

## LETTER TO THE EDITOR

**RE: NUTRITION ISSUES IN  
GASTROENTEROLOGY, SERIES #205  
Enhanced Recovery After  
Surgery and Immunonutrition:  
An Evidence-Based Approach**

Dear Carol Rees Parrish MS, RDN:

We read with great interest the article titled, "Enhanced Recovery After Surgery (ERAS) and Immunonutrition (IMN): An Evidence-Based Approach" by Friedman & Thiele in your December 2020 issue.<sup>1</sup> We appreciate the importance of this area of on-going research and the work that went into putting such an article together. However, after our review, we believe this article contains some important omissions and interpretation inaccuracies of the literature (particularly those in Table 2) that could skew the overall interpretation of the benefits of IMN to the reader.

In Table 2, Friedman & Thiele inaccurately report the study design and results of Thornblade et al., 2017.<sup>2</sup> First, this was not a randomized controlled trial (as the title of Table 2 and inclusion criteria would suggest) but rather a prospective cohort study. Secondly, Thornblade et al. states "Although differences in serious adverse events were non-significant (RR = 0.76, 95% CI: 0.49-1.16), prolonged length of stay (RR = 0.77, 95% CI: 0.58-1.01 p = 0.05) was lower in those receiving IMN." Friedman & Thiele report in Table 2 that the "IMN group had increased LOS".

Table 2 also references a study by Hamilton-Reeves et al. published in 2016.<sup>3</sup> Hamilton-Reeves et al. published two manuscripts from their pilot study; one in 2016 and one in 2018.<sup>3,4</sup> The data in Table 2 are the findings from the 2018 article, not the 2016 article as indicated. In 2016, Hamilton-Reeves et al. reported, "Participants receiving specialized IMN had a 33% reduction in postoperative complication rate (95% CI: 1-64; p = 0.060) and a 39% reduction in infection rate (95% CI: 8-70; p = 0.027) during late-phase recovery."<sup>3</sup> These positive findings were omitted in Friedman & Thiele's review.

Friedman and Thiele also omitted positive results from Uno et al., 2016.<sup>5</sup> In addition to reporting a significant decrease in postoperative infectious complications and serum IL-6, Uno et al., also reported that length of stay was significantly shorter, and severity of complications was significantly lower in the IMN group compared to control.<sup>5</sup> These inaccuracies and omissions of positive findings may mislead the reader about the results reported by recent trials of IMN. Additionally, the publications listed in Table 2 are not included in the reference list making it difficult for readers to identify the primary source of these findings.

Friedman & Thiele raise the concern that, "there is some data that IMN can be harmful in certain populations" yet, mortality outcomes of recently published trials were not reported by Friedman & Thiele. Mortality rates were monitored in 9 of the 12 studies listed in Table 2.<sup>2,5-12</sup> Of these nine studies, seven reported no difference in mortality between groups.<sup>2,5-10</sup> The remaining two studies reported higher mortality in the control groups.<sup>11-12</sup> Specifically, Lewis et al., stated that "death within 30 days postoperative was twice as high for those in the standard nutrition group versus the IMN group, with no deaths in the per-protocol analysis for those in the IMN group" and Klek et al. reported significantly increased mortality with standard nutrition compared to IMN at three months (16.7% versus 0.0%, p = 0.004).<sup>11-12</sup> We echo Friedman & Thiele's concerns about small sample sizes in these recently published trials, however, given the importance of this outcome, we believe it is an unfortunate omission of this review.

Friedman and Thiele highlight three societies which recommend or have favorable guidance on IMN use including the European Society for Clinical Nutrition and Metabolism (ESPEN), the American College of Surgeons Strong for Surgery Campaign and the American Society for Enhanced Recovery. Unfortunately, they omit that other societies also have recent guidelines which support the use of IMN. For example, the 2016 guidelines from the American Society for Parenteral and Enteral Nutrition and Society of Critical Care Medicine suggest the routine use of an immune-modulating formula (containing both

arginine and fish oil) in the surgical ICU and the 2018 ERAS Guidelines for Colorectal Surgery state that perioperative IMN is beneficial with a strong recommendation grade.<sup>13,14</sup>

Finally, regarding the “Oxepa® experience,” mentioned by Friedman & Thiele, it is worth clarifying that the subsequent RCT performed by Rice et al., did not use Oxepa® as their intervention.<sup>13</sup> Instead, this intervention consisted of bolus feedings of omega-3 fatty acids, g-linolenic acid, and antioxidants provided twice per day. Importantly, the control formula was isocaloric, but not isonitrogenous to the intervention.<sup>15</sup> In fact, Rice et al., reported that the control formula contained five times more protein than the intervention formula (20g protein/240ml versus 3.8g protein/240ml, respectively). Given these prominent differences in study design, the results of Rice et al. do not necessarily negate the findings reported by Pontes-Arruda, et al. as is implied by Friedman & Thiele.<sup>16</sup>

Although we highlight these concerns, we agree with Friedman & Thiele that all research should adhere to the scientific method and be challenged by peer-review regarding scientific design, analysis, and interpretation and add that this caution should be practiced regardless of funding source. We also agree that further health economics and outcomes research will prove meaningful moving forward. It is essential to critically review healthcare practices to ensure that patients are provided the best possible care within the context of growing cost constraints. We truly appreciate the opportunity to discuss our concerns in order that your readers have the most accurate data when making decisions with their patients regarding immunonutrition.

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