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Total Nutrient Admixtures (3-in-1) Pros vs Cons for Adults

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Abstract

Total nutrient admixture (TNA) is a complete parenteral nutrition (PN) formulation composed of all macronutrients, including dextrose, amino acids, and intravenous fat emulsions (IVFE), in one bag. The TNA may be safely administered to the patient, with all components aseptically compounded and minimal administration manipulation required, lending itself to decreases in risks of catheter contamination and patient infections. The TNA is compatible and stable at recommended concentrations, and since the IVFE is in the TNA, it is infused at slower rates, allowing for better fat clearance. The TNA offers convenience of administration and a potential cost savings to the healthcare institution both directly and indirectly. Unfortunately, the TNA is not without concerns. At low macronutrient concentrations (lower than recommended), the formulation is compromised. Greater divalent and monovalent cation amounts and increased concentrations of phosphate and calcium may destabilize the TNA or result in precipitation, respectively. With the addition of IVFE in the TNA, catheter occlusion is greater and larger pore size filters are necessary, resulting in less microbial elimination. Determining if the implementation of the TNA is appropriate for an institution requires a recognition of the advantages and disadvantages of the TNA as well as an understanding of the institution's patient population and their nutrition requirements.

Total nutrient admixture (TNA), sometimes referred to as 3-in-1, is the combination of all macronutrients (dextrose, amino acids, and intravenous fat emulsion [IVFE]) with electrolytes, vitamins, minerals, trace elements, and sterile water for injection in 1 intravenous (IV) solution. It is administered to patients when oral and/or enteral nutrition is contraindicated or inadequate and may be used for short-term periods to a lifetime of therapy. Likewise, 2-in-1 parenteral nutrition (PN) formulations may be used to meet patients' nutrition requirements. Two-in-1 PN formulations are the combination of dextrose and amino acids along with electrolytes, vitamins, minerals, trace elements, and sterile water for injection, with IVFE infused separately as a source of calories and for the prevention of essential fatty acid deficiency. Which of the 2 therapies is superior has been debated, with the use of TNA considered conventionally acceptable and preferred in most institutional and home settings, but careful consideration must be given when choosing which therapy is best for one's institution.¹ Decisions should be made, giving thoughtful deliberation to patient safety, formulation compatibility with respect to patient populations, individual and institution convenience, and cost. An appreciation for each aspect of the process is necessary with patient safety and compatibility being imperative. Table 1 addresses each aspect of consideration for determining if the TNA is appropriate for implementation in healthcare institutions with further rationalization of each consideration explained in greater detail below.

Table 1. Total Nutrient Admixture Considerations.^{1,9,12,14,18,19,20,24,25}

Categories	Institution Considerations for Use
Patient safety	<p>All components aseptically compounded by the pharmacy</p> <p>Less manipulations of the system during administration; potential decrease risk for catheter contamination and bacteremia/sepsis</p> <p>Inhibited or slower bacterial growth if contamination does occur compared with separate IVFE</p> <p>Fat clearance may be better when IVFE is administered over more than 12 hours (rapid infusion associated with decreased RES system)</p>
Compatibility/stability	<p>TNA formulations should maintain final concentrations of amino acid $\geq 4\%$, monohydrated dextrose $\geq 10\%$, and IVFE $\geq 2\%$; formulation stability may be compromised if final concentrations are lower than recommended</p> <p>TNA formulations are more sensitive to destabilization with greater concentrations of divalent and monovalent cations and certain electrolyte concentrations</p> <p>Certain medications are incompatible with the IVFE portion of admixture</p> <p>1.2-μm filter required (precluding the use of a 0.22-μm filter, which eliminates a greater amount of particulate matter, including some bacteria)</p> <p>Catheter occlusion and shorter catheter life associated with home TNA</p>
Convenience	<p>Preparation is more efficient for pharmacy personnel, especially if automated</p> <p>Less nursing time needed for one container and no piggyback IVFE to administer; nursing preference</p> <p>Easier administration in home care setting; possible increased patient compliance</p>
Cost	<p>Reduced inventory (infusion pump, IV tubing, related supplies)</p> <p>Indirect cost saving from decreased administration time</p> <p>May be more cost-effective overall in certain settings</p>

IV, intravenous; IVFE, intravenous fat emulsion; RES, reticuloendothelial system; TNA, total nutrient admixture.

