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Original Research Article

The Effectiveness of Tocotrienol Rich Fraction and Alpha Tocoferol with Combination of Vitamin C in The Management of Systemic Inflammatory Response Syndrome (SIRS)

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Abstract

The pathophysiology of systemic inflammatory response syndrome (SIRS) had been described to involve various strong oxidative reactions affecting the status and progress of the patients. Antioxidant therapy had been suggested in many studies involving SIRS management. The objective of this study was to compare the role of vitamin E Tocotrienol and vitamin E Tocopherol combined with vitamin C as antioxidant therapy in the management of critically ill patients diagnosed with SIRS, admitted to the intensive care unit and high dependency wards of Universiti Kebangsaan Malaysia Medical Centre (UKMMC). It was a single blind randomized clinical trial with a total of 72 patients in which 44.4% Malays, 34.7% Chinese, 19.4% Indians and 1.4% others with 59.7% males and 40.3% females were recruited. Patients in TRI E group received Tocotrienol with Vitamin C while TOCO group received Tocopherol with Vitamin C and a control group did not receive any antioxidant. The clinical parameters (heart rate, respiratory rate, systolic blood pressure) showed improvements with significant difference at the end of study (post-intervention) as compared to admission (pre-intervention).Whereas, the sepsis (temperature, PCT, CRP and WBC) and oxidative stress (8-OHdG/Creatinine) parameters showed improvements with significant difference at the end of study (post-intervention) as compared to admission (pre-intervention). The TRI E group showed obvious improvement in clinical, sepsis and oxidative stress parameters, as compared to TOCO and control groups. This study showed that Vitamin E Tocotrienol and Vitamin E Tocopherol in combination with Vitamin C demonstrated significant improvement in the clinical and laboratory parameters during the management of SIRS. Therefore, Vitamin E in combination with Vitamin C had therapeutic benefits in the treatment of critically ill patients with SIRS.

Keywords: Antioxidant, systemic inflammatory response syndrome, tocotrienol, tocopherol, vitamin C

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Introduction

Systemic Inflammatory Response Syndrome (SIRS) is defined as a widespread inflammatory response that manifested as an array of clinical insults. It is clinically recognized by the presence of two or more of the following: temperature > 38°C or < 36°C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or arterial carbon dioxide partial pressure (Pa CO2) < 32 mmHg and white blood count >12,000 cells/mm^3 or < 4000 cells/mm^3. Severe SIRS is associated with organ dysfunction, hypo perfusion, or hypotension which may lead to shock (1). SIRS has been found as an important etiology for the morbidity and mortality

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Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
ICU,HDU,HDS patient defined SIRS criteria	When expected or anticipated survival were less than 48 hours diagnosed by the attendant doctors.
Age limit: >16 and < 76	Bile and GIT absorption disorders interfering with fat soluble enteral medications documented on patient workout by medical teams.
	Any Other Contraindications for enteral medications documented on patient workout by medical teams
	Apache II ICU scores more than 13 or less than 8

among the critically ills after trauma, burns, and sepsis (2). SIRS presenting with definitive evidence of infection is recognized as sepsis.

There were many approaches for treatment of SIRS and its related consequences. However, those therapeutic strategies are not always able to control the excessive inflammatory response, either because of global immune suppression or agents used, targeted specific inflammatory mediator ineffectively. It was suggested, by modulating the activation of inflammatory cells, even at very proximal stages of activation such as during inflammatory stimulus signal transduction may control excessive inflammation (3). The importance of oxidative stress in the early phases of critical illness is underscored by the relative antioxidant depletion reported in patients admitted to the ICU as they are recorded to have reduced total antioxidant capacity (4). There is a strong relationship between a decrease in antioxidant capacity and the severity of illness and increasing levels of organ dysfunction (5).

The evidence for oxidative stress in the critically ill patient, coupled with direct oxidative tissue injury and induction of the systemic inflammatory response provides a sound biologic rationale for antioxidant supplementation (6). Vitamin E is the principal antioxidant of the lipid domains of the body such as cellular membranes. It is a peroxyl radical scavenger protecting the polyunsaturated fatty acids within membrane phospholipids and in plasma lipoproteins, against oxidation. All forms of vitamin E possess antioxidant activity. The relative antioxidant activity of the tocopherols with regards to peroxyl radical scavenging is $\alpha > \beta > \gamma > \delta$. The order is similar among the tocotrienols (21). The aim of this study is to compare the effectiveness of tocotrienol rich fraction and α-tocoferol with combination of vitamin C as antioxidant in the treatment of Systemic Inflammatory Response Syndrome (SIRS).

