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Reply to MS #201309065, Saikia P, The Vitamins in Nitrous Oxide (VINO) Randomized Trial: A Few Concerns

Peter Nagele, M.D., M.Sc.^{*}, Frank Brown, B.Sc.^{*}, Amber Francis, B.S.N, R.N.^{*}, Mitchell G. Scott, Ph.D.[‡], Brian F. Gage, M.D., M.Sc.^{||}, and J. Philip Miller, A.B.[§]

^{*}Division of Clinical and Translational Research, Department of Anesthesiology, Washington University in St. Louis, St. Louis, MO

[‡]Department of Pathology & Immunology, Washington University in St. Louis, St. Louis, MO

^{||} Division of General Medical Sciences, Department of Internal Medicine, Washington University in St. Louis, St. Louis, MO

[§]Division of Biostatistics, Washington University in St. Louis, St. Louis, MO

We welcome the opportunity to respond to Dr. Saika's letter and clarify two aspects of the manuscript, adherence to the intention-to-treat principle and the role of novel high-sensitivity cardiac troponin in the diagnosis of perioperative myocardial injury and infarction.

Intention-to-treat analysis

As Dr. Saika correctly points out, the intention-to-treat principle is the accepted gold standard in the statistical analysis of randomized controlled trials. The intention-to-treat principle was invented to circumvent two main problems during drug trials where the treatment continued over longer periods of time, namely patients stopping the treatment early (attrition) and patients switching from one trial arm to the other (crossover) in a non-random fashion. Intention-to-treat principle allowed clinicians to determine *effectiveness* of a novel treatment under more realistic conditions rather than judging the merits of a novel drug by its maximum *efficacy* under ideal conditions. The Vitamins in Nitrous Oxide (VINO) trial analysis fully adhered to the intention-to-treat principle.¹ The intervention in the VINO trial was an infusion of B-vitamins or placebo. The 57 patients that were excluded from the analysis were withdrawn from the study *before* receiving any treatment and therefore had to be excluded. What typically happened with these patients was that they were informed about the study, agreed to participate, signed the consent form and then – before any intervention occurred – either the surgery was cancelled, or the anesthesia team refused to use nitrous oxide, or the patient changing his mind. Thus, the intention-to-treat principle was applicable not applicable to these withdrawn patients. Of the true intention-to-treat population (n=500), five out of 250 patients (2%) in the B-vitamin arm and three out of

250 patients in the placebo arm (1.2%) did not receive nitrous oxide. Given these small numbers, we don't expect a strong influence on the study results.

High-sensitivity cardiac troponins in the diagnosis of perioperative myocardial injury and infarction

This is without a doubt a topic of high interest to the perioperative community and an area of active investigation. In a recently published ancillary study of the VINO trial, we were able to expand on these findings.² Based on three points of evidence, we have to disagree with the statement that perioperative elevation of high-sensitivity cardiac troponin reflects an inflated diagnosis of myocardial infarction. First, among higher-risk patients, i.e., patients with pre-existing coronary artery disease, the risk for major perioperative cardiac events is high: the POISE trial found a 6.9% 30-day event rate for myocardial infarction, cardiac death or non-fatal cardiac arrest.³ Second, using continuous perioperative 12-lead Holter monitoring, Landesberg et al. showed nicely that more than 20% of their patient population developed myocardial ischemia.⁴ Therefore, perioperative myocardial infarction is likely under- not over-reported. Third, according to the Third Universal Definition of Myocardial Infarction, the diagnosis of myocardial infarction requires both a rise/fall pattern of a cardiac biomarker with at least one value above the 99th percentile, and evidence for new ischemic electrocardiograph changes, such as ST-segment elevation or depression, in continuous leads in a setting consistent with myocardial ischemia.⁵ Most clinical 12-lead electrocardiographs are performed as spot measurements easily missing temporary ischemic events. On the other hand, cardiac troponin represents a cumulative measure of myocardial damage and its kinetics allows the detection of myocardial injury and infarction that occurred several hours prior to the measurement. Thus, we believe that novel high-sensitivity cardiac troponin assays will allow us to detect more cases of perioperative myocardial infarction. This not with standing, there are definitely instances where perioperative cardiac troponin elevation may be caused by non-ischemic factors such as acute renal failure.⁶ Thank you for giving us the opportunity to clarify these points.

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