Safety

When considering TNA and patient safety, microbial contamination and, ultimately, patients' infectious complications are paramount. The compounding of both PN formulations and the potential of the formulation serving as a bacterial growth medium, as well as the administration of the PN, are all considered potential sources for microbial contamination resulting in patient infections. With the compounding of TNA, all components are aseptically prepared by the

pharmacy following the United States Pharmacopeia and National Formulary General Chapter <797> required for all healthcare institutions.² Therefore, the TNA compounded in the pharmacy is considered a sterile formulation. Since the aseptic technique occurs with the compounding of 2-in-1 PN formulations, the question of contamination and bacterial growth becomes the following: (1) Is there a difference between the 2 PN formulations as a growth medium, and (2) does the administration of the TNA vs 2-in-1 plus IVFE increase the risk of bacterial contamination and patients' infections?

In vitro studies have shown IVFE to serve as a growth medium for microorganisms, including *Staphylococcus aureus* and *Candida albicans*; however, 2-in-1 formulations did not foster growth of these microorganisms.^{3,4} In addition, the microorganisms grew only minimally to none when studied in TNA formulations.⁴ To determine if there is an observed difference between the 2 PN formulations and the risk for bacterial growth when administered to patients, Vasilakis and Apelgren⁵ cultured both 2-in-1 PN and IVFE given separately, as well as TNA. Two hundred PN fluid cultures were obtained from the distal most connection before the PN formulation was changed every 24 hours. Of the cultures obtained, 116 (83%) were negative, and with respect to the positive cultures, no significant differences were observed in the distribution between the TNA system (n = 19; 17% of 112) and the 2-in-1 PN and IVFE system (n = 15; 17% of 88). The investigators concluded that the TNA system did not increase the risk for contamination compared with the 2-in-1 PN system.⁵

To determine if TNA administration influenced the rate of infection in clinical practice, investigators conducted a prospective randomized trial.⁶ Patients received either TNA or IVFE separately administered with the PN (L/PN). Ninety-six well-matched patients were evaluated. The incidence of infection was 12.6 and 10.3 per 1000 days of PN in the TNA group and L/PN group, respectively ($P = .89$). Microorganisms responsible for infection and the types of infections that developed were similar in both groups, leading the investigators to conclude that TNA administration does not influence the rate of infection in patients receiving PN.⁶ Since the IVFE does not need to be infused separately, there is arguably less risk for manipulation of the system and potentially a decrease in catheter contamination. However, concerning the adult population, this is theoretical as associations with the administration of IVFE and coagulase-negative staphylococcal bacteremia have been reported only in neonatal populations.⁷ With the research available, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) PN Safety Guidelines suggest "there is no clinical difference in infectious complications between the two PN delivery systems."⁸

Another consideration with patient safety, which may be advantageous for administration of TNA, includes the slower infusion of IVFE. TNA may be infused for 24 hours, but because of the potential for IVFE to support microbial growth, the Centers for Disease Control and Prevention has recommended a maximal infusion time of 12 hours (eg, IVFE, propofol).⁹ IVFE for PN compounding currently used in the United States is composed of long-chain triglycerides from soybean oil-egg yolk phospholipid. When IVFE is rapidly infused at rates >1 kcal/kg/h (>0.11 g/kg/h), the reticuloendothelial system (RES) and pulmonary, hepatic, and platelet function may be impaired.¹⁰ A 20% IVFE solution administered as a 10-hour infusion for 3 days was shown to

decrease the RES function by as much as 40%.¹¹ No RES impairment was reported when IVFE was administered as 43% of nonprotein calories as a TNA. The administration of a continuous IVFE infusion appears to allow adequate lipid metabolism without adversely affecting the RES function.¹² IVFE may depress the immune system, but the significance of these findings and their effect on patient outcome require further study.¹³

