The Magic Bullet in Sepsis or the Inflation of Chance Findings?

To the Editor:

In the June 2017 issue of CHEST, Marik et al\(^1\) presented a single-center retrospective before and after study assessing the effects of treating patients with severe sepsis/septic shock with IV vitamin C, hydrocortisone, and thiamine. Forty-seven patients were treated with IV vitamin C, hydrocortisone, and thiamine within 24 hours of ICU admission during a 7-month period (treatment group) and compared with 47 patients admitted to the same ICU over the preceding 7 months (control group). The authors reported a hospital mortality of 8.5% in the treatment group compared with 40.4% in the control group, \(P < .001;\) adjusted odds of mortality, 0.13; 95% CI, 0.04-0.48. They concluded that vitamin C, corticosteroids, and thiamine may reduce organ dysfunction and mortality in patients with severe sepsis/septic shock.\(^1\)

Although we commend the authors for exploring strategies to improve outcomes in this vulnerable population,\(^2\) we are concerned that spurious findings, biased results, and overstated conclusions are presented. First, there is no high-quality evidence that any of the three interventions individually improves survival in patients with sepsis.\(^2\) Second, an absolute risk reduction of > 30% (relative risk reduction of 87%) in mortality is biologically implausible. Third, the nonrandomized retrospective design, and lack of blinding and a predefined protocol and statistical analysis plan substantially increase the risk of bias.\(^3\) Fourth, the single-center design increases the risk of inflated estimates.\(^4\) Fifth, hospital mortality is considered an inadequate outcome measure, as it is affected by discharge criteria. Finally, with a study population of 94 patients, with 47 in each group implying selection bias, the results are almost certainly affected by a type I error.

The substantial methodological flaws of the study bring into question its external validity and veracity. Our confidence in the estimates is very low due to concerns about risk of bias and imprecision, implying large uncertainty about the results. This is at variance with the authors’ interpretation of the results and conclusions.

Many apparently promising ICU interventions have proved neutral or even harmful following detailed assessment and confirmation by high-quality trials. In a review of critical care trials, eight of 15 ICU interventions used in daily clinical practice over the years proved to increase mortality.\(^5\)

In conclusion, we highly recommend meticulous assessment of all patient-important benefits and harms of vitamin C, hydrocortisone, and thiamine prior to adopting this unproven strategy in clinical ICU practice.

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References

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References

Response

To the Editor:

We appreciate Dr Møller et al for their correspondence regarding our experience with the use of IV vitamin C, hydrocortisone, and thiamine in patients with severe sepsis/septic shock.1 First and foremost, it is important to state that we do not refute, nor did we attempt to mask, the characteristics of our study: a retrospective, single-center, nonrandomized, and unblinded. We initiated this therapy after our review of small trials in similar populations.2,3 We agree that the supporting data on efficacy were as not robust but believed that the available safety data on these particular interventions justified their introduction as salvage therapy in patients who were unlikely to survive. Our anecdotal experience was impressive and led to our use of this treatment in a number of consecutive patients. Our decision to describe and publish our experience occurred afterward; thus, the methodological characteristics were unmodifiable. As a consequence of this study design, we understand why the results of our study have been met with some skepticism by the scientific community. We are in agreement with Dr Møller et al that additional trials should be performed to support or refute the findings of our study. As stated in our conclusion, “…additional studies are required to confirm our preliminary findings.” However, given our experience, we felt that publication of these results was necessary and, indeed, our ethical responsibility. Sepsis is common, debilitating, and often lethal. Despite exhaustive attempts at therapies to interrupt the mechanism of a dysregulated immune response and subsequent organ damage, we are currently limited to antibiotics and supportive care as our only consensus therapeutic measures. We recognize that the decision to use three readily available pharmacologic agents, each with limited supporting clinical data, can be viewed as “unconventional.” However, therapeutic interventions in the absence of high-quality randomized controlled trials are commonplace in the ICU. When using such interventions, the clinician must balance the potential consequences of the disease with the safety of the proposed therapy. It is our opinion that the safety profile of vitamin C, thiamine, and hydrocortisone2,6 in the setting of a disease without alternative treatments and an exceedingly high mortality allows clinicians to use this therapeutic intervention with the goal of preventing death and limiting the complications and long-term sequelae of this devastating disease. However, we continue to support the effort to investigate this therapy further in studies across the world.

The mortality reductions described in retrospective studies are often not reproduced in large multicenter randomized controlled trials; however, a therapy that effectively targets pivotal pathways in patients with sepsis could plausibly result in a large reduction in mortality. The associated reduction in the dose of vasopressors, Sequential Organ Failure Assessment score, and procalcitonin clearance in our treated patients, all independent markers of the successful treatment of sepsis,7 suggest a true biological effect. In addition, we have independent validation that the sepsis mortality in our hospital has been dramatically impacted since the introduction of this novel therapeutic intervention. It has previously been suggested that “...the best hope for therapeutic advances [in sepsis] will depend on broad-base targeting, in which multiple components are targeted at the same time.”8 Such combination “chemotherapy” targeting multiple biological pathways is the standard approach in the treatment of malignant disease. Although the benefits of vitamin C, hydrocortisone, and thiamine alone are likely limited,2,3,6,9 we believe that