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Use of Piggyback Electrolytes for Patients Receiving Individually Prescribed versus Premixed Parenteral Nutrition

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Abstract

Background—Parenteral nutrition (PN) is available as individualized prescriptions frequently prepared with an automated compounding device, or as commercially prepared premixed solutions. Our institution exclusively used individualized PN until an amino acid shortage forced a temporary switch to premixed solutions. In general, premixed solutions contain lower electrolyte levels than individualized formulations prescribed for patients with normal organ function. We aimed to quantify supplemental intravenous piggyback (IVPB) electrolyte use in adult patients receiving individualized and premixed PN, and to quantify any effect on difference in the cost of therapy.

Methods—We compared use of supplemental IVPB electrolytes administered to patients receiving PN during consecutive periods prior to and during the amino acid shortage. Electrolyte IVPBs tabulated were: potassium chloride 10 and 20 mEq, magnesium sulfate 2 g and 4 g, potassium phosphate 7.5 and 15 mmol, sodium phosphate 7.5 and 15 mmol IVPB.

Results—There was no statistical difference in the number of PN formulations administered per day during each period (14.7 + 3.9 vs. 14.0 + 2.6, individualized vs. premixed, respectively). Total IVPB electrolytes prescribed per day increased significantly from the individualized PN period to the premixed PN period (7.03 + 3.8 vs. 13.8 + 6.8, $p < 0.0001$). The additional IVPB electrolyte supplementation required in patients receiving premixed PN was associated with an additional \$11,855.74 cost per 30 days of therapy compared to those who received individualized PN.

Conclusion—Inpatient use of premixed PN results in a significant increase in IVPB electrolyte supplementation and cost when compared to individualized PN use.

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Introduction

Individualized PN formulations for hospitalized patients in the United States are usually compounded in hospital pharmacies or outsourced for compounding by a sterile compounding pharmacy.³ These formulas contain up to 40 different components and are frequently compounded using automated compounding devices, while PN as a commercially manufactured, “premixed” solution has been popular in Europe.^{2, 4} Premixed PN is a sterile product requiring minimal manipulation prior to administration. Currently, only 16 premixed formulas are available in the US, which limits their use as they are unable to meet the needs of all patients. Europe has many more premixed formulas available.

PN therapy is provided under the management of a Nutrition Support Team (NST) consisting of dietitians, pharmacists and a physician at our institution. PN prescribing is restricted to the NST. As a result of an amino acid shortage in 2010, we were obligated to restrict use of individualized PN and provide premixed PN to the majority of the patients requiring PN. Since individual and premixed PN solutions are roughly equivalent in cost per bag at our institution, we compared supplemental IVPB electrolyte use in individualized PN patients to use in patients receiving premixed PN to determine any differences in cost of therapy. We found large differences in electrolyte profiles of premixed formulations compared to individualized prescriptions, Table 1. Based on these differences, we expected a significant increase in the use of supplemental IVPB electrolytes in our adult patients receiving PN with resulting cost increases for PN administration. Our aims during this study were 1) to quantify any difference in orders for supplemental IVPB electrolytes in adult patients prescribed individualized versus premixed PN and 2) to quantify any cost difference in therapy between individualized and premixed PN attributable to supplemental IVPB electrolyte prescription.

Methods

Adult patients receiving PN between 8/1 and 8/31/2010 and between 9/28 and 11/1/2010 were considered eligible for analysis. This timeframe captures the periods one month prior to the amino acid shortage, when all patients received individualized PN, and one month following the amino acid shortage, when individualized PN use was restricted and premixed PN use was implemented. Data from 9/1–9/27 were excluded because of inconsistent use during the transition from individualized PN to premixed PN. Our limited amino acid supply was restricted to use in pediatric patients and adult patients unable to tolerate premixed PN. These patients were therefore excluded from our study. The study was approved by the Minimal Risk Institutional Review Board of the University of Wisconsin-Madison and a waiver of authorization and consent was granted (Protocol#: 2013-1161).