Stability/Compatibility

Total nutrient admixtures compounded with final concentrations of amino acid $\geq 4\%$, monohydrated dextrose $\geq 10\%$, and IVFE $\geq 2\%$ are more likely to remain stable for up to 30 hours at room temperature (25°C) or for 9 days refrigerated (5°C) followed by 24 hours at room temperature according to the A.S.P.E.N. PN Safety Guidelines. These recommendations serve merely as a guide, and specific stability data on an individual TNA formulation should be sought.^{8,14} The stability of IVFE in the TNA is influenced by many factors, including pH, temperature, lipid globule, light exposure, container size, and storage conditions, and significant alterations may result in lipid globule coalescence (“cracking”) and precipitant formulation.¹³ IVFE is generally most stable at its manufactured pH ~ 8 . While amino acids are generally considered safe to combine with IVFE, dextrose in solution is acidic and can significantly decrease the pH of IVFE and consequently reduce surface potential and stability.¹⁵ In addition to the IVFE instability risk, a greater incidence of medication incompatibility with the IVFE is recognized. Generally, the addition of medications to the PN solution should be limited or none. If medications are added to the TNA or y-sited (preferred), compatibility and solubility charts should be consulted prior to infusion.

Consideration of the institution’s patient population and whether the required macronutrient concentrations are appropriate to meet the needs of the patients is essential if the use of TNA is to be incorporated. If lower concentrations are warranted, 2-in-1 PN needs to be considered; however, similarly to the TNA, solution stability must be determined.

Electrolytes and their concentration must also be considered when determining the appropriateness of TNA use. Trivalent (iron) > divalent (calcium, magnesium) > monovalent (sodium, potassium) cations may all cause a decrease in the surface potential of the lipid droplets, resulting in aggregation and coalescence.¹⁴ The concentration of electrolytes that will cause aggregation in a TNA with a given surface potential is called the critical aggregation number (CAN) and is calculated using the summed concentrations of mono-, di-, and trivalent cations.¹⁴ The CAN is influenced by factors such as the pH, amino acid concentration, and type of amino acid but can provide a guideline for predicting possible states of aggregation; however, no definitive studies exist for using the CAN with IVFEs commercially available in the United States.

In the study by Driscoll et al,¹⁴ 45 different TNA formulas were evaluated with final concentrations of monohydrated dextrose ranging 5%–20%, amino acids ranging 2.5%–7%, IVFE ranging 2%–5%, monovalent cations ranging 0–150 mEq/L, divalent cations ranging 4–20 mEq/L, and trivalent cations (elemental iron/L) ranging 0–10 mg/L. Stability assessments, including particle size analysis, pH determination, and visual inspection, were performed. Monovalent, divalent, and trivalent cations clearly influenced the final admixture stability, with divalent concentrations

between 16 and 20 mEq/L requiring final concentrations of monohydrated dextrose >10% and amino acids >4% to prevent lipid destabilization.¹⁴ Therefore, if greater quantities of monovalent and divalent cations are required in an institution's patient population, the use of TNA would not be feasible. This is supported by the A.S.P.E.N. PN Safety Recommendations, which state that "healthcare organizations should develop policies and/or protocols to allow modification of PN orders when potential incompatibilities may exist (eg, incompatibilities associated with calcium and phosphate salts, adjustment of IVFE dosing when it is not expected to be stable as a TNA, ordering IVFE separately or adjusting IVFE dosing such that the daily dose achieves minimum concentration for stability)."¹⁶

