Review Article and Clinical Experience

BASIC PRINCIPLES OF PARENTERAL NUTRITION FOR DIABETIC PATIENTS (INTRODUCTION WITH SEVERAL EMPIRICAL FORMULAS)

Askandar Tjokroprawiro

ABSTRACT

To date, complete reports of studies and detailed information about Parenteral Nutrition (PEN) for patients with Diabetes Mellitus (DM) are unavailable. However, clinical experiences with several "Empirical Formulas" on such patients will be presented. To maintain and restore nutrition of diabetic patients parenterally requires the infusion of Non-Protein Calories (NPC) and a protein source, usually amino acids, in- sufficient amounts, in the appropriate ratio, and in a volume of fluid content with normal water balance. Ideally, the amino acids should be spared for protein synthesis rather than utilized as an energy source. Micronutrients and Vitamins, Albumin, Insulin, other drugs and medications may also be added under certain circumstances. Glucose is the carbohydrate of choice in PEN, because it is the normal physiologic substance, which naturally occurs in blood, and it is abundant, inexpensive, and really purified for parenteral administrations. In clinical experiences, it be can given to diabetic patients peripherally in high concentrations up to 20 % as long as the osmolarity of the mixture solution does not exceed 800 – 1.000 mOsm/l. At least 100 to 150 g of glucose should be supplied for maximum impact on nitrogen balance, and to provide the energy substance for certain key tissues, such as: CNS, Peripheral Nerves, Erythrocytes, Leucocytes, Active Fibroblasts, and certain Phagocytes, which normally require glucose as the sole or major energy source. If such is not the case, gluconeogenesis may happen. Glucose is better to be infused in a mixture with nitrogen source (e.g Triparen with Pan–Amin G, or KA-EN MG3 with Amiparen), because this regimen is associated with an improvement in nitrogen balance as compared to their consecutive or separate administration. To date, clinical evidence has been with fat emulsions providing only LCT (16 to 18 carbon atoms), and currently, MCT (8 to 10 carbons) and LCT emulsion mixture solutions of 20% is increasingly accepted (because MCT may show more rapid triglyceride plasma clearance and oxidation of fat). Recently, it was recommended that in order to get the best nitrogen balance, other than using intermittent administration of carbohydrates, lipid emulsions, and amino acids, the most effective way of administering such substrates, is by three-in-one Big Bag, continuous infusion. Ten Sequential Guidelines of Peripheral PEN for patients with DM are summarized, such as: Osmolarity of Nutrient Solutions < 800 – 1000 mOsm/l; Hemodynamic condition is the first priority of treatment before PEN to be started at blood glucose < 250 mg/dl; Rapid Glycemic Control should be done if blood glucose level > 250 mg/dl; Either solution of amino acids or fat emulsions are recommended to be infused continuously (not intermittently) within 24 hours; Amino Acid solutions are designed for "protein – sparing" rather than nitrogen equilibrium or anabolism, whereas fat emulsions are needed for source of energy and essential fatty acids; etc. Based on clinical experiences, rapid glycemic control ("Formula Minus One" and "Formula Times Two") and Insulin Syringe Pump ("Formula Times Twelve") can be used as guidelines in daily practice and emergency cases (Acute Coronary Syndromes, Acute Strokes, and Septic Cases due to Gangrene & Cellulitis, etc). All such "Formulas" will be on presentation at this symposium. Empirically, each nutrition of 500 ml f.e. Martos (Maltose) 10% or Dextrose 5% can be covered with 8-12 units Actrapid (AR) injected into the bottle of such solutions, 6-10 Unit AR into Potacol-R, and 30-35 units AR into Triparen No.1 or Triparen No.2. Such insulin doses are calculated by Formula 2.5-1 and Formula 5-1 in which both "Formulas" will be presented at the session. Conclusions: Ten Guidelines of basic principles of Peripheral PEN (Osmolarity < 800 - 1000 mOsm/l and blood glucose < 250 mg/dl) should be recognized by all internists and other associated specialists. However, osmilarity of solutions > 1000 mOsm/l can be given through the central vein. Mixture of nutrients such as KA-EN MG3 (Electrolyte + D 10%) – Amiparen (AA 10%) – Fat Emulsions, or Triparen (GFX 4:2:1) – Pan Amin G (AA 2.72 %) – Fat Emulsions can be safely and rationally given to patients with DM, and insulin dose regimen can be adjusted by injecting such a dose into the bottle (use Formula 2.5 – and Formula 5-1)

