradrenaline infusion in all the three groups. **Conclusion-** We conclude that addition of ascorbic acid has improved mean arterial pressure and reduction in dose and duration of noradrenaline in all the three groups indicating early reversal of shock. It also has led to marked reduction in Sofa score, serum lactate levels, CRP and red cell distribution width.

INTRODUCTION-

Vitamin C is focus of intense interest with respect to its role in treatment of critically ill patients. [1] Ascorbic acid (Vitamin C) is an essential nutrient with potent antioxidant properties. [2,3] Since the 'Age of Exploration', many of us have associated Vitamin C deficiency with sailors dying from scurvy only. However, it has become evident that Vitamin C deficiency is certainly not a thing of past but develops during extreme conditions. There is strong evidence that Vitamin C is also effective for many conditions other than scurvy. In controlled trials, Vitamin C has improved endothelial function[4,5,6], lowered blood pressure[7], increased left ventricular ejection fraction[8,9,10,11,12], decreased the incidence of atrial fibrillation[13,14,15] , protected against contrast-induced acute lung injury[16,17], decreased glucose levels in patients with type 2 Diabetes[18], decreased bronchoconstriction[19] , shortened the duration of colds[20,21,22,23,24,25,26], decreased the incidence of colds in physically stressed people[27,28,29] and it has prevented pain[30,31,32) .There is also evidence that Vitamin C has a beneficial effect on pneumonia [26,33]. Previous studies have shown that patients with critical illness, particularly sepsis, have low levels of ascorbic acid in the plasma, which also holds prognostic value due to its inverse correlation with multiple organ failure.

In recent studies, due to low levels of ascorbic acid in critically ill patients, supplemental ascorbic acid has been administered to animal models of sepsis and intensive care unit (ICU) patients. Results from these studies suggest that ascorbic acid improves the condition of critically ill patients, particularly patients having sepsis. Its beneficial effects include the attenuation of lipid peroxidation, reduced vascular permeability, lower levels of microvascular dysfunction, preservation of endothelial function and microcirculatory flow, improved endogenous vasopressor synthesis, increased vasopressor sensitivity and hemodynamic stability. This ultimately leads to reduced organ injury and dysfunction in critically ill patients. [34]

A study conducted by Fowler et al showed that patients receiving the ascorbic acid infusions had significant reduction in inflammatory markers like C- Reactive protein and procalcitonin. There were no adverse events noted during and after the ascorbic acid infusion. Patients receiving ascorbic acid infusion also showed reduction in SOFA scores and there was no rise in thrombomodulin levels in ascorbic acid-infused patients. [33]

A study by Zabet et al also concluded that high dose of intravenous ascorbic acid could be considered as an effective and safe adjunct therapy in critically ill surgical patients having septic shock. [34]

The present study was conducted to compare the effect of different doses of ascorbic acid on Sequential Organ Failure Assessment (SOFA)Score, acute inflammatory markers - C-reactive protein (CRP), serum lactate levels, Red Cell Distribution width, dose and duration of norepinephrine administration.

MATERIAL AND METHODS

Institutional Ethics Committee approval (No. BFUHS/2K21p-TH/14757 dated 15/12/21 was taken prior to study. 262 patients admitted from Nov 2020- Nov 2022 to ICU of Government Medical College and Rajindra Hospital, Punjab having severe sepsis/ septic shock were screened for eligibility. 29 of these patients did not meet the inclusion criteria. Hence, a total of 233 patients were enrolled in study. Of these, 23 patients died before completing the study

duration of 96 hours (10 in group A, 8 in group B and 5 in group C). Hence, data of 210 patients (70 in each of the three groups) was analyzed.

Inclusion Criteria:
All patients, having severe sepsis/ septic shock based on Surviving Sepsis Campaign 2016 admitted to the ICU of Rajindra Hospital, except the patients who met exclusion criteria.

Exclusion Criteria:
age less than 18 years pregnancy do not resuscitate or limitation of care order organ transplantation during ICU stay Episodes other than the first admission episode during the study period were excluded.