Materials and Methods

Subjects

The ethic approval was obtained from the Universiti Kebangsaan Malaysia Research and Ethics committee. This is a randomized single-blinded study. It included patients that were admitted to ICU, HDU, and HDS fit with at least two or more of the following SIRS criteria: temperature >38°C or < 36°C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or arterial carbon dioxide partial pressure (Pa CO2) < 32 mmHg, white blood count >12,000 cells/mm^3 or <4000 cells/mm^3. Patients were chosen according to inclusion and exclusion criteria as shown in Table 1. Written informed consent was obtained from 72 patients diagnosed with SIRS that fulfill the inclusion criteria aged between 16 and 76 years who admitted to UKMMC ICU, HDU and HDS. These patients were recruited and randomized into the following three groups: 1) tocotrienol rich fraction (TRI E); 2) α-tocoferol (TOCO); 3) no medication (control) according to the sequence of enrollment.

Vitamin E and C administration protocol

All intervention groups received study medications 3 times daily for the 9 days, while the control group received no medication. The intervention group, TRI E received tocotrienol (TRF) with vitamin C and TOCO received α-tocoferol with vitamin C. All patients continued to have their conventional therapy for the clinical presentation or diagnosis. TRI E group received TRF 400 IU (Sime Darby Sdn. Bhd) and TOCO group received α-tocoferol 400 IU (Sime Darby Sdn. Bhd) 8 hourly in oil form via nasogastric tube or soft gel capsules (Hovid Sdn Bhd). Both TRI E and TOCO groups' patients received vitamin C 500mg every 8 hourly.

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Measurements

After randomization, patients were subjected to base line measurements in which clinical measurements of temperature in celcius (°C), heart rate in beats/minute, blood pressure in mmHg and respiratory rate in cycles/minute. The urine output in ml/hour, Apache II score, inotropics & vasopressors used were also recorded. Blood samples were sent for baseline blood tests: PCT, CRP, LFT, WBC, ABG and PT and APTT. The urine sample was collected for 8OHdG test from every patient according to the study plan. Blood samples were collected from all the groups (72 patients) at admission and at day 9 after intervention. Urine is collected and stored immediately at – 20°C and centrifuged prior to 8OHdG test to purify it from any sediment. Patients who had serious persistent abnormal LFT, PT, APTT values or severe acidosis at the beginning of the study or in the course of the study were either not selected or dropped from the study.

The WBC analysis was performed in pathology hematology laboratory of UKMMC and blood run through Coulter LH 750 Analyzer with 2 models which are LH2 –LH 750 and LH2 – 755. LFT, PT, APTT, CRP and PCT analysis were performed in pathology biochemical laboratory of UKMMC. All of LFT, PT, APTT, CRP and PCT blood samples were centrifuged at room temperature with 4000 Rpm for 5 minutes and supernatants were taken for analysis. PT and APTT were carried out by STA Compact Diagnostica Stago. LFT and CRP were carried out by either ROCHE COBAS INTEGRA 800 or ROCHE COBAS 8000. PCT was carried out by KRYPT B.R.A.H.M.S and ABG was carried out by ABL 800 BASIC Radiometer Copenhagen.

The 8-OHdG ELISA kit is a competitive in vitro enzyme linked immunosorbent assay used for quantitative measurement of the oxidative DNA product of 8-OHdG in the tissue, urine and other biological fluids. The 8-OHdG analysis was performed in microbiology immunology laboratory of UKMMC and urine run through 8-hydroxy-2- deoxy Guanosine EIA kit (Cayman Chemical Co.).

Statistical Analysis

The data collected from various quantitative parameters were presented as a mean ± standard error of the mean (SEM) of sample size. The parametric mean was compare using paired Student's T tests where it usually compares each parameter before and after the intervention, in each group individually. One-way ANOVA test was used to compare the results between 3 groups (TRI E, TOCO and Control). Chi-square was used to analyze the results of Inotropes as results was by coded by yes or no type of data All statistical analysis was performed using the version 17.0 SPSS software. The differences at $p<0.05$ was considered significant.

