

# Brief History And Development Of Parenteral Nutrition Support

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## ABSTRACT

Patients who are unable to use their gastrointestinal system for feeding purposes are now usually started on parenteral nutrition. It is a therapeutic tool used in the clinical management of patients requiring special nutritional care both in the hospital, and at home (home parenteral nutrition). The idea of providing nutrients intravenously in humans was first realised when Sir Christopher Wren injected wine and ale in dogs way back in the middle of the 17<sup>th</sup> century. The historic experiment initiated further investigation and studies on this novel approach to nutrition. Better understanding of the metabolic and pharmacological properties of the macronutrients (protein, carbohydrates, and lipid), the micronutrients (trace elements, and vitamins), and the electrolytes have made it possible to administer parenteral nutrition safely to all types of patients where it is indicated. Continuous development and improvement in the pharmaceutical presentations of these nutrients have helped to minimise the metabolic problems seen in the early days of parenteral nutrition administration. Production of the single- or multilayered parenteral nutrition bags using materials which are inert and capable of reducing oxygen permeability such as the combination of ethylenevinylacetate-polyvinylidene chloride has ensured better stability of the parenteral nutrition admixture. The multicompartamental bag has provided a much more simpler and convenient way of initiating parenteral nutrition. The increase in knowledge, development and improvement in parenteral nutrition support has made it possible to provide parenteral nutrition support at home.

**Keywords:** *parenteral nutrition, enteral nutrition, macronutrients, micronutrients, convenience bags*

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## INTRODUCTION

Parenteral nutrition (PN) is a relatively new therapeutic tool used in the clinical management of patients. Arguably, the era of modern clinical nutrition can be said to have dawned around 35 years ago when Dudrick and colleagues reported their work on the successful administration of long-term PN in an infant (1). In Malaysia, PN service was established in late 1986 at the Kuantan General Hospital (Hospital Tengku

Ampuan Afzan, Kuantan, Pahang) (2), while Bahari reported that formal parenteral nutrition rounds led by pharmacists were initiated at the university hospital of Universiti Sains Malaysia (HUSM) a year later (3).

PN is a mode of providing nutritional supplement that involves the administration of nutrients through the intravenous route (*viz par*

enteral). It is also widely and affectionally known as total parenteral nutrition or TPN, although intravenous nutrition, and artificial nutrition are accepted terms to convey the same meaning. Hyperalimentation, that is the provision of nutrients at high concentration intravenously, was the term used during the early days of this novel nutritional approach (which, literally, was the reason for most of the adverse effects of PN therapy back then!). Nowadays, the term PN is widely used in the literature to denote the administration of nutrients intravenously.

Basically, PN is only indicated when the oral, or enteral route (i.e. the use of the gastrointestinal system) of nutrition cannot be established, or is insufficient for the maintenance of the patient's nutritional requirements in relation to his/her clinical status. Partial parenteral nutrition (PPN) is the concurrent intravenous administration of nutrients together with oral or enteral nutrition for the same therapeutic objective.

The dietary components of a standard PN regimen are the macronutrients (protein or amino acids, carbohydrate, and lipids or fats), the electrolytes, the micronutrients (trace elements, and vitamins) and water. Carbohydrate, in the form of glucose or dextrose, and lipids are the major energy providers.

#### **Early work on intravenous nutrition**

The main role and function of the major components of the diet in human growth and development were recognised only around a century ago (4). Nevertheless, the history of intravenous infusion of nutrients began in 1665, when Sir Christopher Wren injected wine and ale to dogs, and noted that intravenously administered alcohol had the same effect as alcohol taken orally (5).

Indeed, investigators and clinicians have long realised the importance of providing adequate nutrition to patients, more so to those with gastrointestinal problems. The intravenous route of nutrient administration was seen to be one possible avenue to venture into in the nutritional management of patients who cannot consume food orally. Ever since the historic experiment by Wren, various workers had experimented providing nutrients such as carbohydrates and lipids in animals, and also humans in their effort to understand and develop this novel approach to nutrition.

Stirius, in 1668, published a review on this subject of intravenous experiments in which he deduced that intravenous infusions were, or could be applicable to nearly all disease states, except where pregnant women and newborn children were involved. These patients were considered by Stirius as difficult and bad subjects to treat (6).

Although the deduction of Stirius still holds some relevance today, advances in the knowledge and technical capabilities in the administration of PN over the last two decades have made it possible to administer intravenous nutrition even to pregnant mothers (7) and low birth-weight neonates (8,9), the so called difficult and bad subjects!