***Keywords**: diabetes mellitus, parenteral nutrition, empirical formulas, non-protein calories*

INTRODUCTION

Normally nourished patients (but not diabetic patients) unable to eat for as long as 7 to 10 days generally do not require PEN (Parenteral Nutrition); the protein-sparing effect of 100 to 150 gram of glucose provided in a 5 percent solution is sufficient. However, if the resumptions of adequate intake are not imminent after 7 to 10 days, potential feedings are recommended. At least 100 – 150 gram of carbohydrates should be supplied to provide the energy substrate for certain key tissues: Central Nerve System, Erythrocytes, Leucocytes, Active Fibroblasts, and certain Phagocytes. To maintain and restore nutrition of diabetic patients parenterally requires the infusion of Non-Protein Calories and a Protein Source (Amino Acids: AAE_S and Non-AAE_S), which should be accompanied, with appropriate doses of insulin by using 'Formulas": "Minus One", "Times Two", and "Formula Times Twelve".

Diabetes and Nutrition Center
Dr. Soetomo Teaching Hospital
Airlangga University School of Medicine, Surabaya

According to ADA report (1998), glycosylated hemoglobin (HbA_{1C}, now it has been changed to AIC) is a good marker (HbA_{1C} < 7 % or AIC < 7%) of long-term glucose control (during proceeding 6-8 weeks) and should be measured; however, short term blood glucose monitoring is also needed (FBG 80-120 mg/dl, Bedtime Glucose < 200 mg/dl). Glucose and Amino Acids such as [Triparen (GFX 4:2:1) plus Pan-Amin G (AA 2.72 %) or KA-EN MG3 (Electrolyte + Dextrose 10%) plus Amiparen (AA 10%)] are better to be infused together with fat emulsions (f.e Ivelip 20% or Lipofundin LCT 20 %) simultaneously, and these mixtures are associated with an improvement in nitrogen balance as compared to their consecutive or separate administration. Based on clinical experiences since 1993, "Formulas: Minus One, Times Two, Times Twelve" can be used as guidelines to control the blood sugar levels of diabetic patients with PEN.

This paper is aimed to describe shortly on PEN in patients with Diabetes Mellitus and to demonstrate the above "Formulas" to cope with the fluctuations of blood sugar levels either in daily practice or emergency cases (f.e. in Acute Coronary Syndromes, Acute Strokes, Gangrene or Cellulites with sepsis, etc).

PARENTERAL NUTRITION: GLUCOSE AMINO ACIDS, AND LIPIDS

Glucose may be used as the exclusive Non-Protein Calories Source, or it may be administered in varying proportions with lipid. When glucose is used as the major calorie source, glucose must be infused through a central vein (if the osmolarity of the solution exceeds 1000 mOsm/l, f.e. Triparen No.1, Triparen No. 2, Aminovel 600, etc), and through a peripheral vein if the osmolarity of the mixture less than 800-1000 mOsm/l (f.e. Dextrose 5%, 10%, KA-EN 3A, KA-EN 3B, KA-EN MG3, Amiparen, Pan-Amin G, Ivelip 20%, Lipofundin LCT 20 % etc). The Amino Acids profiles can be summarized: 8 Essential Amino Acids = EAA_S, and 11 Non-EAA_S (two of them are Histidine and Arginine). The Three Non-EAA_S Histidine, Glutamate, and Arginine are called conditionally EAA_S. Selected amino acids and its specific roles can be shortly summarized below by the author (Table 1).