Results

Demographical

This study included 72 randomized patients that were admitted to the ICU, HDU and HDS. Of these patients, 48 patients received antioxidant supplements and were grouped into either TRI E or TOCO, while another 24 patients received critical care management without antioxidant supplements.

The study population consisted mainly of middle aged men and predominantly of Malay race followed by Chinese then Indian. Majority of the patients (48%) were admitted to ICU. Statistically, there were no significant differences between patients' age (42.88 ± 9.83, 40.04 ± 9.56, 42.04 ± 11.46), weight ((70.54 ± 13.39, 74.04 ± 6.56, 69.56 ± 11.47) and APACHE II score (11.29 ± 1.16, 11.13 ± 1.23, and 11.17 ± 1.27) for TRI E, Control and TOCO groups, respectively (Table 2).

Hemodynamic parameters

The haemodynamic parameters in all intervention group (TRI E, TOCO or control) showed significant changes at the end of study (post-intervention) as compared to admission (pre-intervention) results for all parameters except systolic and diastolic blood pressure (Table 3.1).

In the TRI E group, heart rate decreased while urine output increased and both were statistically significant ($p<0.001$). Use of inotropes decreased, as at the end of the study 24 patients were not on inotropes ($p<0.001$). The same changes were documented in the control group for heart rate and urine output ($p<0.001$). However, the number of patients on inotropes was statistically not significant. In the Toco group, the mean heart rate decreased and the number of patients on inotropes was less. Both changes in heart rate and the use of inotropes were statistically significant with $p<0.001$ and $p<0.05$ respectively, whilst the decrease in mean urine output was not.

There was improvement in blood pressure where the systolic and diastolic blood pressures was increased in the control and TRI E groups, however the blood pressure was slightly decreased in the TOCO group. There was no significant difference in both systolic

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Table 2: Demographical distribution, data are expressed as mean ± SD. with no significant differences between patients' age, weight and APACHE II for TRI E, Control and TOCO groups, respectively.

	TRI E n=24	**TOCO** n=24	**Control** n=24	***p* value**
Age, years	42.88 ± 9.83	40.04 ± 9.56	42.04 ± 10.24	0.62
Weight, kg	70.54 ± 13.39	74.04 ± 6.56	69.56 ± 11.47	0.33
Race:				
Malay	11	12	9	
Chinese	7	8	10	
Indian	5	4	5	
Others	1	0	0	
Location:				
ICU:HDS:HDU	17:4:3	16:3:5	15:5:4	
APACHE II Score	11.29 ± 1.16	11.17 ± 1.21	11.13 ± 1.23	0.89

Table 3.1: Pre and post-intervention results of hemodynamic parameters, data are expressed as mean ± SD with significant statistical analysis *p<0.05 and **p<0.001.

Parameters	**TRI E**	**TOCO**	**Control**
Heart rate (admission)	131.33 ± 25.44**	119.67 ± 18.83**	114.92 ± 24.39**
Heart rate (end of study)	86.54 ± 7.81**	96.33 ± 13.18**	92.08 ± 12.22 **
Systolic blood pressure (admission)	117.54 ± 32.13	125.58 ± 26.56	120.42 ± 25.26
Systolic blood pressure (end of study)	129.67 ± 7.47	117.33 ± 13.89	125.92 ± 12.49
Diastolic blood pressure (admission)	71.33 ± 17.22	75.04 ± 17.35	74.50 ± 19.59
Diastolic blood pressure (end of study)	76.17 ± 10.51	68.75 ± 13.30	76.33 ± 11.24
Urine output (admission)	55.42 ± 24.71**	110.21 ± 121.44	79.58 ± 55.11 **
Urine output (end of study)	121.96 ± 55.76**	138.25 ± 92.06	109.38 ± 71.93**

and diastolic blood pressures in all groups. The blood pressure was stable on admission and maintained until end of the study, with or without inotropes support. The use of inotropes decreased in both TRI E and TOCO groups and the difference was significance with p< 0.001 and p< 0.05, respectively.

When comparisons were made in between the three groups, it showed significance difference for all parameters except for the urine output (Table 3.2). Comparing the means of inotropic agent used between the groups showed significant relationship for TRI E group over TOCO and control group (p<0.02, p<0.001) (Table 3.3).