Treatment of septic shock in the ICU was based on the Surviving Sepsis Campaign recommendations. Fluid resuscitation strategy was the administration of a crystalloid solution (0.9% saline) to maintain central venous pressure >12 mmHg. In patients who had MAP <65 mmHg despite adequate fluid administration for 6 h, a vasopressor drug (norepinephrine) was started. Norepinephrine was started with a dose of 0.3 mcg/kg/min and was titrated based on the patient's hemodynamic status. Antibiotic regimens were guided based on the hospital recommendations. Stress ulcer prophylaxis (pantoprazole 40 mg daily as intravenous injection) and deep venous thrombosis prophylaxis (heparin 5000 IU every 8 h as subcutaneous injection) were considered for patients.

After taking a written informed consent, these patients were randomized by using randomization table from website www.randomisation.com.

Group A(n=70): Patients allocated to this group were given intravenous ascorbic acid 50mg/kg/24hours in the form of intravenous infusion for 96 hours.

Group B(n=70): Patients allocated to this group were given intravenous ascorbic acid 100mg/kg/24 hours in the form of intravenous infusion for 96 hrs.

Group C(n=70): Patients allocated to the study group were given intravenous ascorbic acid 200 mg/kg/24 hours in the form of intravenous infusion for 96 hours.

The dose of ascorbic acid therapy had been decided on its favourable historical safety profile, and its potential clinical efficacy from previous studies. This therapy was started within 2 to 4 hours following admission to ICU.

Assessment of organ failure Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) score described by Vincent and colleagues. Scores were calculated at enrollment and at 24, 48, 72, and 96 hours. Laboratory daily and recorded.

Table 1. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2 > 400 SpO_2/FiO_2 > 302	PaO_2/FiO_2 < 400 SpO_2/FiO_2 < 302	PaO_2/FiO_2 < 300 SpO_2/FiO_2 < 221	PaO_2/FiO_2 < 200 SpO_2/FiO_2 < 142	PaO_2/FiO_2 < 100 SpO_2/FiO_2 < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP ≥ 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x $10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

According to Sepsis-3, a new (or presumed new) increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with incremental increases in mortality.

Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

Table/ Figure1- Sequential Organ Failure Assessment Score(sofa)

Study Drug Infusion And Safety Monitoring
Vital signs were monitored continuously and were documented every 5 minutes during infusion. Four objective indices were monitored during and after ascorbic acid infusion: Hypotension: Defined as a fall in mean arterial blood pressure of 20 mm Hg during or following infusion from the baseline.

- Tachycardia: Defined as an increase in heart rate of 20 beats per minute during or following infusion from the baseline.
- Hypernatremia: L-Ascorbic acid preparation used for this study presents a minor sodium load, therefore a potential for hypernatremia to develop exists.
- Nausea or vomiting: will be monitored both during and after ascorbic acid administration by investigators and by ICU nursing staff.

If one of the adverse events listed above was observed, ICU nursing was equipped with bedside algorithms designed to manage the adverse event. If an event was observed, drug infusion was halted. If the event resolved, drug infusion was restarted at 50% of the original infusion rate. If the event recurred, the patient was removed from the study.

Blood Samples Biomarkers and routine investigation protocol of ICU was strictly followed and documented. 1) C-Reactive Protein (CRP): A high sensitivity C-reactive protein (hsCRP) assay was performed on an automated chemistry analyser every 24 hourly. 2) Serum lactate levels: A high sensitivity serum lactate levels were performed on automated arterial blood gas analyser every 24 hourly. 3) Red Cell Distribution Width.

Statistical Analysis
The ICU admission and treatment data of the study patients were obtained from hospital medical records. The information included age, sex, body weight, hospital and ICU admission record, ICU admission diagnosis, site of admission, comorbidities, duration of mechanical ventilation, duration of ICU stay, hospital and ICU discharge date, date of death, levels of serum lactate and CRP on the day of ICU admission and SOFA scores.

Data collected was then assessed statistically. Descriptive statistics was done for all data and was reported in terms of mean, SD and percentages.

Appropriated statistical tests of comparison were applied. Categorical variables were analyzed with the help of chi square test and Fisher Exact Test.

Continuous variables were analyzed with t-test , kruskal wallis test and Mann Whitney U test where-ever applicable. $p>0.05$ was taken as nonsignificant. The p value <0.05 was taken as significant and value <0.001 was taken highly significant.

