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A STUDY TO DETERMINE ROLE OF VITAMIN C AS AN ADJUVANT THERAPY IN CHILDREN WITH SEPSIS

Paediatrics

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ABSTRACT

Introduction: Shock is an acute process characterized by the body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues. Insufficient oxygen at the tissue level is unable to support normal aerobic cellular metabolism, resulting in a shift to less efficient anaerobic metabolism. During sepsis, vitamin C prevents neutrophil-induced lipid oxidation and protects against endothelial barrier loss. Therefore, early intravenous supplementation for sepsis would be beneficial in preventing microcirculation loss and lipid oxidation. **Methods:** The present study was hospital based Prospective Interventional study carried out on all Pediatric Intensive Care Unit (PICU) admitted patients in inclusion criteria, in the Department of Paediatrics at Dr. Susheela Tiwari Government Hospital Haldwani (Uttarakhand) during study period January 2020- September 2021 after obtaining ethical clearance from Institutional Review Committee and informed consent from patient or patient relatives. Statistical testing has been conducted using R Studio Software version 4. **Results:** The difference in mean dose of dopamine and mean duration of norepinephrine therapy and number of vasopressors used was statistically significant between group 1 and 2, where group 1 was given Vitamin C as adjuvant therapy along with protocol-based treatment of septic shock and Group 2 was not given Vitamin C. **Conclusion:** The present study concluded that significant role of Vitamin C is present in reducing the mean dose and duration of vasopressors in children presenting with septic shock. While no role is seen in reducing duration of ventilator therapy, total duration of oxygen support, duration of PICU and hospital stay and outcome of patients with septic shock.

KEYWORDS

Septic Shock, Vitamin C, Vasopressors, PICU.

INTRODUCTION

Shock is an acute process characterized by the body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues. Insufficient oxygen at the tissue level is unable to support normal aerobic cellular metabolism, resulting in a shift to less efficient anaerobic metabolism. As shock progresses, increase in tissue oxygen extraction is unable to compensate for this deficiency in oxygen delivery, leading to progressive clinical deterioration and lactic acidosis. If inadequate tissue perfusion persists, adverse vascular, inflammatory, metabolic, cellular, endocrine, and systemic responses worsen physiologic instability.[1] Vitamin C may increase endothelial nitric oxide by protecting it from oxidation and increasing its synthesis thus ameliorating endothelial dysfunction. Low Vitamin C levels are associated with impaired endothelial functions.[2] Vitamin C plays a role in mediating inflammation through antioxidant activity and is an important co-factor/co-substrate for the synthesis of endogenous adrenaline, cortisol and vasopressin. During sepsis, vitamin C prevents neutrophil-induced lipid oxidation and protects against endothelial barrier loss. Therefore, early intravenous supplementation for sepsis would be beneficial in preventing microcirculation loss and lipid oxidation.

MATERIALS AND METHODS

This was a hospital based Prospective Interventional study, carried out on all PICU admitted patients who fulfilled the inclusion criteria, in the Department of Paediatrics at Dr. Susheela Tiwari Memorial Hospital and associated Government Medical College, Haldwani (Uttarakhand) from January 2020 to September 2021.

Treatment of septic shock in the PICU was based on the Surviving Sepsis Campaign recommendations.[1] The study included total 80 number of patients of age group 5-15 years who were admitted in PICU who fulfilled the inclusion and exclusion criteria. Patients were divided in group 1 and group 2 alternately. Odd number taken in group 1 and even number taken in group 2. 40 patients were included in group 1 and 40 patients in group 2. In group 1, vitamin C was given at the dose of 100mg/kg/day[3] in two divided doses [max. 6g] diluted in distilled water [1g vitamin C/25ml DW] for 72 hours as adjuvant therapy along with protocol-based treatment of septic shock. Group 2 was not given Vitamin C. A detailed history was taken from patients attendants. Patients demographic data (including age, sex, baseline diseases) were taken from their medical charts and the patients clinical characteristics (such as vital signs and hemodynamic parameters) were monitored. Laboratory data such as serum electrolyte, blood urea nitrogen (BUN), and serum creatinine levels were also taken from the patient's medical charts. Acute Physiology and Chronic Health Evaluation II (APACHE II) and Paediatric sequential organ failure assessment (PSOFA) scores were calculated at the time of recruitment.

Vasopressor dose and duration were evaluated on a daily basis for 72 hours and were considered as the primary outcome. Duration of ventilator support, total duration of oxygen support, duration of ICU and hospital stay and outcome were considered as secondary outcomes. During the hospital stay and after 1 month, patients were followed for any ascorbic acid related adverse effects including nausea, vomiting, abdominal pain, hematuria, flushing and blood pressure change.