Predetermined standard IVPB electrolyte concentrations tabulated are depicted in Figure 2. These electrolytes are the most frequently used formulations for intravenous supplementation at our hospital. Electrolytes were repleted to maintain serum potassium > 4.0 mEq/L, serum magnesium > 2.0 mEq/L, and serum phosphate > 3.0 mg/dL as measured by daily blood chemistry during the first week of PN administration and at least twice weekly measurements during subsequent weeks. The daily number of IVPB electrolytes

administered for PN supplementation was quantified. While the NST typically manages supplementation for patients receiving PN, IVPB electrolytes ordered by other prescribers (resident physician, nurse practitioner, attending physician, NST) were included in the analysis. Costs of IVPB electrolyte supplements were calculated based on the cost to patients. Of note these cost estimates are based on patient charges which include pharmacist verification and mixing, delivery, nursing administration, intravenous catheter and needle use, and waste disposal. All values were analyzed by Student's *t*-test. A *p*-value < 0.05 was considered statistically significant.

Results

All individualized formulations were compounded in the hospital pharmacy of a 566-bed academic tertiary referral hospital using ExactaMix 2400 Automated Compounding Device (Baxter, Deerfield, IL). Premixed PN formulations included ClinimixE 4.25/10 (Baxter, Deerfield, IL) (4% protein, 10% dextrose) or ClinimixE 5/15 (5% protein, 15% dextrose) concentration. Both forms of ClinimixE contain electrolytes in limited quantities. No additional electrolytes were added into the premixed bags due to safety concerns and labor limitations. Additives regularly added to individualized PN such as insulin, ranitidine, multivitamin and trace elements were ordered for premixed PN consistent with previous prescribing methods for individualized PN. Intralipid 20% (Baxter, Deerfield, IL) was the intravenous fat emulsion source for all patients. All bags had a 30 hour expiration time after activation.

During our time periods, 162 adult patients received PN. Sixty patients were evaluated for PN by the NST during the individualized PN period. One home PN patient who received therapy as an inpatient was excluded from the analysis because he was stable on his home regimen prior to admission. A total of 103 patients received PN during the premixed PN time frame. Twenty-two patients were excluded from analysis. Fourteen of these patients received Clinimix 5/20 (5% protein, 20% dextrose) which does not contain electrolytes. Seven patients were not candidates for premixed PN because of increased protein requirements due to continuous renal replacement therapy (1 patient) or other metabolic abnormalities including hyponatremia (3 patients), metabolic acidosis (2 patients), and hyperphosphatemia (1 patient). Lastly, one home PN patient who received therapy as an inpatient was excluded from analysis because he was stable on his home regimen prior to admission.

457 patient-days of individualized PN solutions were prescribed to 59 patients during the 31 days prior to the amino acid shortage. 490 patient-days of premixed PN solutions were prescribed to 81 patients during the 35 days after complete transition to premixed formula use. There was no difference in the number of PN prescriptions per day during each period (Individualized: 14.7 ± 3.9 prescriptions/day vs. Premixed: 14.0 ± 2.6 , *p* = 0.7). There was a significant increase in use of IVPB electrolytes per day after the transition from individualized to premixed PN (Individualized: 7.03 ± 3.8 piggybacks/day vs. Premixed: 13.8 ± 6.8 , *p* < 0.0001).

Potassium chloride 20 mEq IVPB and potassium phosphate 7.5 mmol IVPB prescriptions significantly increased in patients who received premixed PN, Table 3. The remaining IVPB prescriptions, except for the potassium chloride 10 mEq IVPB dose, increased although not significantly with premixed PN. The only IVPB electrolyte supplementation ordered in nonstandardized doses was magnesium sulfate (i.e. 1 g, 3 g, and 5 g). There was no significant difference in ordering of these non-standardized doses between groups.

Increased IVPB electrolyte use indirectly increased cost of premixed PN therapy. Patient charges for supplemental IVPB electrolytes administered to patients who received premixed PN totaled \$24,791.09 during 30 days. Conversely, patient charges for supplemental IVPB administered to patients who received individualized PN was only \$12,935.35, representing a cost difference of \$11,855.74 for 30 days of treatment.

Discussion

An amino acid shortage forced our institution to convert from prescribing individualized PN to prescribing premixed PN. The amino acid shortage provided the opportunity to evaluate premixed PN as a treatment option in our patient population. We hypothesized that baseline differences in the composition of these prescribing methods would increase our need for supplemental electrolytes. Further, since the patient charge for the formulas are roughly the same at our institution, we hypothesized that the change in prescribing method during the shortage would increase costs. Our data show that treatment with a premixed formula at a tertiary referral center significantly increases clinical requirements for supplemental IVPB electrolytes resulting in increased costs.