RESULTS
Demographic Parameters-
the distribution of patients according to age, gender, weight and comorbidities was similar in the three groups. All the three groups were comparable and statistically non-significant (p value >0.05). (table/figure2)

Clinical Diagnosis-
Table/figure 3: Distribution of patients according to Diagnosis
Baseline and Follow-up Parameters of All Patients-
Hemodynamic parameters and laboratory tests showed highly significant difference between the groups.

In addition, changes in these parameters during the study period were also statistically highly significant. Data regarding these parameters are shown in Table/figure 4.

Table/figure 2

Demographic parameters	Group A n (%)	Group B n (%)	Group C n (%)	P value (Chi square)
Age (years)				
18-30 Years	10 (14.29%)	20 (28.57%)	18 (25.71%)	0.527 (NS)
31-50 Years	29 (41.43%)	20 (28.57%)	17 (24.29%)	
51-60 Years	31 (44.28%)	30 (42.86%)	35 (50%)	
Gender				
Female	30 (42.86%)	39 (55.72%)	35 (50%)	0.315 (NS)
Male	40 (57.14%)	31 (44.28%)	35 (50%)	
Weight(kg)				
Mean± SD	71.70±9.88	69.16±10.11	70.76±11.88	0.08 (NS)
No Comor bidities	47 (67.14%)	39 (55.71%)	32 (45.71%)	0.476 (NS)
Comorbidities (DM/TN/BA/HIV/HCV /COPD/CKD)	23 (32.86%)	31 (44.29%)	38 (54.29%)	

Table/figure 3: Distribution of patients according to Diagnosis

Diagnosis	Group A (N=70)		Group B (N=70)		Group C (N=70)	
	Patients	Percentage	Patients	Percentage	Patients	Percentage
Acute Gastroenteritis	1	1.43%	0	0%	0	0%
Acute Pancreatitis	0	0%	1	1.43%	1	1.43%
Psoas Abscess	0	0%	1	1.43%	1	1.43%
APPENDICULAR ABSCESS	2	2.86%	1	1.43%	1	1.43%
Brain Abscess	1	1.43%	0	0%	0	0%
Bed Sores	1	1.43%	0	0%	1	1.43%
BRONCHIECTASIS	1	1.43%	1	1.43%	1	1.43%
COPD	2	2.86%	0	0%	0	0%
LOWER LIMB CELLULITIS	1	1.43%	0	0%	3	4.29%
CVA with aspiration pneumonitis	1	1.43%	0	0%	0	0%
DEEP NECK SPACE INFECTION	0	0%	0	0%	1	1.43%
Diabetic Foot	1	1.43%	0	0%	0	0%
Emphysematous Cholecystitis	1	1.43%	0	0%	0	0%
ENTERIC FEVER	1	1.43%	0	0%	0	0%
FOURNIER GANGRENE	0	0%	1	1.43%	2	2.86%
Gangrene/GANGRENE FOOT	1	1.43%	1	1.43%	2	2.86%
HEPATIC ENCEPHALOPATHY	0	0%	0	0%	1	1.43%
Mucormycosis	1	1.43%	2	2.86%	0	0%
Meningoencephlitis	0	0%	2	2.86%	0	0%
MENINGITIS	1	1.43%	1	1.43%	2	2.86%
NACROTIZING PANCREATITIS	1	1.43%	1	1.43%	1	1.43%
Pancreatitis/acute pancreatitis	0	0%	2	2.86%	0	0%
Pneumonia/PNEUMONITIS	1	1.43%	2	2.86%	1	1.43%
Perforation Peritonitis	8	11.43%	2	2.86%	5	7.14%
post lscs septicemia	0	0%	2	2.86%	0	0%
Intestinal obstruction	3	4.29%	5	7.14%	1	1.43%
PYELONEPHRITIS	2	2.86%	0	0%	1	1.43%
RUPTURED LIVER ABSCESS	1	1.43%	0	0%	2	2.86%
RETROPHARYNGEAL ABSCESS	0	0%	0	0%	1	1.43%
SARI	32	45.71%	31	44.29%	37	52.86%
RSA with sepsis	2	2.86%	15	21.43%	4	5.71%
TB/ Pulmonary TB	1	1.43%	0	0%	0	0%
UROSEPSIS	2	2.86%	1	1.43%	0	0%
PERINEPHERIC ABSCESS	1	1.43%	1	1.43%	1	1.43%
Kruskal Wallis	3.793					
p value	0.150 (NS)					