Patients attendants were counselled about the objectives of the study, and written consent obtained. Structured interviews were conducted at first contact with the patients attendants. During hospital stay and at discharge, they were explained in detail about the nature of the patients condition and counselled regarding further follow up.

Data collection tool was a pre-coded, pretested questionnaire which was also translated in the local dialect. All the patients details were followed till they were discharged/expired. Data was analysed using R Studio Software version 4. Categorical variables were reported as percentages. Two sample z-test for proportion was used for comparing categorical variables between the groups. Continuous variables were compared by Welch Two Sample t-test. P value <0.05 was defined as statistically significant.

Selection Criteria:

Inclusion Criteria

Children of either gender, age group 5-15 year admitted in PICU with septic shock (SIRS+ Suspected or proven infection + Cardiovascular system dysfunction).

Exclusion Criteria

- Concomitant use of other antioxidants (such as Vitamin E, selenium and N-acetylcysteine).
- Any contraindication for high dose ascorbic acid including bilateral ureteric obstruction.
- Chronic hemodialysis
- Oxalate stone formers
- Not giving consent
- H/O Urinary stones

RESULTS:

Table 1: Baseline characteristics of the study subjects

Variables	Categories	Frequency (Percentage)		P value
		Group 1	Group 2	
Age Group (in years)	5-10 11-15	26 (65) 14(35%)	23(57.5) 17(42.5)	0.8
Gender	Female Male	23(57.5) 17(42.5)	25(63) 15(37)	0.1
Systemic Involvement	Respiratory System Central Nervous System Cardiovascular System Gastrointestinal System	18(45) 14(35) 5(12.5) 3(7.5)	14(35) 14(35) 9(22.5) 3(7.5)	-
Baseline Diseases	Pneumonia Meningitis Febrile illness Dengue Liver Abscess Hepatitis Pulmonary Kochs	18(45) 13(32.5) 4(10) 3(7.5) 1(2.5) 1(2.5) -	14(35) 14(35) 6(15) 3(7.5) 2(5) - 1(2.5)	-
SIRS Parameters	Pulse rate Respiratory rate TLC (<4000/>11000) Temperature (>101.3/<96.5)	37(92.5) 33(82.5) 27(67.5) 8(20)	39(97.5) 39(97.5) 24(60) 14(35)	0.6 0.06 0.6 0.2
Lab Parameters	Anemia (Hb<11mg/dl) Leucocytosis (11000/mm3) Thrombocytopenia (<1.5 lakh/µL) Abnormal SGOT Abnormal SGPT Leucopenia(<4000/mm3) Abnormal Creatinine	30(75) 21(53) 20(50) 15(37.5) 13(32.5) 6(15) 4(10)	26(65) 23(57) 15(38) 18(45) 17(42.5) 1(2.5) 9(22.5)	0.4 0.8 0.3 0.6 0.4 0.1 0.2

Systemic involvement was comparable in the two groups with Respiratory system as the most commonly involved. Pneumonia was the most common baseline disease in our study.

Table 2: Clinical and laboratory markers of the study subjects

Variables	Group 1 (Mean±SD)	Group 2 (Mean±SD)	p value
Hemoglobin(g/dl)	9.9± 1.54	10.2± 1.89	0.5
Total leucocyte count (/mm3)	12996± 8779	14445± 8942	0.4
Platelet Count (lakh/µL)	1.87± 1.33	1.88± 1.26	0.9
Hematocrit(%)	31.2± 4.54	31.7± 5.33	0.6
Sodium (meq/L)	135.1± 6.37	134.2± 8.98	0.5
Potassium (meq/L)	4.3± 0.64	4.2± 0.64	0.5
Urea(mg/dl)	37.55± 11.6	40.25± 25	0.5
Creatinine(mg/dl)	0.6± 0.27	0.8± 0.42	0.04
BUN(mg/dl)	17.9± 5.43	20.5± 12.03	0.2
SGPT(U/L)	85± 132	60± 47	0.2
SGOT(U/L)	109± 145	70± 53	0.1
pSOFA score	6.75± 2.20	6.8± 1.88	0.9
APACHE	13.4± 4.27	14.7± 3.75	0.1

Most of the lab parameters were comparable in the 2 groups that is p value >0.05. Although mean creatinine value was in normal range in both the groups, the difference was statistically significant (p value=0.04).

