

## A safety profile is sufficient for using a drug?

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On January 17th 2020, it was published in JAMA the Vitamins trial<sup>1</sup>. Alongside the paper, JAMA published the presentation and debate that followed it (<https://edhub.ama-assn.org/jn-learning/video-player/18172764>), which occurred in Dublin, Ireland, on the same day. After Dr. Fujii's presentation, Dr. Paul Marik has stated with emphasis that Vitamin C didn't have any side effects, implying that a high level of evidence confirming efficacy would not be necessary in order to have it implemented as treatment. That statement disregards clinical and scientific reasoning and should not be taken as good advice.

Considering that each patient is unique and sepsis is a syndrome with very different phenotypes<sup>2</sup>, the single variable in this equation is the cocktail. In spite of that, we don't completely know what can happen when vitamin C, thiamine, and hydrocortisone are combined together. We know the pharmacokinetics and pharmacodynamics of many drugs, including those in the cocktail separately, but mixing them together brings much more uncertainty to the table.

Hierarchically, the first justification of implementing a treatment is its beneficial effect, not its safety; secondly, the prior probability of a beneficial effect is usually lower than that of our enthusiasm, so some dose of skepticism is important before interpreting data as proof. Finally, in a complex biological system, it is naive to put faith in the safety profile of a new treatment before properly testing it<sup>3</sup>.

Plausible ideas, with strong physiopathological basis to try and explain their mechanisms, still do not justify the adoption of any treatment. Medicine's history has taught us that only a good RCT can provide data supporting that a treatment offers enough benefit and safety for it to be safely deployed. The classic example of CAST trial<sup>4</sup> tested an excellent hypothesis that suppression of ventricular ectopy after a myocardial infarction would reduce the incidence of sudden death. But the trial showed the opposite: an excess of deaths due to arrhythmia and deaths due to shock after acute recurrent myocardial infarction in patients treated with encainide or flecainide. There are many good hypotheses being discarded after being tested in a adequately designed RCTs. It is absolutely needed to do an RCT before trying and implementing any treatment. Furthermore, the burden of proof is on the real benefit of any

intervention and, in the Vitamin C case, the jury is still out. Thus, it is unscientific for the medical practice to apply the logic of utilizing things based on the combination of safety and faith.

### Is vitamin C really safe?

We have to understand that the only way to assert anything that is by testing it with an RCT. Recently, a single-center trial showing that strict glycemic control had a huge impact on mortality<sup>5</sup> was tested by the multicenter Nice Sugar trial<sup>6</sup>. The later trial presented us with setbacks of being so aggressive in treating hyperglycemia. They found that intensive glucose control increased mortality among adults in the ICU. It is naive to suppose that the interaction of vitamin C and sepsis is safe without proper testing. It is essential to have a control group, to compare both efficacy and harm. And to be conscious that small studies often are unable to find harm. There is no such thing as "no side effects" or no adverse drug reaction (ADR). Any drug or treatment has side effects, and these should be considered in the decision-making process. The fact is: we don't know what these side effects really are as of yet. And this is dangerous.

Concerning ADR, most of us think about drug-drug interaction and side effects. We should also be aware of problems related to logistics, such as IV lines available, administration (with nurse workload), and fluid overload. We must be aware of unintentional consequences.

Common sense states that vitamins are safe or innocuous. We are talking about a water-soluble vitamin, which is an acid. What is the interaction with an antibiotic? No one knows. But there are also some side effects: large doses of vitamin C may cause gastrointestinal discomfort, headache, trouble sleeping, and flushing of the skin. There is also a two fold risk of kidney stones<sup>7</sup>.

Adding 3 drugs to the treatment brings together the risk of a medication error, fluid overload, missing other important drugs administration because of lack of IV lines. "Get another line!!" one may say. Indeed, but this also increases risks of phlebitis and infection. Imagine vitamin C prescribed to be given at the same time as Piperacillin-Tazobactam. Which one should be administered first? Would the patient be harmed? This scenario is very prone to increase nurse workload and more medication error. Another issue is the amount of fluid used to dilute and administer these drugs. Fluid overload is associated with worse outcomes<sup>8</sup>.

Science and research require that we must maintain a higher standard of reasoning to inform conduct. The usage and advocating for the use of a drug before adequate evidence is misleading and maybe unethical. The message could be interpreted as a flexible rule for the implementation of any drug or device. This is extremely dangerous.

When we choose any path, either in medicine or in life, we wonder what the odds of success and the risks are. If a particular path has no risks, it seems more appealing. But there are always setbacks in any path taken, even if we don't completely know what they are yet. Instead of being so sure of everything, we should embrace the uncertainty<sup>9</sup>.

As physicians, we would be pleased to have options of treatments to deploy for the best care of our patients undergoing septic shock. But it is also true that we have the golden rule of Hippocrates whose statement said "*primum non nocere*" or "do no harm". To date, we do not know that the cocktail does not do any harm. For every treatment we choose we have also a price to pay in side effects and other unintentional consequences. In this scenario, we really do not know the price regarding safety to achieve an also unknown benefit.

## Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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