Table 1. Selected AA_S and Specific Roles (Summarized: Tjokroprawiro 2001)

1.	Leucine	• Energy Source in Mitochondrium • Stimulates : Protein Synthesis in Skeletal Muscle
2.	Iso Leucine & Valine	• Ammonia Detoxification
3.	Histidine, Arginine*),Glutamine **): Conditionally EAA	• Increased Requirements during Stress • Anticatabolic Properties • Immunomodulator • Precursor of Nitric Oxide*) • Prevent Hyperammonemia*)
4.	Glutamine **):	1. Serves importance function in inter organ N transfer, 2. An important substrate for rapidly replicating cells, f.e Gl tract Mucosa 3. Provides a source of N for nucleotide and protein synthesis 4. Source of energy for tissue oxidation esp. in Kidney, etc
5.	Phenylalanine***) & Tyrosine	• Responsible for Disturbances in CNS • Insulin Secretagogue***)
6.	Alanine	• The Main Gluconeogenic AA • Antiproteolytic Effect in Liver Cells
7.	Proline : Collagen Synthesis → Tissue Repair and Wound Healing	

Approximately 5 percent of the total calorie intake during parenteral nutrition should be provided as amino acids. Ideally, the amino acids infused should be spared for protein synthesis other than utilized as an energy source. Nitrogen-sparing effect can be achieved when the nitrogen = N (gram) non-protein calorie = NPC (kcal) ratio maintained above 1: 150 or NPC : N ratio > 150. Along with amino acids and glucose, fats are an essential compartment of a parenteral nutrition regimen.

There are at least three major advantages for using fats intravenously:

1. Source of EFA_S = Essential Fatty Acids (Linoleic Acid = ω6, and Linolenic Acid).
2. High calorie density (1 gram = 9 Kcal)
3. Low osmolarity, thus, makes them suitable for peripheral vein use.

There are currently two fat emulsions available for clinical use: soybean and safflower oil emulsion. (Table 2). Both products are manufactured at concentration of 10 and 20 percent and are comparably effective in preventing EFA deficiency and sparing of nitrogen, especially in diabetic patients with cellulitis – gangrene.

Table 2. Fatty Acid Composition of Fat Emulsions

Fatty Acid %	Soy Bean Oil	Safflower Oil
Linoleic Acid (ω-6)	50	75
Linoleic Acid	9	0.5
Oleic Acid (18:1, ω-9)	26	12.9
Palmitic Acid (16:0)	10	6.7
Stearid Acid	2.5	2.7
Others	2.5	2.2
Total	100	100

TEN GUIDELINES OF PEN FOR PATIENTS WITH DIABETES MELLITUS

For a practical point of view, Ten Guidelines of PEN for patients with Diabetes Mellitus can be summarized (in sequence) as follows.

Start Slow - Go Slow - Stop Slow

1. Osmolarity < 800 - 1000 mOsm/l
   If osmolarity is > 1000, provide infusion to Branch 1 and Branch 2.
   For example, hypertonic fluid (Branch 1, e.g. NaCL 3% 8 drops/minute) with Isotonic or Mild-Hypertonic fluid [Branch 2, e.g. Martos infusion 10% (16 drops/minute) followed subsequently with Protacol R infusion 16 drops/minutes].
2. Fluid concentration: ± 30 ml/kg BW; Energy: ± 30 kcal/kg BW
   Cbh (glucose) minimally 100 - 150 g/day
   Addition: - 300 ml per 1 °C increase
   - 300 ml more for intracellular (Anabolic) fluid addition

3A. Hemodynamic recovery first, then PEN.