Table 3: Outcome of the study subjects

PARAMETERS (MEAN±SD)	GROUP 1	GROUP 2	P value
Mean dose of nor epinephrine (µg/kg/min)	0.25 ± 0.05	0.29 ± 0.20	0.25
Mean dose of Dopamine (µg/kg/min)	10.3 ± 1.33	11.6 ± 2.41	0.047
Mean dose of Dobutamine (µg/kg/min)	11 ± 2.23	11.7 ± 2.48	0.5
Mean duration of nor epinephrine in hours	74.3 ± 37.64	92.1 ± 30.47	0.02
Mean duration of dopamine in hours	85.8 ± 61.43	99.2 ± 37.40	0.4
Mean duration of dobutamine in hours	120.1 ± 83.9	110.3 ± 36.8	0.7
Mean duration of mechanical ventilation in hours	79.5 ± 57.54	101 ± 38.21	0.2
Mean duration of oxygen support in hours	98.6 ± 41.75	95.6 ± 35.3	0.7
Duration of PICU stay in hours	103.2 ± 39.14	103.6 ± 30.39	0.9
Mean duration of hospital stay in days	11.37 ± 3.98	11.55± 4.08	0.8
Proportion of survived patients	0.85	0.82	1

Table 3 shows that mean dose of dopamine (p value-0.047) and mean duration of nor epinephrine (0.02) showed statistically significant difference in the two groups.

DISCUSSION

Septic shock in paediatric age group is a major cause of morbidity and mortality worldwide particularly in developing countries. Implementation of additional layers in the management of septic shock may increase the overall efficacy of the protocol-based treatment of septic shock in children. Vitamin C plays a protective role in sepsis by acting on impaired endothelium, production of endogenous vasopressors and through its antioxidant activities.

In our study septic shock was more common in age grp 5-10 years in both the groups. Incidence in females was more common as compared to males in our study. In the study conducted by Singh D et al male female ratio was 1.6:1. [4] In a study done by Kaur G et al 30 males and 20 females were included in the study.[5]

Pneumonia was the most common cause of septic shock in our study followed by Meningitis/Meningoencephalitis. Similar findings were observed in past studies. Fisher JD et al reported predominance of respiratory illness and isolation of respiratory pathogen from the septic shock patients. [6] In a study conducted by Gaines et al in children with clinically diagnosed sepsis they found that 13% had lobar pneumonia, 12% had bacteremia and 10% viral infections. No etiologies were found in 76% cases. [7] Study by Kurade A et al, also reported Pneumonia as the most common cause of septic shock.[8]

In our study Tachycardia and Tachypnea were the most common abnormalities observed in subjects fulfilling SIRS criteria followed by total leukocyte count and temperature respectively. In the study conducted by Kurade A et al, total leukocyte count and temperature were the most common abnormalities observed. Militaru M et al observed the most common abnormal criteria to be temperature followed by leukocyte count.[9] As compared to above studies in our study abnormal heart rate and respiratory rate were seen more commonly.

Lab parameters were comparable in the 2 groups, in our study. Anemia (70%) followed by leukocytosis (55%) was the most common hematological abnormality seen followed by thrombocytopenia (43.75%), abnormal SGPT (41.25%), abnormal SGOT (37.5%), leukopenia (8.75%) and abnormal creatinine (16.25%) respectively. Similar results were reported in other studies. In the study by Kurade A et al anemia (62.79%) followed by leukocytosis (60.46%) and

thrombocytopenia (55.81%) were most commonly seen. Elevated liver enzyme was the most (86.04%) common biochemical abnormality seen in this study. In a study by Benamer et al, they observed leukocytosis in 50%, anemia in 40%, leucopenia in 10% and raised liver enzymes in 43%. They observed thrombocytosis (38%) more frequently than thrombocytopenia (10%). [10]

No statistically significant difference was observed in baseline pSOFA and APACHE 2 Score between the two groups in our study. In the VITAMIN Trial by Fujii T et al, mean pSOFA and APACHE 2 score at admission was higher in Group 1 compared to Group 2.[11] In our study the two groups had comparable pSOFA (p value=0.9) and APACHE 2 (p value=0.1) score.

In our study, the difference in mean dose of norepinephrine in the two groups was not statistically significant (0.25 ± 0.05 and 0.29 ± 0.20, p value=0.27). A statistically significant difference was observed in the mean dose of dopamine between the two groups (10.3 ± 1.33 and 11.6 ± 2.41, p value=0.047). The difference in mean dose of dobutamine was statistically insignificant (11 ± 2.23 and 11.7 ± 2.48, p value=0.5). In the study done by Zabet et al, mean dose of norepinephrine during the study period (7.44 ± 3.65 vs. 13.79 ± 6.48 mcg/min, p = 0.004) was significantly lower in the ascorbic acid than the placebo group. They used norepinephrine only but we used norepinephrine, dopamine than dobutamine respectively as the vasopressor of choice for septic shock.

