LETTER TO THE EDITOR

Author Response: Appropriately Designed Studies are Needed before Thiamine and Vitamin C Plus Hydrocortisone are Judged Nonbeneficial in Septic Shock

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Dear Editor,

We thank Finsterer et al. for their valuable input regarding our recently published study about the effects of adding vitamin C and thiamine to hydrocortisone on intensive care unit (ICU) outcome in patients with sepsis and septic shock.

With regard to their concern about the rationale for choosing patients with sepsis and septic shock to evaluate the effects of vitamin C, it has been known for over 20 years that acute illness, endotoxemia, and sepsis result in an acute deficiency of vitamin C, characterized by low serum and intracellular levels of the vitamin.[1–3] It has also been shown that vitamin C reverses the microcirculatory injury and organ dysfunction in experimental models of sepsis.[4–6] The role of hydrocortisone in reducing vasopressor-free days has already been established in previous clinical trials.[7,8] At the time we commenced this study, there was growing evidence that addition of vitamin c and thiamine to hydrocortisone resulted in significant mortality benefit in patients with septic shock.[9] We, therefore, chose to evaluate the effects of vitamin C in patients with sepsis and septic shock. Moreover, in CITRIS-ALI study, the use of vitamin C was evaluated in patients with acute respiratory distress syndrome (ARDS), which occurred secondary to sepsis.[10] The ARDS was a sequelae of sepsis, where the use of vitamin C was found to be useful for that subset of patients.

With regard to the concern about checking the levels of vitamin C in intervention and control groups, we have admitted our inability to check the level of vitamin C in either group of patients as one of the limitations of our study, which needs to be addressed in future studies. It is clearly a possibility that the increase in mortality seen in control group could be due to low baseline levels of vitamin C and the failure to supplement vitamin C in this group of patients. Further studies can be designed to observe the level of vitamin C at baseline in both the intervention and control groups before beginning the drug administration in intervention group.

With regard to another concern about the discrepancy between the statement in Table 1 that none of the patients in the intervention group or those receiving hydrocortisone alone had neurological disease and the statement that the central nervous system (CNS) was the primary organ from which sepsis originated in nine patients each in the intervention and control groups, we want to clarify that the subheading Neurological Disease denoted the pre-existing long-term neurological comorbidity of the patient before he/she developed sepsis, which was found to be zero in both the control and intervention groups. On the contrary, CNS dysfunction as the primary organ source of sepsis was the CNS etiology, which was responsible for the origin of sepsis, e.g., encephalitis. The origin of sepsis from a CNS source was found to be nine each in intervention and control groups.

Regarding the fourth concern about the statement in Table 1 that the heart was not the primary organ from which sepsis originated in either the vitamin C-treated patients or the control subjects and the query that whether patients with endocarditis, myocarditis, and pericarditis were systematically excluded from participation in the study, we want to make it clear that the presented data was about the primary organ source of sepsis at the time of ICU admission. This was found to be zero due to a primary cardiac cause. The patients included in our study were either admitted from the emergency room or inpatient wards or referred from other hospitals. Therefore, most of them had been worked up to identify the primary organ source of sepsis before they were transferred to ICU. All the patients clearly had a primary organ system involved apart from cardiovascular system as the source of sepsis. There were two patients in intervention group in whom the primary organ source of sepsis was blood, as they had catheter-related blood stream infection. As part of the routine protocol of our ICU, we perform a point-of-care ultrasound of

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lungs, an echocardiography, and a compressibility test of bilateral femoral veins using ultrasound to rule out deep vein thrombosis after the patient gets admitted to the ICU. We did not encounter any features suggestive of myocarditis or endocarditis in these two patients during the echocardiography, and therefore, classified the primary organ source of sepsis as blood.

Regarding the 5th concern, we strongly agree that the mortality may depend on the infectious agent responsible for sepsis. We also agree that it is important to know the spectrum of pathogens that have been blamed for sepsis, the number of patients in whom no infectious pathogen could be identified, and the sensitivity pattern of the antibiotics that were used in eliminating the identified infectious agents. Though all the patients did not have an infectious agent isolated in relation to their primary organ source of sepsis, we used the antibiotic sensitivity pattern to choose antibiotics for the patients in whom an infectious agent could be isolated. Though it would have been better in keeping a record of the same, it is equally important to remember that not all septic patients will have an infectious agent isolated in relation to their primary organ source of sepsis. Many a times, the patient is in sepsis from an assumed primary source, but no microorganisms can be isolated because of many reasons. In one systematic review and meta-analysis by Li et al., the proportion of patients with culture-positive sepsis or septic shock was only about 40.1% (9,086/22,655).[11] The median percentage of sepsis episodes, which were culture negative, was 49.3% in that systematic review and meta-analysis.[11] We still treat such patients as having sepsis with broad-spectrum antimicrobials depending upon the local antibiotic guidelines and antibiograms.

Having said so, we strongly agree that there could have been many limitations in our study, which need to be addressed in future studies. Assessing mortality outcome due to a single intervention in itself is a difficult task, as there can be many confounders that can affect the outcome of mortality in critically ill patients. We, therefore, agree that further studies addressing all the above-mentioned concerns should be designed and performed to further strengthen the conclusion about the utility of vitamin C in sepsis.

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