3B. If glucose > 250 mg/dl, no PEN, rapid regulation should be firstly established

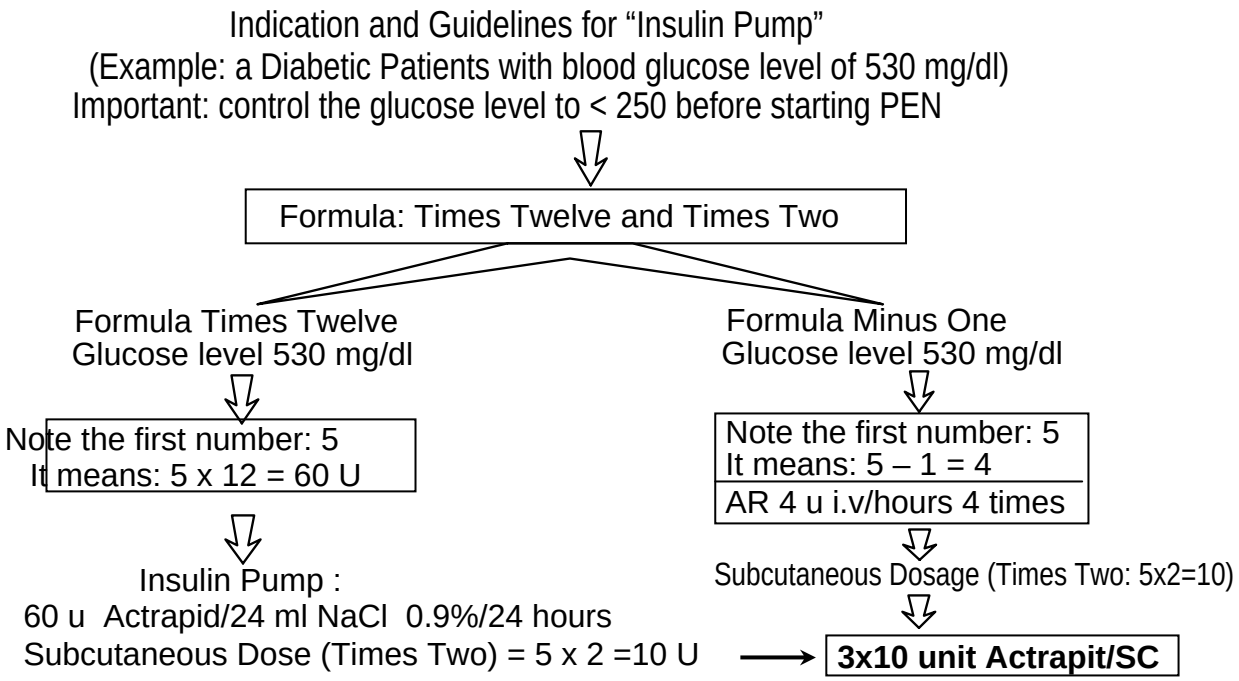
4. If glucose < 250 mg/dl, provide PEN. Objective: Glucose ≤ 200 mg/dl
5. Calorie day 1 - 3: Basal (400-800 Kcal), Increase slowly (Start Slow & Go Slow).
6. Glucose 5% or Maltose 10%; try to provide carbohydrate minimally 100 - 150 g/day (or: 3 - 4 g/kg BW): For Brain, Erythrocytes, Renal Medulla
   Glucose 5% or Maltose 10% "safe", Insulin 8 - 12 U in infusion flask.
   1 unit insulin in flask per 5 g Maltose; 1 unit for each 2.5 g Glucose.
   Martos Dose 10% Max 1 L/day if BW < 60 kg and 1.5 L for BW > 60 kg
7. AA infusion ± 5% Cal. Total: day 2 - 3, minimally 12.5 - 25 g/d
   Basis: 25 Kcal/1g AA or the ratio of Cal. NPC : N (gram) > 150
8. Lipid infusion ± 20-40% Cal. NPC for energy (since beginning) and ALE (day 4)
   ALE dose: 2-4% Total Calorie (2 x weeks)
9. Continuous administration of Lipid Emulsion in 24 hours is better than Intermittent one.

