

New sepsis cocktail – thanks for the new marik protocol

Mini Review

Sepsis mortality is still remarkably high and according to the latest surviving sepsis campaign guidelines, sepsis related mortality is around 15% while septic shock is associated with 40% in-hospital mortality¹ and in poor countries, the mortality goes even higher up to 60%.

Thousands of interventions have been tried over decades failed to improve sepsis survival. Even drugs that were able to reduce mortality in one study, failed to do so in another study. The best example was the recombinant activated protein C, which didn't show any survival benefits in PROWESS-Shock trial while was associated with decreased mortality in PROWESS Trial.^{2,3}

Also Annane et al.,⁴ was able to prove that sepsis is associated with high incidence of relative adrenal insufficiency and usage of stress dose Hydrocortisone in addition to Fludrocortisone in both Annane and APROCCHSS trials was associated with significant reduction in mortality.^{4,5} While CORTICUS and ADRENAL Trials failed to reveal any benefits related to using steroid in septic shock.^{6,7}

So it sounds that, the problem is the difficulty to find a magic drug to work effectively alone in septic shock.

Dr. Marik and his group used a very intelligent idea. They used mixture of drugs assuming their perfect synergism and looked at their effect on sepsis mortality.⁸

The magic cocktail contains vitamin C, thiamine and stress dose hydrocortisone.

Interestingly, most of the scientists were waiting for more than 44 years to have a strong evidence to use vitamin C in patients with sepsis until Dr. Marik published his study.

Actually 169 studies have been published to elaborate clearly the role of vitamin C in sepsis, the earliest dated 1972.

Also, Dr. Tynl and his team from Canada, found that using a single large dose of vitamin C early on the disease can prevent capillary blockage and a similar dose later, may also facilitate opening of the blocked capillaries. Interestingly, these positive effects continued for up to 24 hours. Dr. Tynl concluded that high dose Vitamin C may offer potential life-saving treatment for sepsis not only to prevent but to reverse sepsis.⁹

Thiamine also is very important to be replaced in sepsis and several studies identified the presence of thiamine deficiency in critically ill patients especially in patients with lactic acidosis. Thiamine deficiency ranges between 20% to 70% depending on the cutoff value and associated with poor outcome.¹⁰⁻¹²

Thiamine deficiency decreases the pyruvate flux to the Krebs cycle so it increases the production of lactate by altering the aerobic metabolism (Figure 1). The author concluded that because of the crystal clear benefit of thiamine in sepsis, he suggested not to forget to give thiamine for patients with septic shock.^{13,14}

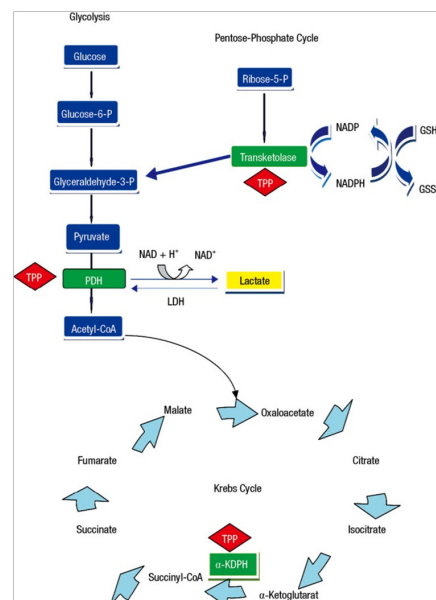
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Study design

They used a retrospective approach to compare the outcome of their cocktail in sepsis and septic shock before and after clinical study.

- Control Group: received a standard of care.
- Treatment Group: received IV Vitamin C, Thiamine and Hydrocortisone within 24 hours of their admission to ICU.

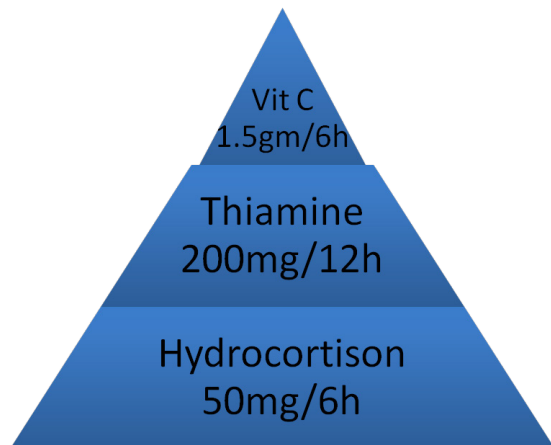
Outcome

- Primary outcome: Hospital mortality.
- Secondary outcome:
 - Mean duration of vasopressor therapy.
 - Requirement for renal replacement therapy in patients with AKI.
 - PCT clearance (initial PCT minus PCT at 72 hours divided by the

initial PCT multiplied by 100.

- iv. The 72-hour delta SOFA score (difference between subsequent scores).

Marik cocktail



- i. All given Intravenous.
ii. Vitamin C and Thiamine given for 4 days or until ICU discharge.
iii. Hydrocortison given for 7 days or until ICU discharge.

Results

Outcome	Control Group	Treatment Group	P value
Hospital Mortality	19/47 (40.4%)	4/47 (8.5%)	<0.001
ICU LOS (days)	4 – 10	3-5	-----
Time on Vasopressors (hrs)	54.9(+/-28.4)	18.3(+/-9.8)	<0.001
CRRT for AKI	11/30 (33%)	3/31(10%)	0.02
Delta SOFA at 72hrs	0.9 (+/-2.7)	4.8 (+/-24)	<0.001
Delta PCT Clearance at 72hrs	33.97(62.4 – 64.3)	86.47 (80.1 – 90.8)	<0.001

Conclusion

It sounds that the Marik cocktail works perfectly in sepsis based on the study result, which showed that early use of IV Vitamin C, Thiamine and Corticosteroids may be useful in reducing in-hospital mortality as well as preventing organ dysfunction e.g. AKI requiring CRRT and speed up shock reversal in patients with sepsis/septic shock. Actually, only 4 patients died out of 151 patients, 3 of them have been died due to causes unrelated to sepsis. Only 1 patients died because of sepsis.

Despite the result is very promising but it has to be taken very carefully because of many limitations in the study which includes, small sample size, retrospective, single center and non RCT. But because of tremendous reduction in mortality, a lot of centers in the world started already to use Marik protocol without waiting further studies.

We hope by the end of 2019, the result of VICTAS large prospective MC RCT will be available to confirm that Dr. Marrik cocktail does work effectively in sepsis without any safety concerns.¹⁵

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