The respiratory rate at the end of the study showed significant changes in all the groups. Comparison of the means between all groups showed significant difference with p value of <0.001. The TRI E group showed obvious improvement in respiratory rate as compared to TOCO and control groups (Table 3.4).

Laboratory parameters

Sepsis parameters

The patients in TRI E and Control group had shown significant decrease in temperature at the end of study as compare to admission with the p value of < 0.001. However, the temperature changes in TOCO group were not significant although it showed improvement. There were significant different temperature in between TRI E and TOCO group with p value < 0.02 (Table 4).

The plasma level of procalcitonin (PCT) at the end of study as compare to admission showed significant reduction in all intervention groups with p value of less than 0.001, 0.001 and 0.05 respectivel. However, there were no statistical differences of PCT level in between all the three groups at the end of study (Fig. 1).

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Table 3.2: Comparison post-intervention results of hemodynamic parameters in all intervention groups, data are expressed as mean ± SD with significant statistical analysis *p<0.05 and **p<0.001.

	TRI E	TOCO	Control	*p*
Heart rate	86.54 ± 7.81	96.33±13.18	92.08±12.22	0.01*
Systolic blood pressure	129.67 ± 7.47	117.33±13.89	125.92±12.49	0.001**
Diastolic blood pressure	76.17±10.51	68.75±13.30	76.33±11.24	0.04*
Urine output	121.96±55.76	138.25±92.06	109.38±71.93	0.41

Table 3.3: Post-intervention results of inotropes used by all intervention groups, data are expressed as percentage (%) with significant statistical analysis *p<0.05 and **p<0.001.

Inotropes	GROUP		χ^2	*p*
	TRI E	TOCO		
No	24 (100)	19 (79.2)	5.581[a]	0.02*
Yes	0	5 (20.8)		
	TOCO	**Control**		
No	19 (79.2)	15 (62.5)	1.61	0.20
Yes	5 (20.8)	9 (37.5)		
	TRI E	**Control**		
No	24 (100)	15 (62.5)	11.07	0.001**
Yes	0	9 (37.5)		

Table 3.4: Pre and post-intervention results for respiratory rate of all intervention groups, data are expressed as mean ± SD with significant statistical analysis *p<0.05 and **p<0.001.

	TRI E	Control	Toco
Respiratory rate at admission	31.59±9.33	38.13±8.71	35.71±7.34
Respiratory rate at end of study	15.14±1.88	19.22±2.43	22.00±2.86
p value	0.001**	0.001**	0.001**

Table 4: Pre and post-intervention results of temperature, data are expressed as mean ± SD with significant statistical analysis *p<0.05 and **p<0.001.

Temperature	TRI E	TOCO	Control
Admission	38.63±1.19	37.91±1.18	38.27±1.43
End of study	36.96±0.15	37.49±0.78	37.27±0.79
p value	0.001**	0.12	0.001**

The plasma level of C-reactive protein (CRP) showed significant reduction in each group at the end of study as compare to admission with p value < 0.001 for TRI E, Control and TOCO groups. The mean CRP of the TRI E group and the TOCO group showed significant difference with p value of <0.03 (Fig. 1).

The white blood cell (WBC) count showed significant reduction in plasma, in all intervention groups with p value of < 0.001. The comparison of the mean WBC's in between groups at the end of study were statistically significant between in all interventions group with p<0.01. The TRI E group demonstrated a larger reduction in WBC count as compare to TOCO and control group (Fig. 1).

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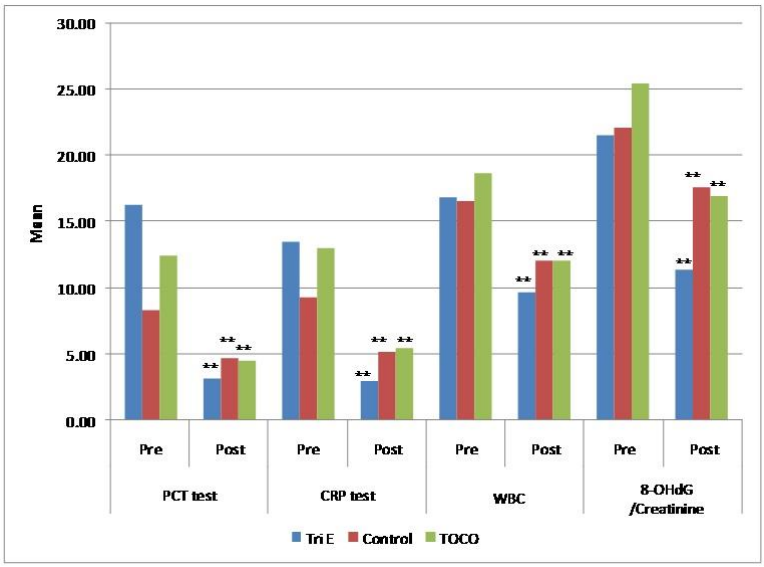