In 2005, The Joint Commission (TJC) called for standardization of all intravenous formulations.^{1, 3, 5} This guideline led to controversy in the field of specialized nutrition support since practitioners frequently prescribe individualized PN, changing ingredients on a daily basis depending on clinical needs. One of the most Frequently Asked Questions associated with this guideline was, “Does [it] require that PN solutions be standardized in their component concentrations, including electrolytes,” i.e. “premixed” solutions.⁶ In conjunction with the American Society for Parenteral and Enteral Nutrition (ASPEN), the TJC revised the guideline defining PN as a more complex, multi-component solution than the drugs for which the recommendation was originally intended. Therefore, premixed PN solutions were not required; however, the ASPEN Task Force on Parenteral Nutrition Standardization subsequently released a statement calling for standardization of the process for PN ordering, labeling, screening, compounding and administration, which may include use of premixed PN solutions.^{3, 7} ASPEN’s statement concluded that “The evidence suggests advantages in efficiency, economy, and clinical appropriateness with the use of standardized PN formulations compared with individualized PN formulations in select patient populations.” ASPEN further specified that organizations supplying standardized PN should have individualized PN available for certain patient populations. These guidelines sparked interest in the introduction and promotion of premixed PN in US hospital settings.

The rationale for a premixed formula includes reduction in errors, reduced formula manipulations, and decreased labor costs. However, each step in the PN process (ordering,

transcribing, compounding, and delivery) is subject to error.² NSTs were implemented to reduce errors associated with PN therapy, but a recent prospective observational study found that 1.6% of prescriptions written (74 PN prescriptions) contained a human error which occurred during any phase: transcription (39%), preparation (25%), and administration (35%).⁷ PN is also associated with increased risk for infectious complications. In one cohort study, PN was an independent risk factor for blood stream infection (BSI) in patients with central venous catheters,⁸ while other reports link BSI to PN contamination.^{3, 9, 10} A simulation study of PN compounding in a hospital pharmacy demonstrated contamination rates ranging from 4.4–5.2% during preparation.¹¹ The most common source was inadvertent contamination by humans during complex manipulations. However, the authors failed to identify any changes in practice which avoided inadvertent contamination of complicated medium-risk-level preparations. The study concluded that complex, multi-component, medium-risk-level sterile preparations be limited to those essential for patient care. Conversely, use of premixed or otherwise standardized PN formulations may be a source for other medication errors. For example, a report on standardized hospital compounded parenteral nutrition demonstrates how a system based error on standardized ordering forms led to adverse events as individual patient needs were overlooked on the standardized ordering form.¹² The authors appropriately conclude that standardization does not imply safety unless critical individual dosing information is accounted for in prescribing PN.

Premixed PN formulations reduce manipulation of PN components compared with compounded solutions potentially decreasing PN related medication errors and infectious complications. Retrospective reviews examining observed and adjusted BSI rates demonstrate fewer associated infections with premixed, commercially prepared PN solutions compared with pharmacy-prepared PN.^{4, 13, 14} It seems logical that fewer manipulations decreases opportunities for both error and contamination.³ Premixed PN provides the advantage of end product sterilization prior to use, which is not an option for individualized PN. Premixed formulation still requires the manual addition of additives including supplemental electrolytes, multivitamins, and trace elements. These supplements potentially reintroduce error and/or microbial contamination, particularly if premixed PN administration significantly increases IV manipulation due to increased need for IVPB electrolytes.¹⁵

Finally, premixed PN may decrease labor costs offsetting any increase in expense of commercial premixed solutions.^{1, 3, 16} One study noted a 10% decrease in labor costs to the pharmacy department due to better time efficiency with premixed solutions.¹⁷ However, our results demonstrate that use of premixed PN solutions at a tertiary referral hospital in the care of complex, critically ill patients significantly increases the demand for IVPB electrolytes which shifts the work-load of the pharmacist from compounding PN to preparing IVPB electrolytes.

