Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study.

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Context

While the global burden of sepsis remains high, attempts at developing a "magic bullet" to reduce the morbidity and mortality associated with it remains elusive. Vitamin C has been shown to be deficient in patients with sepsis and has many potential benefits: 1) is a free radical scavenger, 2) down regulates the production of pro- inflammatory cytokines, 3) is required for the synthesis of catecholamines, and 4) increases vasopressor sensitivity. Vitamin C and steroids appear to work synergistically which may be supported by the lack of effect seen by steroids alone in the HYPRESS trial. Large doses of vitamin C may increase the production of oxalate and the potential for crystallization and subsequent acute kidney injury. Thiamine deficiency appears common in sepsis and is associated with increased oxalate production. Therefore, Thiamine was added in an attempt to reduce this potential complication.

Methods

This was a retrospective before and after clinical study performed in one hospital. Patients were enrolled if they were admitted meeting criteria for severe sepsis or septic with procalcintonin level ≥2. From 1/2016 - 6/16 patients received a cocktail of vitamin C, 1.5gm q6h IV, hydrocortisone 50mg q6h, and thiamine 200mg q6h. They received the cocktail for 4 days or until DC from the SICU. Primary outcome was hospital survival. Secondary outcomes included duration of vasopressor therapy, requirement for renal replacement therapy in patients with AKI, ICU LOS, change in serum procalcitonin levels, and SOFA scores over 72hrs. Propensity scores were generated to adjust for potential baseline differences in patient groups.

Findings

- There were 47 patients in each group
- No significant differences in baseline characteristics
- 75% of the patients were admitted for either pneumonia, urosepsis or primary bacteremia.
- No surgical patients included
- Vitamin C levels were low in the 22 patients measured
- Hospital mortality was 8.5% in the treatment group, 48.4% in the control group ($p<0.001$)
- The propensity adjusted odds of mortality in patients treated in the vitamin C protocol was 0.13(95% CI 0.04-0.48, $p=0.02$)
- In the treatment group, there was a reduction in: renal replacement therapy, more rapid weaning of patient's from vasopressors, and a more rapid improvement in SOFA score at 72 hours
- No difference in ICU length of stay or fluid balance

Commentary

This extremely controversial study has received significant media attention. The authors have stated that the use of this cocktail has become standard of care in their institution and suggest that it should be

standard of care outside their institution. While it would be nice if such a cocktail could significantly reduce sepsis-related mortality without any significant negative impact, approaching this new information with caution is probably appropriate. There are a few easy criticisms of this study:

- it is not a randomized prospective study,
- the mortality rate of the control group appears to be much higher than in similar studies,
- four patients that died in the treatment group reportedly died from patient disease and *not* complications of sepsis. We do not feel that can be absolutely determined.
- No surgical patients enrolled and the use of steroids in surgical patients cannot be taken lightly.
- No comment on infectious complications in the treatment group,
- Unclear why the authors decided to use hospital mortality instead of the more standard 28 day mortality

Implications

While some institutions have already begun this practice, we believe that generalizing the findings of this study to all patients with severe sepsis or septic shock may be premature. It is not clear if this protocol would have same apparent benefit in surgical/trauma patients given the possible detriment to wound healing and infections. Further studies using this cocktail will soon be in the literature and will allow us to better assess whether or not this indeed is a “magic bullet”.