Figure 1: Pre and post-intervention results of sepsis parameters (PCT, CRP and WBC) and oxidative stress parameter (8-OHdG/Creatinine), data are expressed as mean ± SD with significant statistical analysis *p<0.05 and **p<0.001.

Oxidative Stress parameter

8-OHdG/Creatinine test results showed significant reduction in plasma level in each group when the result on admission was compared with the result at end of the study. The reduction was significant with p value < 0.001 for all three intervention groups. The mean of 8-OHdG/Creatinine ratio showed statistical significant reduction in comparison between the three groups (p<0.01). The TRI E group demonstrated a larger reduction in 8-OHdG/Creatinine level as compare to TOCO and control group (Fig. 1).

Discussion

The goal of this study was to compare the benefits of two types of Vitamin E in SIRS patients. Vitamin E tocotrienol isotype was compared with Vitamin E α-tocopherol isotype (both in the presence of vitamin C) for the management of critically ill patients diagnosed with SIRS. Previous studies had concentrated on the effect of α-tocopherol in the presence of Vitamin C in this group of patients (6,7) and Maria et al. (8) showed that tocotrienol is a better antioxidant as compared to tocopherol in both in vitro and in vivo environments. A combination of various clinical and laboratory investigations were performed in this study to quantify sepsis and oxidative stress parameters. While other studies mainly investigated oxidative stress markers and observed 28 days mortality rate and degree of organ dysfunction (6,7). The most salient result of our study is that the relatively moderate oral dose of vitamin E tocotrienol supplementation reduces oxidative stress and inflammatory sepsis markers (CRP, WBC and 8-OHdG/Creatinine) as compared to vitamin E α-tocopherol. However, both vitamin E supplementations showed beneficial effect in reducing oxidative stress and inflammatory sepsis markers as compared to critically ill patients diagnosed with SIRS that are not received any supplementation.

In this study we observed significant changes in the clinical parameters (heart rate, systolic and diastolic blood pressure, urine output, the need of inotropic support, respiratory rate and temperature) of the SIRS patients in the TRI E and TOCO groups when compared to the control. These findings were similar with previous study (9), which showed a positive association between antioxidant therapy and improvements in hemodynamic parameters. Another study showed a potential benefit when antioxidants were administered early to protect against significant organ dysfunction and infection (6). Interestingly, our study states that those benefits could be obtained by patients with significant co morbidity, included varieties of different diagnoses. Earlier, Nathens et al. (6) had questioned the benefits of various SIRS patients with different varieties of diagnoses and co morbidities. Our study results were also consistent with those obtained in an experimental model of septic shock (10). Our study showed that PCT levels between the groups (inter groups) had no significant difference although there were significant changes observed within each group (intra group results) comparing their pre and post interventions levels.

In healthy people, plasma PCT concentrations are found to be below 0.05 µg/L, but PCT concentrations

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can increase up to 1000 µg/L in patients with sepsis, severe sepsis or septic shock. PCT levels are usually low in viral infections, chronic inflammatory disorders or autoimmune processes. PCT compared to other parameters has an early and highly specific increase in response to bacterial infections and sepsis. Thus, in septic conditions increased PCT levels can be observed 3-6 hours after infectious challenge (11). The most potent stimulator for PCT induction under experimental conditions is the systemic effect of bacterial endotoxins (12). Plasma PCT is very stable and is not degraded to hormonally active calcitonin (13). In pulmonary injury and pulmonary infection, the circulating concentrations of procalcitonin and other calcitonin precursors increase rapidly, probably in response to sepsis related cytokine release from pulmonary neuroendocrine cells of the bronchial epithelium or mononuclear cells (14). Low PCT values (<0.25 µg/L) in patients with clinical signs of infection indicate a low probability for blood culture proof of bacterial infection, whereas elevated PCT values (>0.25 µg/L) seem to correlate with the bacterial load and positive blood culture result. PCT levels in sepsis are generally greater than 1-2 µg/L and often reach values between 10 and 100 µg/L, or considerably higher in individual cases, thus enabling the diagnostic differentiation between various clinical conditions and a severe bacterial infection (11). PCT and CRP both are infection-related parameters. However, both proteins are also induced during non-infectious causes of systemic inflammation (SIRS) and in patients with organ dysfunction (15). The process of lipid peroxidation seems to correlate with the degree of infection as indicate by PCT levels (16). PCT also was found as a guide to antimicrobial therapy in patients with lower respiratory tract infections (17). PCT is a marker suggested for sepsis specifically while CRP was more as inflammatory marker. (18,19). Patients included in our study were diagnosed with SIRS and they may not necessarily had sepsis.