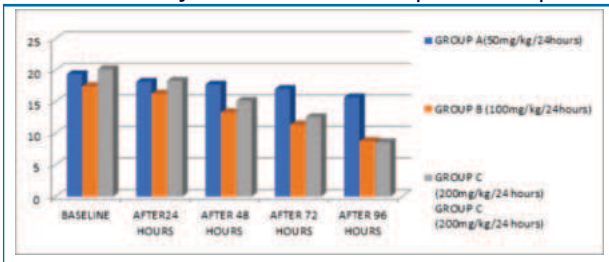
Table/figure4

Parameter	hours	Group A		Group B		Group C		P value
		MEAN	SD	MEAN	SD	MEAN	SD	
Mean temperature	baseline	100.64	1.21	102.03	0.85	102.34	1.09	0.001
	24	101.00	1.20	101.51	1.18	102.16	1.30	0.001
	48	100.65	1.08	100.53	1.15	101.46	1.11	0.001
	72	100.44	1.27	101.23	1.44	101.06	1.49	0.003
	96	100.07	1.21	100.49	1.75	100.33	1.64	0.288
Mean heart rate (in beats per min)	baseline	149.69	8.26	139.90	11.16	144.56	16.23	0.001
	24	143.04	11.02	131.20	12.75	147.00	14.94	0.001
	48	140.37	11.65	119.10	12.32	137.51	16.38	0.001
	72	143.77	9.46	127.74	12.12	136.16	9.71	0.001
	96	137.09	10.42	118.21	18.41	137.77	15.87	0.001

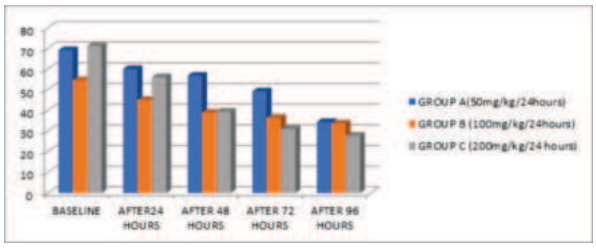
Mean of Mean arterial pressure (in mmHg)	baseline	63.69	3.26	65.10	3.22	64.26	3.06	0.032
	24	67.80	2.71	70.41	3.49	68.37	4.08	0.001
	48	70.27	3.12	73.19	4.91	67.44	1.72	0.001
	72	70.47	2.38	75.29	2.89	75.20	3.10	0.001
	96	71.27	2.17	76.16	2.65	75.16	2.93	0.001
Mean oxygen saturation (%)	baseline	87.19	4.25	85.46	2.44	86.64	1.95	0.03
	24	92.23	1.69	87.73	1.78	89.26	2.07	0.001
	48	92.54	1.86	91.09	2.05	88.29	2.41	0.001
	72	93.24	2.31	90.86	2.18	89.04	2.98	0.001
	96	92.97	2.11	92.49	1.63	90.11	1.40	0.001
Mean urine output (in ml)	24	1428.86	567.02	1633.57	509.24	1644.29	167.36	0.007
	48	1791.00	599.08	1640.00	410.87	1940.00	307.59	0.001
	72	1789.43	582.13	1958.57	269.99	2044.29	312.83	0.001
	96	1915.71	498.22	1928.57	259.40	1781.01	371.13	0.047
Mean GCS	baseline	11.77	1.42	10.94	1.47	11.26	1.32	0.002
	24	11.66	1.63	11.69	1.34	11.46	1.69	0.641
	48	11.93	1.57	12.03	1.42	12.14	1.43	0.692
	72	12.73	1.39	12.94	1.78	12.37	1.09	0..65
	96	12.77	1.37	12.99	1.55	13.30	1.13	0.072
Mean Pao2/ FiO2	baseline	138.67	40.40	89.61	18.75	104.70	26.97	0.001
	24	166.81	46.05	118.90	25.91	170.80	41.82	0.001
	48	211.07	51.76	173.80	38.41	224.47	48.19	0.001
	72	202.70	57.20	204.56	47.23	245.67	51.16	0.001
	96	240.46	54.26	226.90	45.01	311.07	43.83	0.001
Mean total leucocyte count	baseline	38739.10	8654.25	36514.29	7617.19	31128.57	2340.08	0.001
	24	37682.17	8940.25	30142.86	7907.59	31085.71	2205.02	0.001
	48	32142.74	6992.66	24557.14	6087.85	29228.57	2915.09	0.001
	72	28160.23	8234.41	26274.29	5429.62	19700.00	5988.76	0.001
	96	25713.86	7054.73	28200.00	3661.79	15442.86	3043.81	0.001

