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Validating hyperbilirubinemia and gut mucosal atrophy with a novel ultramobile ambulatory total parenteral nutrition piglet model☆,☆☆

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ABSTRACT

Total parenteral nutrition (TPN) provides all nutrition intravenously. Although TPN therapy has grown enormously, it causes significant complications, including gut and hepatic dysfunction. Current models use animal tethering which is unlike ambulatory human TPN delivery and is cost prohibitive. We hypothesize that using ultramobile infusion pumps, TPN can be delivered cost-effectively, resulting in classical gut and hepatic injury, and we thus aim to establish a new model system. Neonatal pigs (n = 8) were implanted with jugular vein and duodenal catheters. Animals were fitted in dual-pocket jackets. An ultramobile ambulatory pump was placed in one pocket and connected to the jugular vein or duodenal catheter. Isocaloric TPN or swine formula was placed in the other pocket. Rigorous Wifi-based video and scheduled monitoring was performed. After 14 days, the animals were euthanized. The mean (±SD) daily weight gain (in grams) for enteral-fed control (EN) vs TPN animals was 102.4 ± 10.8 and 91.03 ± 12.1 respectively ($P < .05$). Total parenteral nutrition resulted in significant conjugated bilirubin elevation and hepatomegaly. Mean (±SD) serum conjugated bilirubin (in μmol/L) was 1.5 ± 0.7 for EN and 6.3 ± 2.8 for TPN ($P < .05$). Marked gut atrophy was noted with TPN. The mean (±SD) gut weight as a percent of body weight was 4.30 ± 0.26 for EN and 2.62 ± 0.48 for TPN ($P < .05$). Surgical sites healed well. All animals remained completely mobile. We thus established that TPN can be successfully delivered using ultramobile pumps and believe that this remains the first such description of an ambulatory piglet TPN model system. In addition to cholestasis and gut atrophy, classical TPN-induced injury was documented.

Abbreviations: EN, enteral nutrition; PNALD, parenteral nutrition–associated liver disease; SLU, Saint Louis University; TPN, total parenteral nutrition.

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1. Introduction

Total parenteral nutrition (TPN) therapy involves providing all of a patient's nutritional needs intravenously and is lifesaving in clinical settings where enteral-based delivery of nutrition is not possible [1,2]. Such infusion has grown enormously over the last few decades and remains a critical strategy in sick neonates, pediatric and adult patients. There are more than 30000 patients in the United States permanently dependent on TPN, and several-fold higher numbers require TPN for varying duration [3,4]. Although administration of TPN is lifesaving, unfortunately, it is also associated with important clinical complications resulting in significant morbidity and mortality. One of the complications of patients on TPN is parenteral nutrition–associated liver disease (PNALD), the hallmark of which is conjugated bilirubin elevation. Parenteral nutrition–associated liver disease can ultimately progress to cirrhosis and liver failure [5–7]. Recent studies indicate that gut growth is hampered with TPN infusion [8–11]. The mechanisms of such TPN-associated pathologies remain poorly defined, and research for preventive or ameliorative intervention is a major research focus in gastroenterology and hepatology [12–14].

Although several TPN animal models have been adopted, the most promising have been those that use pigs on TPN. Pigs present striking homology of both anatomy and physiology with humans in respect to numerous organ systems, especially the liver and the gastrointestinal tract [15,16]. In particular, the neonatal pig has been shown to be highly comparable to humans with regard to numerous aspects of metabolism, body composition, and organ function [17–19].

Because TPN therapy involves intravenous infusion over long duration of time and stability, feasibility of long-term maintenance of indwelling catheters in animal models is a big concern. Current technology has allowed human patients on TPN to use a portable, ambulatory, unobtrusive mobile pump as the method of delivery [20,21]. However, the only TPN infusion animal model identified and described in the current literature involves tethering of pigs to maintain catheters, which is costly, resource-intensive, stressful for animals, and significantly different from TPN delivery in humans (Supplementary Fig. 1).

To effectively assess interventions to ameliorate or prevent TPN pathologies, it is imperative that an animal model be developed that replicates or closely mimics such therapy in humans and yet remains cost-effective for large-scale studies. We hypothesize that using ultramobile infusion pumps, TPN can be delivered in an ambulatory manner to induce classical TPN-related hepatic and gut injury. We thus aim to establish a new model system superior to current TPN animal models.

2. Methods and materials

2.1. Animal procurement

Saint Louis University (SLU) is a registered US Department of Agriculture research facility. The study protocol was approved by the Institutional Animal Care and Use Committee of SLU (SLU No. 2346, US Department of Agriculture registration 43-R-011) and was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* [22]. Seven-day-old, neonatal domestic pigs (piglets) were procured from an approved class A vendor and immediately placed in heated cages. Piglets were identified by ear tags.

2.2. Acclimatization and housing

All animals were group housed until after surgery. After surgery, animals were single housed in an animal incubator that allowed for the provision of external thermal support for the entire duration of the study. The animals were acclimatized during the first 3 days upon arrival. Piglets were hand fed every 6 hours (4 times/d) by trained study personnel using swine milk replacer (LitterLife; Merrick's Inc, Middleton, WI, USA). In addition, a bowl with the milk replacer was placed in the primary enclosure to allow for ad lib feeding.

2.3. Surgery and catheter placement

Postacclimatization at day 10 of life, piglets were individually placed in a chamber that contained 3% to 5% isoflurane for anesthetic induction. The animals were then transferred to a heated surgery table and masked with a cone for maintenance anesthesia (2%-4% isoflurane) with appropriate waste gas scavenging. Vital signs (oxygen saturation as measured by pulse oximetry, temperature, heart rate, and respiratory rate) were continuously monitored throughout the surgical procedure. Once deeply anesthetized, the abdomen and neck were surgically prepared and draped for aseptic surgery.

2.3.1. Jugular catheter placement

A jugular catheter was placed in the left jugular vein by a vascular cut-down technique. The catheter was secured to the vessel. Patency was confirmed by injecting sterile heparinized saline (3 mL), and the catheter was tunneled subcutaneously via trochar to exit the skin just caudal to the scapulae (Supplementary Fig. 2A).

2.3.2. Duodenal catheterization

A small midline (4-5 cm) abdominal incision was made cranial to the umbilicus. A portion of the nonglandular stomach was exteriorized exposing the duodenum. A full-thickness poke incision was made in the proximal duodenum with a 20-gauge hypodermic needle. A sterile silastic catheter was transluminally placed inside the duodenum and secured to the duodenal wall with nonabsorbable suture (Prolene, Ethicon Somerville, NJ 08876). The serosa of the duodenum was folded around the catheter and further secured to act as a seal to prevent inadvertent leakage of intestinal contents into the abdominal cavity (Supplementary Fig. 2B). The catheter was sutured to the abdominal wall. Both catheters were exteriorized through the same incision just caudal to the scapulae. The catheters were flange secured and additionally secured with a purse string suture at the body wall. The skin was closed in a continuous subcuticular pattern with absorbable suture (Vicryl, Ethicon Somerville, NJ 08876). Both catheters were secured at the skin with 2 interrupted nonabsorbable monofilament sutures (Nylon, Ethicon Somerville, NJ 08876).