Our study found the cost difference in the therapies to be difficult to determine. While the cost of bulk ingredients (dextrose, amino acids, sodium acetate, potassium phosphate, sodium chloride, magnesium sulfate or magnesium chloride, calcium gluconate or calcium chloride, and sterile water) or IVPB supplements is easily quantifiable, the costs of therapy also include clinician time for developing the medication prescription, compounding and

dispensing by pharmacists, administration by nurses, and disposal. These costs are determined by the hospital and incurred on a per order basis independent of medication dosage. Therefore, prescribing one 20 mEq potassium chloride IVPB could prove cheaper than prescribing two 10 mEq potassium chloride IVPBs which would require twice as much processing labor. With these considerations, individualized PN becomes less expensive at our institution since it requires substantially less electrolyte supplementation.

Delivery of premixed PN may also indirectly increase costs with regard to equipment use. Our hospital typically administers individualized PN as a 3-in-1 formulation requiring one medication pump. However, we prescribed premixed PN as a 2-in-1 formulation with lipids administered separately, thereby requiring 2 medication pumps for delivery. We did not use 3-in-1 premixed PN solutions as they are currently unavailable in the US.

The most important question regarding individualized or premixed PN remains the appropriateness of the medication for an individual hospital and patient population.³ Many hospitals do not have the resources to compound PN so the service is frequently outsourced to sterile compounding pharmacies. Premixed PN may be a more economic option for these hospitals. However, for other facilities with adequate resources for sterile compounding individualized PN and a disproportionate number of high-acuity patients, the premixed PN formulas may fail to adequately meet individual needs of many patients, especially given the limited number of choices of premixed formulas available in the US.¹ The solutions available to our institution contain relatively low protein concentrations which are inadequate to meet the needs of many critically ill patients who frequently require fluid restriction or other nutrient limitations due severe organ dysfunction. Currently available premixed formulas are also of limited use in obese patients where high protein, low calorie diets are recommended.³

Conclusion

PN can be a life-saving treatment for patients unable to be fed enterally. The best means to provide PN, as an individualized or premixed solution, has yet to be fully elucidated. At our tertiary care referral center however, we found that use of a premixed PN significantly increased the need for supplemental IVPB electrolytes resulting in significantly increased cost to the patient.

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Clinical Relevancy Statement

Parenteral nutrition (PN) can be a life-saving therapy for patients who cannot be fed enterally. PN may be provided as individualized formulations, frequently prepared using an automated compounding device, or as commercially prepared premixed solutions. The best method for providing PN formulations is not clear.^{1,2} We found use of premixed PN results in increased supplemental IVPB electrolyte use, resulting in increased treatment cost.

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Table 1

Electrolyte concentrations for individualized and premixed PN.

Individualized PN	Premixed PN
Na 0–130 meq/L	Na 35 meq/L
K 20–80 meq/L	K 30 meq/L
Ca 5 meq/L	Ca 4.5meq/L
Mg 0–15 meq/L	Mg 5 meq/L
Phos 0–30 mmol/L	Phos 15 mmol/L

Na, sodium; K, potassium; Ca, calcium; Mg, magnesium; Phos, phosphate.

Table 2

Standard piggyback electrolytes and concentrations

Standard Piggyback Electrolyte Concentrations
Potassium Chloride 10 mEq
Potassium Chloride 20 mEq
Magnesium Sulfate 2 g
Magnesium Sulfate 4 g
Potassium Phosphate 7.5 mmol
Potassium Phosphate 15 mmol
Sodium Phosphate 7.5 mmol
Sodium Phosphate 15 mmol

Table 3

Per day prescriptions.

Supplement	Individualized PN N = 31 days	Premixed PN N = 35 days	p-value
PN bags	14.7 ± 3.9	14.0 ± 2.6	0.36
Total supplements	7.03 ± 3.8	13.8 ± 6.8	0.0001*
Potassium Chloride 10 mEq	0.77 ± 2	0.63 ± 2	0.71
Potassium Chloride 20 mEq	2.4 ± 2	6.4 ± 5	0.0001*
Magnesium Sulfate 2 g	0.94 ± 1	1.6 ± 2	0.10
Magnesium Sulfate 4 g	0.29 ± 0.5	0.43 ± 0.7	0.39
Potassium Phosphate 7.5 mmol	0.03 ± 0.2	0.54 ± 1	0.027*
Potassium Phosphate 15 mmol	1.1 ± 1	1.7 ± 2	0.12
Sodium Phosphate 7.5 mmol	0.10 ± 0.3	0.31 ± 0.6	0.066
Sodium Phosphate 15 mmol	1.39 ± 2	2.2 ± 2	0.10