Table/figure 5

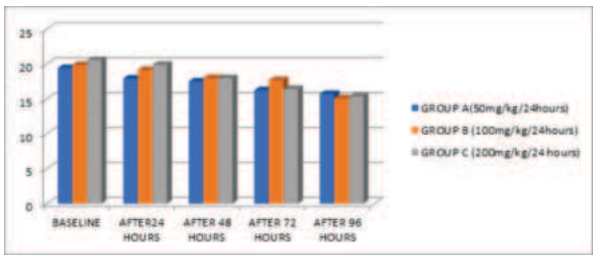
Parameter	hours	Group A		Group B		Group C		P value
		MEAN	SD	MEAN	SD	MEAN	SD	
Mean SOFA score	baseline	19.36	2.13	17.47	4.05	20.14	1.42	0.001
	24	18.17	1.38	16.27	2.65	18.31	1.29	0.001
	48	17.74	1.68	13.34	2.33	15.13	2.19	0.001
	72	17.03	1.99	11.39	1.84	12.56	1.62	0.001
	96	15.70	2.62	8.79	2.07	8.60	2.04	0.001
	% reduction in SOFA score from baseline	18.893%		49.714%		57.305%		
Mean CRP levels (in mg/dl)	baseline	69.16	6.32	54.59	15.94	71.24	11.76	0.001
	24	60.01	5.88	45.06	9.10	56.10	9.81	0.001
	48	56.83	7.89	38.96	5.67	39.41	5.93	0.001
	72	49.26	5.81	36.46	7.75	30.99	6.26	0.001
	96	34.41	8.33	33.71	8.01	27.74	4.37	0.001
	% reduction in CRP from baseline	50.238%		38.236%		61.059%		
MEAN RED CELL DISTRIBUTION WIDTH (in %)	baseline	19.41	1.97	19.83	1.38	20.53	1.75	0.001
	24	17.91	1.47	19.13	1.53	19.87	1.28	0.001
	48	17.49	1.03	17.97	1.50	17.96	1.39	0.049
	72	16.23	1.25	17.66	1.60	16.41	0.50	0.001
	96	15.69	1.35	15.07	1.98	15.33	1.06	0.056
	% reduction in RDW from baseline	19.205%		23.991%		25.331%		
MEAN SERUM LACTATE LEVELS (in mmol/L)	baseline	8.09	1.44	7.93	1.38	9.56	1.75	0.001
	24	6.60	1.42	7.39	1.66	9.59	1.12	0.001
	48	6.56	1.82	6.74	1.69	7.47	1.19	0.002
	72	5.13	1.36	5.76	1.08	4.14	0.97	0.001
	96	5.10	1.43	4.13	1.46	2.63	1.17	0.001
	% reduction in serum lactate from baseline	36.926%		72.496%		47.928%		
MEAN DOSE OF VASOPRESSOR/ NORADRENALINE (in mcg/kg/min)	baseline	0.58	0.55	0.54	0.11	0.52	0.10	0.578
	24	0.50	0.14	0.53	0.10	0.52	0.10	0.399
	48	0.43	0.15	0.39	0.09	0.38	0.08	0.014
	72	0.41	0.15	0.32	0.10	0.24	0.11	0.001
	96	0.34	0.14	0.18	0.08	0.11	0.08	0.001
	% reduction in noradrenaline from baseline	40.741%		65.782%		78.356%		
MEAN DURATION OF NORADRENALINE INFUSION (in hours)		74.74	9.83	71.24	11.22	61.06	11.42	0.001



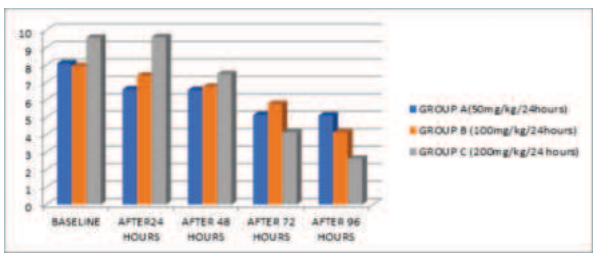
Table/figure 6- Mean Sofa Score At Different Time Interval