The difference in mean duration of norepinephrine therapy in our study was statistically significant between the two groups (74.3 ± 37.64 and 92.1 ± 30.47, p value=0.02). Nonsignificant difference in mean duration of dopamine and dobutamine was observed. Similar results were reported in other studies. Jamshidi et al reported that mean duration of vasopressor dependency was shorter in the intervention group (P = 0.039) compared to control group.[12] Study by Marik et al reported that patients in the treatment group were weaned off vasopressors, a mean of 18.3 ± 9.8 h after starting treatment with the vitamin C protocol. The mean duration of vasopressor use was 54.9 ± 28.4 h in the control group (P < .001).[13] Zabet et al found that duration of norepinephrine administration (49.64 ± 25.67 vs. 71.57 ± 1.60 h, p = 0.007) were significantly lower in the ascorbic acid than the placebo group. Study conducted by Wani et al [14] noted statistically significant difference in duration of vasopressor use (p value =0.010) between the two groups. Studies done Fuji T et al, Mitchell AB et al [15] observed no significant difference in mean duration of vasopressor therapy between treatment and control groups. Significant difference is seen in number of vasopressors used in group 1 compared to group 2 in our study. Single vasopressor was used in 65% patients in group 1 and 40% in group 2, p value=0.04.

A nonsignificant difference in the mean duration of ventilator use was observed between the two groups (79.5 ± 57.54 and 101 ± 38.21, p value=0.2). The total duration of oxygen support also showed no statistically significant difference between the two groups (98.6 ± 41.75 and 95.6 ± 35.3, p value=0.7). The total duration of oxygen support is slightly higher in group 1 compared to group 2 may be because there are more patients with respiratory system involvement in group 1 then in group 2. Similar results were also obtained by Fuji T et al, Kim WY et al [16] wherein they observed no statistically significant difference in ventilator free days between treatment and control group. The mean duration of PICU stay between the two groups was statistically insignificant (p value=0.9). Similar results were obtained in other studies. Mohamed Zu et al, [17] Fuji T et al and Zabet et al, also reported no statistically significant difference in ICU length of stay between group which was given Vitamin C as an adjuvant therapy and the control group. A study done by Fowler AA et al [18] and Mitchell AB et al, observed significant increase in ICU free days.

Similarly the mean duration of hospital stay was more in group 2 compared to group 1 but the difference was statistically insignificant (11.37 ± 3.98 and11.55± 4.08, p value=0.8). Study conducted by Mitchell AB et al observed no significant difference in duration of hospital stay between the two groups.

No statistically significant difference was found in proportion of patients who survived between the two groups (p value=1). No difference in hospital mortality was noticed in study conducted by Mitchell AB et al, Mohamed Zu et al, Fuji T et al, Wani SJ et al. Other studies conducted by Marik et al, Jamshidi et al found a significant reduction in hospital mortality in the treatment group in patients with septic shock.

Vitamin C levels were not done at our centre so serum levels could not be assessed. Although Vitamin C levels were done in some studies. Hypovitaminosis is defined as an Ascorbic Acid (AA) level of 23 µmol/L and severe AA deficiency defined as an AA level 11.3 µmol/L. The measured vitamin C levels in the ORANGES trial, CITRIS-ALI and by Marik et al. were 21.7 ± 14.8, 17.9 ± 2.4, and 14.7 ± 11.8 µmol/L, respectively. Victor Trial compared the pre and post treatment levels of AA in the 2 groups [with 1.49 ± 1.39 and 2.1 ± 2.61 µg/mL in the routine and the HAT groups, respectively (p = 0.6) in Pre-Treatment group and 2.2 ± 4.1 and 94.2 ± 107.42 µg/mL in the routine and the HAT groups, respectively (p < 0.001) in Post Treatment Group]. This shows that hypovitaminosis is a common feature in septic shock patients and supplementation of Vitamin C can be beneficial in this group of patients.

Limitation of the study

1) The major limitation of our study is the small sample size and the fact that this is a single-centre study.
2) Serum Vitamin C level testing was not available at our centre.
3) Because of limited evidence, most effective dose and duration of AA could not be inferred. It should be determined in future studies in pediatric age group.

CONCLUSION

Children between 5-10 years are the most vulnerable group and pneumonia is the commonest underlying cause in our study. The present study concluded that significant role of Vitamin C is present in reducing the mean dose, duration and number of vasopressors in children presenting with septic shock. While no role is seen in reducing duration of ventilator support, total duration of oxygen support, duration of PICU and hospital stay and outcome of patients with septic shock. Larger well-designed studies using uniform protocols are needed to study the most effective dose and duration of Vitamin C therapy in septic shock patients in Indian children. We should consider this safe and cheap adjunctive therapy as a routine in the management of patients with septic shock.

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