Early results of intravenously administered nutrients were not promising because of the adverse effects associated, although the desired outcomes were also observed. These unwanted effects, caused by poor administration techniques, and the use of crude compounds led to some of the work in this field of intravenous nutrition research being prematurely abandoned (10). One such incident is the work of Friedrich in 1904, in which he administered what can be considered the first total PN in man, subcutaneously. These infusions of peptone, fat, glucose and electrolytes were so painful that not even Dr. Friedrich wanted to pursue development in this area of research (10). Also, it can be safely deduced that the lack of pharmaceutical and microbiological knowledge meant that problems of stability (incompatibility and interactions included), and sterility were not recognised and duly addressed during those early years.

#### **Intravenous administration of proteins**

Ever since the 19<sup>th</sup> century, protein has been seen to have an important role in the growth and development of humans (11). The special nature of protein and its metabolism made it a challenge to find suitable ways of administering it intravenously. The first study in the intravenous administration of proteins was made in goats in the form of protein hydrolysates by Herriques and Andersen in 1913 (10). These hydrolysates were products of the naturally occurring proteins such as fibrin and casein. Positive nitrogen balanced was achieved, thus demonstrating the role of intravenous protein hydrolysates as possible alternative to dietary protein in animals.

It was only after 1937, when Elman published his pioneering studies on the intravenous infusion of protein hydrolysates in man (12), that investigations of complete intravenous nutrition (i.e. the intravenous administration carbohydrate, protein, and lipids concurrently) were initiated worldwide. Due to serious complications such as high concentration of di- and tripeptides resulting from incomplete hydrolysis, poor utilisation of nitrogen, and hyperammonaemia (13), the use of protein hydrolysates in PN has now been superseded by the more flexible crystalline amino acids.

Today, various parenteral amino acid preparations for specific clinical states have been developed and marketed such as Aminoplasma<sup>®</sup> Hepa<sup>®</sup> (B.Braun Germany) for PN patients with liver dysfunction; Vaminolact<sup>®</sup> (Fresenius Kabi, Sweden) and Promene<sup>®</sup> 10% (Baxter, UK) for neonates and infants, and Glamin<sup>®</sup> (Fresenius Kabi, Sweden), which is an amino acid formula with a higher concentration of glutamine. For patients with renal impairment, amino acid solutions without electrolytes such as Vamin<sup>®</sup> 14 EF (Fresenius Kabi, Sweden) are recommended.

### **Intravenous glucose infusion**

At the turn of the century, in 1896, Beidl and Kraus administered the first intravenous infusion of glucose solution in man, around 40 years after the importance of glucose for metabolism was first demonstrated. 200-300 ml of a 10% glucose solution was administered with no glucosuria observed although severe fever resulted (10). Glucose infusion was recognised as the only source of energy before the advent of a suitable lipid emulsion that could be safely administered intravenously in humans. In the desire to obtain higher calorie supplement, higher concentrations of glucose solution were infused. Inevitably, vein irritation and thrombophlebitis ensued when high concentrations of glucose solution were infused peripherally. These problems were overcome when Dudrick and co-workers showed that higher concentrations of glucose could be administered safely through the central veins in dogs (1). Ever since then, PN admixtures with high concentrations of glucose have been safely administered in humans through the subclavian vein or the central intravenous route.

### **Early intravenous administration of lipids**

The earliest published record of intravenous lipid

administration was made by Courten in 1712, when he infused 1 g per kg body weight of olive oil in a dog. However, severe respiratory distress symptoms were observed, and the dog eventually died (10). It was then assumed that all oils or fats, for that matter, should only be infused in a specialised and suitable form. Further investigations by Menzel and Perco more than 150 years later, also in dogs, showed that large amounts of lipids could be administered intravenously without adverse effects (10).

The interest in using lipids in PN led various investigators to work on lipid emulsions of various composition such as castor oil (14), olive oil (15) and cottonseed oil (16). All these lipid emulsions caused side effects in humans such as nausea, vomiting and fever. Other serious adverse reactions notably liver damage, jaundice and bleeding tendency were also observed leading the United States of America to ban the usage of lipid emulsions for PN in 1964. During this time in Europe, Schuberth and Wretling developed a safe and efficacious form of lipid emulsion from soybean oil using egg yolk phospholipids as the emulsifying agent (17). This lipid emulsion (consisting of long chain triglycerides, LCT) marketed as Intralipid<sup>®</sup> (Fresenius Kabi, Sweden) became one of the most widely used lipid emulsions in PN administration until today. [N.B. intravenous lipid emulsions were subsequently reintroduced in the U.S. market in 1975 (18)].