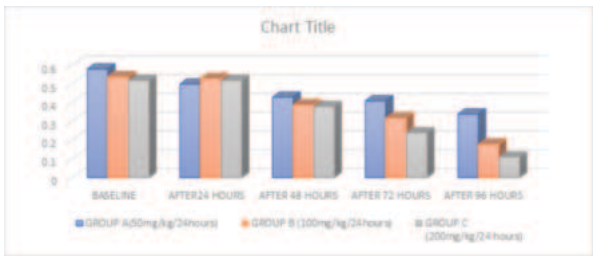
Table/figure 7- Mean Crp Levels (in Mg/dl) At Different Time Interval



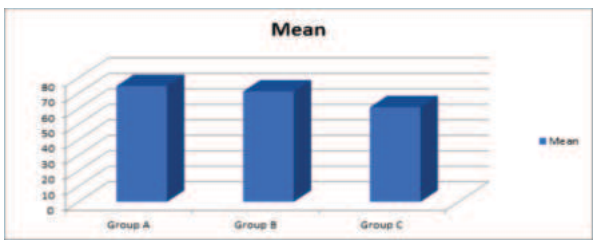
Table/figure 8- Mean Red Cell Distribution Width (in %) At Different Time Interval



Table/figure 9 - Mean Serum Lactate Levels (in Mmol/l) At Different Time Interval



Table/figure 10 Mean Dose Of Vasopressor/ Noradrenaline (in Mcg/kg/min) At Different Time Interval



Table/figure 11 Mean Duration Of Noradrenaline Infusion (in Hours)

DISCUSSION-

Ascorbic acid is a water-soluble vitamin and an essential endogenous trace element that scavenges reactive oxygen species (ROS) and reduces immunosuppression. Previous studies have shown that patients with critical illness, particularly sepsis, have low levels of ascorbic acid in the plasma which also holds prognostic value due to its inverse correlation with multiple organ failure SOFA scores are robust indicators of mortality due to critical illness. in present study SOFA scores at enrollment were 19.36 ± 2.13, 17.47± 4.05, 20.14± 1.42 in group A, group B and group C respectively. 96 hours after ascorbic acid infusion SOFA scores were 15.70± 2.62, 8.79±2.07, 8.60± 2.04 in group A, group B and group C respectively. Mean reduction in SOFA score all the groups was statistically highly significant (p value 0.001). However maximal reduction in SOFA score from baseline was in group C (57.30%). **Our findings are consistent** with study conducted **Fowler et al** 2014 in which there was significant reduction in SOFA score in groups receiving ascorbic acid infusion. Patients receiving higher dose of ascorbic exhibited significantly faster decline in the SOFA score as compared to placebo.[36] **Our findings are also in concordance** with study conducted by **Marik et al (2017)** in which there was highly significant reduction in SOFA score in the group receiving ascorbic acid.[37]However, **our results are contrary** to study conducted by **Moskowitz et al (The ACTS trial)** in which there was no statistically significant difference between intervention group receiving ascorbic acid and control group in change of SOFA score over 72 hours (8.95% reduction) (p value 0.12). The difference in results can be due difference in ascorbic acid dose (1500 mg in ACTS trial) and baseline SOFA score (9.1 and 9.2 in ascorbic acid group and placebo whereas in our study SOFA score was19.36 ± 2.13, 17.47± 4.05, 20.14± 1.42 in group A, group B and group C respectively).[38]

CRP is an acute phase reactant protein primarily induced by IL-6 during the acute phase of inflammatory/ infectious process. In present study table 4 shows that in group A there was 50.238% reduction serum CRP levels from the baseline, while in group B and C it was 38.23% and 61.05% respectively. The difference from baseline is statistically highly significant in all the groups showing that addition of ascorbic acid markedly reduces the inflammation resulting in reduction in inflammatory markers. **Our findings are consistent** with phase 1 trial conducted by **Fowler et al (2014)** in which there was statistically significant reduction CRP levels in patients receiving higher dose of ascorbic acid infusion than placebo (p value <0.05).[36]