10. If all have been met, it is highly recommended to provide PEN comprising Combination of Glucose-AA-and Lipid continuously for 24 hours.

AA Infusion is Not for the Source of Energy, but for Visceral Protein Regeneration and Synthesis

RAPID GLYCEMIC CONTROL INTRAVENOUSLY IN DAILY PRACTICE AND INSULIN SYRINGE PUMP IN EMERGENCY CASES

"Formula Times Twelve" ("Rumus Kali Dua Belas") and " Formula Minus One" ("Rumus Minus Satu") can be used in clinical practice for emergency and daily cases, respectively. The explanation and example will be on presentation, however, such guidelines can be followed below.



Thus, Insulin Syringe Pump can maintain glucose control of diabetic patients with Acute Coronary Syndromes, Acute Strokes, Cellulitis – Gangrene with Sepsis, Etc.

CLINICAL EXPERIENCES ON PEN FOR DIABETIC PATIENTS

Based on clinical experiences, Table 3, 4, 5 and 6 can be used as peripheral or central vein routes of PEN depending on the Osmolarity of the nutrient solution.

Table 3. Peripheral parenteral nutrition

TABLE - 3 PERIPHERAL PARENTERAL NUTRITION
The Administration of TRIPAREN ® No. 1 /No. 2 + PAN - AMIN G®

PRODUCTS	VOL (ml)	AA (g)	KH (g)	Energy (kcal)	ELECTROLYTE (mEq)									Osm Tec (mOsm/l)
					Na^+	K^+	Mg^{++}	Ca^{++}	Cl^-	SO_4^-	Acetate	P (mg)	Zn (µmol)	
PAN-AMIN G	1000	27.2	50	308	-	-	-	-	52	-	-	-	-	507
TRIPAREN® No 1	1000	-	233	933	5	45	8	8	15	8	10	302	17	1406
T O T A L	2000	27.2	283	1241	5	45	8	8	67	8	10	302	17	956

PRODUCTS	VOL (ml)	AA (g)	KH (g)	Energy (kcal)	ELECTROLYTE (mEq)									Osm Tec (mOsm/l)
					Na^+	K^+	Mg^{++}	Ca^{++}	Cl^-	SO_4^-	Acetate	P (mg)	Zn (µmol)	
PAN-AMIN G	1000	27.2	50	308	-	-	-	-	52	-	-	-	-	507
TRIPAREN® No 2	1000	-	292	1168	58	45	8	8	73	8	-	295	17	1468
T O T A L	2000	27.2	342	1476	58	45	8	8	125	8	-	295	17	987

Table 4. Central parenteral nutrition

TABLE - 4 CENTRAL PARENTERAL NUTRITION
The administration of TRIPAREN® No. 1 /No. 2 + AMIPAREN®

PRODUCTS	VOL (ml)	AA (g)	CBH (g)	Energy (kcal)	ELECTROLYTE (mEq)									Osm Tec (mOsm/l)
					Na^+	K^+	Mg^{++}	Ca^{++}	Cl^-	SO_4^-	Acetate	P (mg)	Zn (µmol)	
AMIPAREN	1000	100	-	400	2	-	-	-	-	-	120	-	-	888
TRIPAREN® No 1	1000	-	233	933	5	45	8	8	15	8	10	302	17	1406
T O T A L	2000	100	233	1333	7	45	8	8	15	8	10	302	17	1147

PRODUCTS	VOL (ml)	AA (g)	CBH (g)	Energy (kcal)	ELECTROLYTE (mEq)									Osm Tec (mOsm/l)
					Na^+	K^+	Mg^{++}	Ca^{++}	Cl^-	SO_4^-	Acetate	P (mg)	Zn (µmol)	
AMIPAREN	1000	100	-	400	2	-	-	-	-	-	120	-	-	888
TRIPAREN® No 2	1000	-	292	1168	58	45	8	8	73	8	-	295	17	1468
T O T A L	2000	100	292	1568	60	45	8	8	73	8	120	295	17	1178

