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Alternative Lipid Emulsions As A New Standard Of Care for Total Parenteral Nutrition: Finally Available in The U.S.?

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The development of Total Parenteral Nutrition (TPN) in 1960's by Drs. Dudrick, Wilmore, Vars, and Rhodes was a landmark innovation in the history of modern medicine(1). Undoubtedly, numerous lives have been saved as a result of this discovery. Since that time, great evolution has occurred in our understanding of the optimal and safe use of this vital therapy. As is true with any therapeutic intervention, whether pharmacologic or nutritional, risks and benefits must be considered and carefully designed randomized controlled trials (RCTs) conducted to optimize this balance.

Although nutrition delivery is a fundamental need and vital to our patients' long-term recovery and maintenance of lean body mass (which is key to regaining quality of life post-discharge), it too has been found to have risks and benefits that must be understood and optimal methods of intervention studied. This need has perhaps been the greatest in the field of TPN, particularly in the acutely ill, where fears of increased risk of infection and liver dysfunction (PNALD) have at times limited clinician's use of this vital therapy(2). In many regions of the world, including Europe, earlier TPN use is more commonplace in post-operative and ICU settings based on differences in existing nutrition guidelines for TPN use(2, 3). However in the U.S., the use of TPN is more limited and this appears to hinge on two major concerns: 1) The historical risk of infection from TPN use and 2) the perceived risk to both immune and liver function of over-administration of pure Onega-6 soy lipid, which until quite recently was the only available lipid source approved by the FDA.

The article by Grau-Carmona et al in this issue of Critical Care Medicine ((4)) is one of a growing number of recent multi-center RCTS of TPN examining the efficacy and safety of TPN practice in the ICU. One of the key findings of recent articles examining "standard" TPN practices (i.e. administration of TPN to patients failing to tolerate or unable to receive enteral nutrition, rather then randomizing all-comer ICU patients to TPN or not- as was practiced in the EPaNIC trial(5)) is that standard PN use is no longer associated with any

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increased risk of infectious complications(6, 7). This was recently shown in two large multicenter RCTs(6, 7) and is likely due to a number of key changes to PN practice over the last 10 years. These key improvements in practice include ending the use of the "hyperalimentation", which was commonly practiced in the 1980s and 1990s when > 35 kcal/kg/day of largely dextrose and soy lipid was commonly administered. This practice was commonly associated with another major historical issue with TPN, hyperglycemia. Until the landmark publications by Van Den Bergh and the subsequent NICE-SUGAR trial(8, 9), glucoses levels were commonly left untreated until they were greater then 250 mg/dL or even 300 mg/dL. As a result, hyperglycemia almost assuredly contributed significantly to the increased risk of infection in TPN patients. Now hyperglycemia is aggressively treated with insulin administration when needed during TPN therapy. Further, the risk of line infections in TPN patients, (and line infections in general) has been reduced by the routine of "line-placement checklists" that ensure sterile technique and have been shown to markedly reduce line infections which often contributed to TPN-associated infections(10). Finally, the use of alternative lipid emulsions, rather then pure omega-6 soy lipid have been hypothesized to contribute to reduced TPN complications, particularly infectious and liver related morbidity.

Traditional soy based omega-6 lipid has been demonstrated to impair lymphocyte function and division in both experimental and clinical models, and lipid phytosterol content has been associated with liver-injury and PNALD development(11–13). In response, alternative lipid emulsions have been developed that contain a combination of fish and soy oil, olive and soy oil, or a combination of all three. Until recently, these alternative lipid formulations were hypothesized to improve outcome in acutely ill patients, but data proving this were limited.

The paper by Grau-Carmona et al (4) is among the first multi-center RCTs to study and show a clinical benefit of a fish-soy oil combination versus standard soy lipids in ICU patients. The results of this study show that the administration of n-3 polyunsaturated fatty acids (given as fish oil) significantly reduced the risk of nosocomial infection versus a pure soy lipid. Hospital length of stay (LOS) was also reduced by an average of 11.5 days in the fish oil group, however this just missed statistical significance ($p = 0.059$). No change in mortality or other clinical outcomes were observed. Limitations of this study include that due to challenges in enrollment, the study did not achieve its predetermined enrollment goal based on an enrollment goal intended to detect a reduction of infection of 20%. However, changes in baseline infections rates due to changes in infection control practices during the study made the predicted baseline infection rate no longer accurate. Despite this, this is among the largest RCTs of alternative lipids ever performed. However, additional larger trials of alternative lipids in the ICU outcome are needed and now clearly indicated. These findings are supported by a recent meta-analysis in ICU patients showing that alternative lipid emulsions are associated with statistically significant improvements in ICU and hospital LOS, gas exchange and inflammatory markers(14). A tendency for reduced infectious morbidity was also observed. A second recent meta-analysis of 12 RCTs by Manzaneres et al showed alternative lipid emulsions were associated with clinically important reductions in mortality, LOS, and durations of mechanical ventilation. However, statistical significance was not achieved for these endpoints(15). The Grau-Carmona trial adds to this data, but clearly there is a need for further research. In addition, no clear superiority of one alternative lipid formulation versus another has been demonstrated and

trials of these various formulations are also needed as currently we do not know if the specific lipid components (i.e. fish versus olive) contribute to improved outcomes, or if the reduction of soy lipid exposure may be key to reduced morbidity. It is likely both are important, as reduction of phytosterol content such as by the low-phytosterol containing olive oil formulations has been associated with reduced liver injury and cholestasis.(13) These findings have recently led the Canadian Critical Care Nutrition Guidelines to recommend that strategies to reduce soy lipid administration in ICU patients should be considered in ICU patients (available at www.criticalcarenutrition.com).

In conclusion, although it appears that alternative lipid formulations appear to be associated with improved clinical outcomes in ICU patients, they have not been previously available for use in the U.S.. In an exciting development for U.S. patients and clinicians alike, the FDA recently approved the first alternative lipid formulation for use in the U.S.. This formulation, an olive oil-based lipid, should be available for clinical use near the end of 2014. It is widely felt that this initial approval will lead to subsequent approvals for other alternative lipid formulations. Thus, we believe U.S. clinicians can look forward to a brighter and safer future for TPN practice, as now not only does it appear that TPN is no longer associated with an increased risk of infection, but that the availability of alternative lipid emulsions that may further improve clinical outcomes are now a reality for U.S. patients.

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