Red blood cell distribution width (RDW) is a parameter routinely reported as part of a complete blood count. It measures the size variability of circulating erythrocytes (anisocytosis). Anisocytosis reflects the dysregulation of the iron metabolism and inhibition of erythropoiesis resulting in chronic anemia, mediated by diverse cytokines, mainly IL-6. Moreover, these changes in the red blood cell physiology are particularly common in critical illness, in patients admitted to the ICU and in hyperinflammatory states. In consequence, and since it is a fast and available parameter, several studies have considered RDW as an inflammatory marker or a predictor of mortality in diverse clinical settings including chronic inflammatory diseases, cardiovascular disease, infections and acute respiratory distress syndrome (ARDS).[39] In present study, table 5 shows statistically highly significant reduction in mean red cell distribution width from baseline in group A (19.205%), B (23.991%) and C (25.331%). However, we could not compare our results as on search of literature there were no studies available to study the effect of ascorbic acid on red cell distribution width.

Mean reduction in serum lactate levels in group A was 36.92%, group B was 72.49% and in group C was 47.92%. Mean reduction in serum lactate levels was statistically highly significant showing improved tissue perfusion. It means

improvement in MAP leads to improvement in tissue perfusion resulting in improvement of serum lactate levels. **Our study is similar** to study of **Iglesias et al** as far as reduction in serum lactate levels is concerned. However, our study shows statistically highly significant reduction in serum lactate levels while study conducted by Iglesias shows no statistically significant reduction. This difference in results can be due to use of low dose of ascorbic acid (1500 mg 6 hourly) in their study as compared to our study.[40]

In our study, table 4 show that mean of MAP before starting the infusion, of group A, group B and group C was 63.69 ± 3.26, 65.10 ± 3.22 and 64.26 ± 3.06 mm of Hg respectively (MAP<65mmHg). Infusion noradrenaline was started and mean dose of noradrenaline of group A, group B and group C was 0.58 ± 0.55, 0.54 ± 0.11 and 0.52 ± 0.10 mcg/kg/min respectively (table 5). There was improving trend in MAP and reduction in requirement of noradrenaline which was significant at 48 hours after the admission and then became highly significant. After 96 hours mean of MAP, of group A, group B and group C was 71.27 ± 2.17, 76.16 ± 2.65 and 75.16 ± 2.93 mm of Hg respectively (table 4). Mean dose of noradrenaline, at 96 hours in group A, B, C is 0.34, 0.18 and 0.11 mcg/kg/min respectively (table 5) which is significantly lower than baseline indicating reversal of shock. **Our results are also consistent** with study conducted by **Zabet et al** in which mean dose of norepinephrine in group receiving ascorbic acid was 7.44± 3.65 vs 13.79± 6.48 mcg/min in control group. Difference between both the groups was statistically significant.[35]

Earlier liberation from noradrenaline carries significance as it potentially prevents the immunosuppressive effects of catecholamines minimizing the risk of mesenteric, limb and end organ ischemia. **In present study** table 5 shows that mean duration of noradrenaline, in group A was 74.74±9.83 hours, in group B was 71.24±11.22 hours and in group C was 61.06±11.42 hours. Difference between group A, B and C is statistically highly significant. There is apparent earlier liberation from noradrenaline in group C. **Our results are consistent** with study conducted by **Zabet et al in** which duration of noradrenaline administration was significantly lower in ascorbic acid group than the placebo group (49.64 ±25.76 hours in ascorbic acid group vs 71.57± 1.60 hours in placebo group) (p value 0.007).[35]

CONCLUSION-

As in sepsis there is dysregulated host response to infection. Therefore safe, effective, affordable adjuvant that focus on mitigating dysregulated host response is required. Ascorbic acid is a safe anti-oxidant nutrient having anti-inflammatory, nitric oxide synthase inhibitory, reversing vascular hypo responsiveness to vasopressors, increasing catecholamines and cortisol synthesis in adrenal medulla and improving vascular endothelium integrity properties which may justify the role of ascorbic acid as an adjunct in septic shock. The results of our study conclude that addition of ascorbic acid has improved mean arterial pressure and reduction in dose and duration of noradrenaline in all the three groups indicating early reversal of shock. It also has led to marked reduction in Sofa score, serum lactate levels, CRP and red cell distribution width.

Limitations-

Although the results of our study are promising, the study suffers from some limitations too. No assessment of serum ascorbate levels, no control group and insufficient studies to compare data with are major limitations of our study.

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