Table 5. KA-EN$_S$®

TABLE-5 KA-EN$_S$® → Meet Approximate Daily Requirement of Potassium and Sodium

Daily Homeostasis Requirement of Potassium and Sodium can be met by 1 L of KA-EN 3A®, KA-EN 3B®, or KA-EN MG3®

PRODUCT NAME	Volume (ml)	ELECTROLYTE (mEq)				Calorie (kcal)	Osmolarity (mOsm/L)
		Na^+	K^+	Cl^-	Lactate		
KA-EN 3A®	1000	60	10	50	20	108	290
or with							
KA-EN 3B®	1000	50	20	50	20	108	290
or with							
KA-EN MG3®	1000	50	20	50	20	400	695

Table 6. Practical Therapy Guidelines for Hypokalemia

TABLE - 6 Practical Therapy Guidelines for Hypokalemia
(Clinical Experience 1993)

↓

Hypokalemia: < 3.50 mq/L

↓

Formula 1,2,3,4 : 1 Flask 25 ml a 25 meq K^+

K^+ = 3.0-3.5	K^+ = 3.0-2.5	K^+ = 2.0-2.5	K^+ = < 2.0
↓	↓	↓	↓
Formula 1 : 1 Flask	Formula 2 : 2 Flask	Formula 3 : 3 Flask	Formula 4 : 4 Flask

CONCLUSIONS

Parenteral nutrition is recommended when the enteral route is not accessible or if adequate nutrient administration is not possible via such a route alone. Continuous infusion of PEN of carbohydrate, amino acids and fat emulsions in metabolic terms is better to get positive nitrogen balance rather than using intermittent administration. Glucose control during PEN can be achieved by using several "Formulas", such as: "Formula Minus One"(Minus Satu), "Formula Times Two"(Kali Dua), and or "Formula Times Twelve"(Kali Dua Belas) either for daily practice or for emergency cases. The usage of the such "Formulas" can be easily understood on presentation. Several combinations of nutrients based on clinical experiences are summarized.

REFERENCES

Cerro FB, Benitez MR, Blackburn GL, et al., 1997. Applied Nutrition in ICU Patients. A consensus statement of the American College of Chest Physicians (ACCP). Chest III, 769

Chen WJ, Yeh SL, Wu YP, 1997. Effect of MCT/LCT and LCT Emulsion on Plasma Lipids and Nitrogen Retention in Streptozotonin-Induced Diabetic Rats Receiving Total Parenteral Nutrition. Nutrition 13,882.

Consensus Statement, 1998. The Consensus Roundtable on Nutrition Support of Tube Fed Patients with Diabetes. Clinical Nutrition (Suppl.2) 17,63

Silberman H, 1989. Parenteral and Enterable Nutrition 2nd Edition-Appleton & Lange, p.189.

Tjokroprawiro A, 2001. Parenteral Nutrition in Patients with Diabetes Mellitus (Experiences in Clinical Practice). Symposium: New Insights into the Rationale Parenteral Nutrition in Clinical Practice. Surabaya, 30 May 2001.

Tjokroprawiro A, 2002. Basic Principles of Parenteral Nutrition (Focus on DM: Clinical Experience-Based). Scientific Meeting. Surabaya, 18 April 2002

Tjokroprawiro A, 2003. Medical Nutrition Therapy in Patients with Diabetes Mellitus (Focus on Par Enteral Nutrition). Scientific Meeting: Recent Advances in Clinical Nutrition. Surabaya, 20 May 2003.

Washington C, Kosher F, Davis SS, 1993. Physicochemical properties of parenteral fat emulsions containing 20 % triglyceride: Intra Lipid and Ivelip. J of Clin Pharmacy and Therapeutics 18,123.