Today, various concentrations (10, 20 and even 30%), and composition of lipid emulsion (LCT, and combination of LCT and medium chain triglycerides, MCT [Lipofundin<sup>®</sup> MCT/LCT, B. Braun Germany]) are used in PN therapy. Investigations into the use of parenteral fish oil emulsion (n-3 fatty acids) (e.g. 10% Omegaven<sup>®</sup> [Fresenius, Germany]), and the re-emergence in the use of olive oil in combination with soya bean (ClinOleic<sup>®</sup> 20% [Baxter, UK]) in the last 10 years suggest new alternatives in the use of lipid emulsion in PN (19).

### **Electrolytes and the micronutrients in parenteral nutrition**

The importance of salts in humans was realised when the blood chemistries of cholera patients were investigated by O'Shaughnessy in 1839, and Latta followed up these findings in the same year by infusing, intravenously, solutions of the salts that were found low in the blood of dying

cholera patients. Majority of these patients remarkably recovered (20). Various concentrations of sodium chloride infusions (e.g. 0.9% sodium chloride, and 0.45% sodium chloride) are now used for parenteral fluid and electrolyte therapy. These findings coupled with the work of Beidl and Kraus in 1896 on the infusions of glucose in humans led to the salt-glucose solutions which became the so-called standard parenteral solution of the early part of the 20<sup>th</sup> century (20). These solutions are now still used as dextrose-saline combinations in intravenous fluid therapy in the various clinical settings.

The need to provide trace elements or the micronutrients in PN came to light only around 25 years ago when it was shown by Jeejeebhoy and co-workers that long-term PN caused chromium deficiency (21). Work by Buzzetti and colleagues a few years later confirmed the existence of hypocupraemia in a patient attributed to PN administration (22). Trace elements are now normally added in the PN admixture in the form of standard trace element preparations such as Additrac<sup>®</sup> (Fresenius Kabi, Sweden), Peditrace<sup>®</sup> (Fresenius Kabi, Sweden) and individual injections (e.g. zinc sulphate, and magnesium sulphate injections) to supplement the daily needs for these micronutrients.

The importance of vitamins, another group of micronutrients, in nutrition was first appreciated in the early part of the twentieth century when researchers found that animals required more than carbohydrate, protein, fat, minerals and water to support life and growth (23). In the parenterally-fed malnourished patients, signs of vitamin deficiencies were observed in the blood levels after a few days on vitamin-free PN (24). Vitamins are now routinely added in the PN admixture using various products such as multiple vitamins preparations (Solvit<sup>®</sup>, Vitalipid<sup>®</sup> [Fresenius Kabi, Sweden]) which have been developed based on the American Medical Association guidelines for vitamins for parenteral use (25). These vitamins can also be added as individualised vitamin preparations (e.g. Vit K).

#### **Complete intravenous provision of nutrients from a single bag**

Originally, PN administration constituted the use of separate glass bottles. A 2-in-1 method was adopted where the amino acids solution and

glucose were admixed together with the other components of the PN regimen. Lipid emulsion was administered from a separate bottle. This system, which is still being adopted in some hospitals, requires two sets of intravenous tubings and infusion pumps leading to high cost and problems of sepsis, vein patency and lines management (26).

In the seventies, the All-in-One (AIO) system was introduced by Solassol and colleagues to allow for the direct administration of PN in the ambulatory patient (27). This system involved the mixing of the main components of a PN regimen (the amino acids, glucose and lipid emulsion and other nutrient components – the AIO admixture) in a single silicone rubber bag. They showed that this admixture was stable and safe to be administered to patients leading to a more cost-effective and simple approach to PN administration. This method has now been widely accepted and is used worldwide although the type of bags used has changed considerably.

#### **Development of the PN bag**

When it was shown that mixing of the major nutrients was possible, the components of the PN admixture (except lipids) were first mixed in bottles (26). The use of these bottles slowly lost favour because of their bulkiness, and losses of costly materials if they were inadvertently dropped and broken.

In light of this, a more flexible container was needed leading to the use of polyvinyl chloride (PVC) bags. However, it was later shown that the use of PVC bags were not suitable due to adsorption of the components such as vitamin A to the bags (28, 29) and also the risk of plasticisers from the PVC matrix leaching out or being extracted by the contents of the admixture (30). Plasticisers can be extracted by the organic contents of the admixtures such as the lipids and vitamins.

The practice of adding all the components (including lipid) of the PN regimen together (the AIO admixture) posed the inherent risk of physicochemical stability problems. As the use of materials such as PVC will only compound this problem, the ethylene-vinylacetate (EVA) bag which is more inert was introduced. The EVA bags possess advantageous thermoplastic properties and favourable toxicological and biocompatibility aspects (31). These bags are

now commonly used for the AIO admixtures.