Compatibility and the solubility of calcium gluconate and sodium or potassium phosphate are less in TNA formulations. Low pH concentrations (acidic) are more favorable in maintaining the solubility of calcium and phosphate. The added IVFE increases the pH of the bag, resulting in a greater likelihood of calcium-phosphate precipitate. For some adult patients receiving TNA, this is not a great concern since the intersection of final compounded calcium and phosphate concentrations in the clinical settings may fall below the typical solubility curve; however, this does have potential for complications in patients requiring greater concentrations of these electrolytes.¹⁷

To assist in avoiding the hazards of precipitate, all PN formulations should be filtered according to the 1994 Food and Drug Administration safety alert.¹⁸ A disadvantage of the TNA system with the addition of IVFE is that it requires a larger pore size filter (1.2 µm) as opposed to the 2-in-1 PN formulations, which use a 0.22-µm filter. The smaller pore size filter does eliminate a greater amount of particulate matter, including some bacteria (*Staphylococcus epidermidis*, *Escherichia coli*) than does the larger pore size; however, the 1.2-µm filter is adequate to remove precipitates (calcium-phosphate) and particulate matter as well as large organisms, including *C albicans*.^{13,17,19}

Increased filter occlusion rate and shortened catheter life span have been reported in home patients receiving TNA.^{20,21} The additional inclusion of IVFE associated with increased coalescence and precipitant formulation may be attributed to the reported incidences. And while often reported in pediatrics, increased filter occlusion has been observed in adult patients receiving TNA.²¹ Fibrin occlusions can be resolved by locking the catheter with recombinant tissue plasminogen activator, while IVFE occlusions can be minimized by flushing the central venous catheter with saline before and after TNA infusion and treated, once developed, using a 70% ethanol line lock if compatible with the IV catheter.^{22,23}

Convenience

The convenience of TNA is an advantage to the healthcare providers and the patient. Pharmacy personnel are proficient and skilled at using an automated compounding device. The addition of IVFE into the PN formulation can be efficiently performed by pharmacy personnel and requires minimal additional time, especially if using an automatic compound device. Subsequently, less nursing time is required as an additional piggyback of IVFE is not required; in addition, and not surprisingly, the TNA system is preferred by nursing personnel.^{19,24} With respect to patients, the easier administration associated with TNA is advantageous for the patients and/or caregivers who

are required to administer the formulation. With the ease of only one container to administer, the success of delivery is greater, and potentially, patient compliance is better.

Cost

TNA has been associated with decreased cost.^{25,26} Decreased cost associated with TNA is attributed to a decrease in administration materials and nursing time. IV tubing, infusion pumps, and related supplies associated with the infusion of the IVFE piggyback are saved when TNA is implemented. Nursing time has been reported to decrease by nearly half (2.2 vs 4.3 hours) with the TNA system compared with the 2-in-1 plus a separate IVFE infusion.²⁵

Multichamber Bags

Multichamber bags (MCBs) are industry-compounded, commercially available, ready-to-use PN bags. In the United States, MCBs are available both with and without IVFE. Multichamber bags may be used for standard PN in adults but do not eliminate the need for individualized PN therapy. Patient specific nutrient requirements must be met and MCBs are appropriate only if this is possible. Early research has been conducted demonstrating a decrease in infectious complications and lower cost; however, greater investigation is warranted.^{27,28} As well, whether there will be an advantage between MCBs with and without IVFE will need to be studied.

Conclusion

The TNA formulations, following A.S.P.E.N. PN Safe Practice Guidelines and Recommendations with respect to ordering, reviewing, compounding, labeling, and administering, are safe and appropriate in many institutional settings. As well, both patients and healthcare providers find the use of the TNA to be advantageous with respect to conveniences of the therapy, and potentially, there is an associated cost saving directly with less equipment and supplies used and indirectly with less administrative time involved. However, TNAs are not appropriate for all patients and institutions. Specific patients' nutrition requirements, especially those requiring larger monovalent and divalent cations, as well as calcium and phosphate concentrations, may require the use of 2-in-1 PN formulations. Careful consideration with respect to the institution's patient population in determining the best PN formulation is essential.

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