The pathophysiological role of severe oxidative stress reactions in SIRS has been demonstrated by experimental and clinical studies, in which an increase in measured oxidative stress markers are directly associated with a decrease in serum antioxidants (5,20). In our study, we highlighted that increased levels of 8-OHdG/Creatinine as an oxidative stress marker correlated with increased levels of PCT, CRP and WBC. Oxidative stress reactions induce direct oxidative tissue injury by means of peroxidation of cellular membranes, oxidation of critical enzymatic and structural proteins which in turn activate apoptosis (6). Previous studies have shown a potential increase in oxidative stress markers in critically ill patients (5,20). In accordance with our data 8-OHdG level were dramatically increased in SIRS patients at the onset of their illness. It increases dramatically in vivo secondary to DNA oxidative stress injury and they are decreased in response to antioxidant therapy. We demonstrated that 8-OHdG can be considered as an important and reliable index for oxidative stress in vivo. At present, 8-OHdG is not a diagnostic tool but it is used in research to trend changes in protein oxidation as it is a ubiquitous byproduct found in all normal biological fluids and tissues. Patients who received a relatively moderate dose of tocotrienol with vitamin C supplementation showed a significant reduction in urinary 8OHdG/creatinine level - the major byproduct of global oxidative DNA damage in the body (21) more than others whom supplied by the same relatively moderate dose of α-tocopherol with vitamin C. This result could help in explanation of the significant changes in sepsis parameters of patients in TRI E and TOCO groups as compared to control groups by modulating the oxidative stress activities.

In study done by Gutteridge & Mitchell (22), reported critically ill patients had very small concentrations of vitamin E and C. A prior study investigated high circulating oxidative stress markers which correlated with both vitamin E concentrations (20) and APACHE II scores (5). However, in our study neither vitamin E nor C was measured. A relative decrease in antioxidant capacity appeared to correlate with the severity of the illness and suggested a causal relationship between antioxidant depletion and increasing levels of organ dysfunction (6). In 2004, Crimi et al (7) stated that vitamin E is a nonenzymatic antioxidant present in biological membranes, it reacts as a chain breaking antioxidant inhibiting peroxidation of lipids and is the most important lipid soluble antioxidant in humans. Vitamin E and C act synergistically resulting in tocopheroxyl and tocotrienoxyl radicals reduced back to their original form by Vitamin C. Both studies confirmed the circulating plasma levels of their antioxidants doses were at accepted therapeutic levels. So far our study was conducted according to the previous principles.

Our study had a relatively homogenous population as one of its strengths which reduces the noise and variability and thus increases the likelihood of observing a measurable effect. This homogenous was established by using the APACHE II score to help select relatively patients with same level of illness severity. There were no observed side effects attributable to the use of antioxidants in our study, and administration of relatively moderate dose of tocotrienol, tocopherol and vitamin C did not increase the risk of renal failure or coagulopathy among the patients of this study.

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Conclusion

This study showed that the relatively moderate dose of vitamin E tocotrienol and α-tocopherol with vitamin C supplement as an enteral feeding may prevent oxidative stress damage to DNA as compared to control, in critically ill patients with SIRS as this therapy resulted in significant clinical changes by which positive association between antioxidant therapy and improvements in hemodynamic, pulmonary and sepsis parameters. However, the effect of vitamin E tocotrienol was more superior to vitamin E α-tocopherol. Those benefits could be obtained by patients with significant comorbidity, included varieties of different diagnoses. This study showed that vitamin E in combination with vitamin C have therapeutic benefits in the treatment of critically ill patients with SIRS.

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