Nowadays, multilayered bags have been introduced to ensure a greater stability profile of the PN admixture against oxidation. These bags consist of multiple-layered plastic produced from the combination of EVA-polyvinylidene chloride (PVDC) (32) or EVA-modified EVA ethylvinyl alcohol (EVOH) for example, which reduces the permeability of oxygen by 100 times compared to conventional EVA bags thus ensuring better stability of the admixture (33).

Further understanding of the physico-chemical aspects of the PN regimens, and recent technological advances have led to the development of the prefilled multi-compartmental bags for PN administration. The introduction of these bags has provided easy mixing of the PN regimens and also provided a close system which guarantees sterility of the admixture.

### **The Easy-to-Mix System**

During the late eighties, an easy-to-mix (ETM) system was introduced to facilitate quick and easy mixing of PN regimens by pharmacy and nursing staff. This system comprises of a two-bottle system (Vitrimix<sup>R</sup> [Fresenius Kabi, Sweden]). One bottle contains a glucose-amino acid solution, whereas the lipid component is contained in the other bottle. Compounding of a PN regimen (minus the micronutrients) involves the simple transfer of the lipid emulsion into the glucose-amino acid solution via a transfer pin. This system has now been superseded by another ETM system which was developed in the early nineties.

The new ETM system uses multi-compartmental EVA bags or the convenience bags (please refer preceding section) prefilled with the nutrients and electrolytes required for PN therapy. These bags are presented as the double chamber (Nutriflex<sup>R</sup> [B Braun, Germany]), and triple chamber bags (Kabiven<sup>R</sup> [Fresenius Kabi, Sweden], Clinomel<sup>TM</sup> [Baxter, UK]). The chambers are separated by various mechanisms such as a breakable port, peel-seal system, or a pull-away flexible rod clamp. In the double chamber bag, one compartment is filled with the amino acids solution, while the other compartment is filled with glucose based on a standard nutritional regimen (the lipid component is kept in a separated bottle, which is then added to the system). In the triple-chamber

bags, the third compartment is filled with the lipid emulsion. To use these bags, firm and gentle squeezing of the bag will break the intercompartmental seals; or the separating rod removed, thus mixing the nutrients. Other nutrients such as the electrolytes, trace elements and vitamins can then be added based on the daily allowances, and the bags are ready for administration. The use of these bags, or the ETM system ensure better stability of the AIO admixtures and minimise the risk of contamination during compounding.

### **Home Parenteral Nutrition**

Home parenteral nutrition (HPN) is the provision of parenteral nutrition at home. The need to provide HPN was realised in the effort of reducing treatment cost due to long hospital stay, and to avoid hospital-acquired complications (e.g. infection) in the stabilised patients whose main reason for continued hospitalisation is for PN therapy. With the increase in knowledge, development, and improvement in PN support, the provision of HPN provides a comforting environment, and gives patients the freedom to return to normal activities such as work, and even travelling (34). HPN is indicated in patients who have to rely on long-term PN such as those with Crohn's disease and short bowel syndrome. HPN is also administered to patients suffering from acquired immunodeficiency syndrome (AIDS), chronic pancreatitis, hyperemesis gravidarum, and neoplasm (35).

HPN should be administered exclusively from an AIO admixture in a single bag. As such the compounding of a stable admixture is usually carried out by experienced pharmacy personnel in established centres. A patient needs only to attach the outlet port of the compounded bag, aseptically, to the inserted catheter of the central route (established by the surgeon in the hospital). It is common for the pharmacy department in the hospital where the patient has been treated to supply compounded bags ready for use at home. Storage advice and correct use of the compounded bags for HPN are usually provided by the pharmacist to these patients to avoid physicochemical stability problems, and also clinical complications such as infection, and other metabolic derangements. Monitorings during HPN administration by the nutritional support team help to provide safe and cost-effective nutritional therapy to these patients.

## CONCLUSION

In perspective, PN has now been accepted as part of the overall therapeutic management of the hospitalised patients when indicated. It is not only limited to preventing starvation or correcting deficiencies (36). In more advanced countries, the instigation or cessation of PN therapy is subject to the same legal and moral constraints as apply to other recognised therapies

37). Refinement and sophistication of techniques have made optimal nutrition possible in virtually all patients regardless of the status of their gastrointestinal tract, or the presence of complicating metabolic disorders. Today, these advances have also made home parenteral nutrition possible in stabilised patients who require this mode of nutritional support for a longer period of time.



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