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Intraperitoneal 1.5% Delflex improves intestinal blood flow in necrotizing enterocolitis

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) alters intestinal microvascular control mechanisms causing significant vasoconstriction. Our prior work with intraperitoneal 2.5% dextrose solution demonstrated increased intestinal perfusion in experimentally induced NEC. In the current study, we examine whether a buffered solution with lower glucose and osmolar loads similarly increases intestinal blood flow. We hypothesized that buffered 1.5% dextrose solution would increase ileal blood flow compared with baseline in NEC.

Methods: We randomly assigned pregnant Sprague-Dawley rats to control ($n = 103$) or NEC ($n = 123$) groups, by litter. We induced NEC by previously published methods. Control pups were vaginally delivered and dam-fed. We used laser Doppler flowmetry to evaluate perfusion in the terminal ileum at 12, 24, 48, 72, or 96 h after delivery at baseline and after application of topical 1.5% dextrose solution. We evaluated differences between groups and time points by analysis of variance and Tukey post hoc test.

Results: Baseline blood flow in the terminal ileum increased with gestational age in both groups ($P < 0.05$). Control groups had significantly greater baseline blood flow than NEC groups ($P < 0.05$), and topical application of buffered 1.5% dextrose solution increased blood flow compared with baseline in both groups at all time points ($P < 0.05$).

Conclusions: Topical 1.5% dextrose solution significantly enhanced blood flow in the terminal ileum to the same degree as 2.5% dextrose solution. Thus, the use of buffered 1.5% dextrose solution might be more beneficial in treating clinical NEC, because it places a lower glucose and osmotic load on NEC-injured intestine.

1. Introduction

Necrotizing enterocolitis (NEC) is the most frequent cause of gastrointestinal emergencies in infants [1]. It affects mostly premature neonates, and carries a mortality rate of approximately 15%–30% [2,3]. Although many cases of NEC can be managed medically, close to 40% of NEC patients have severe disease that necessitates surgical intervention [4]. The exact pathophysiology of NEC is still unclear, but it is believed to be multifactorial [5]. Risk factors most commonly associated

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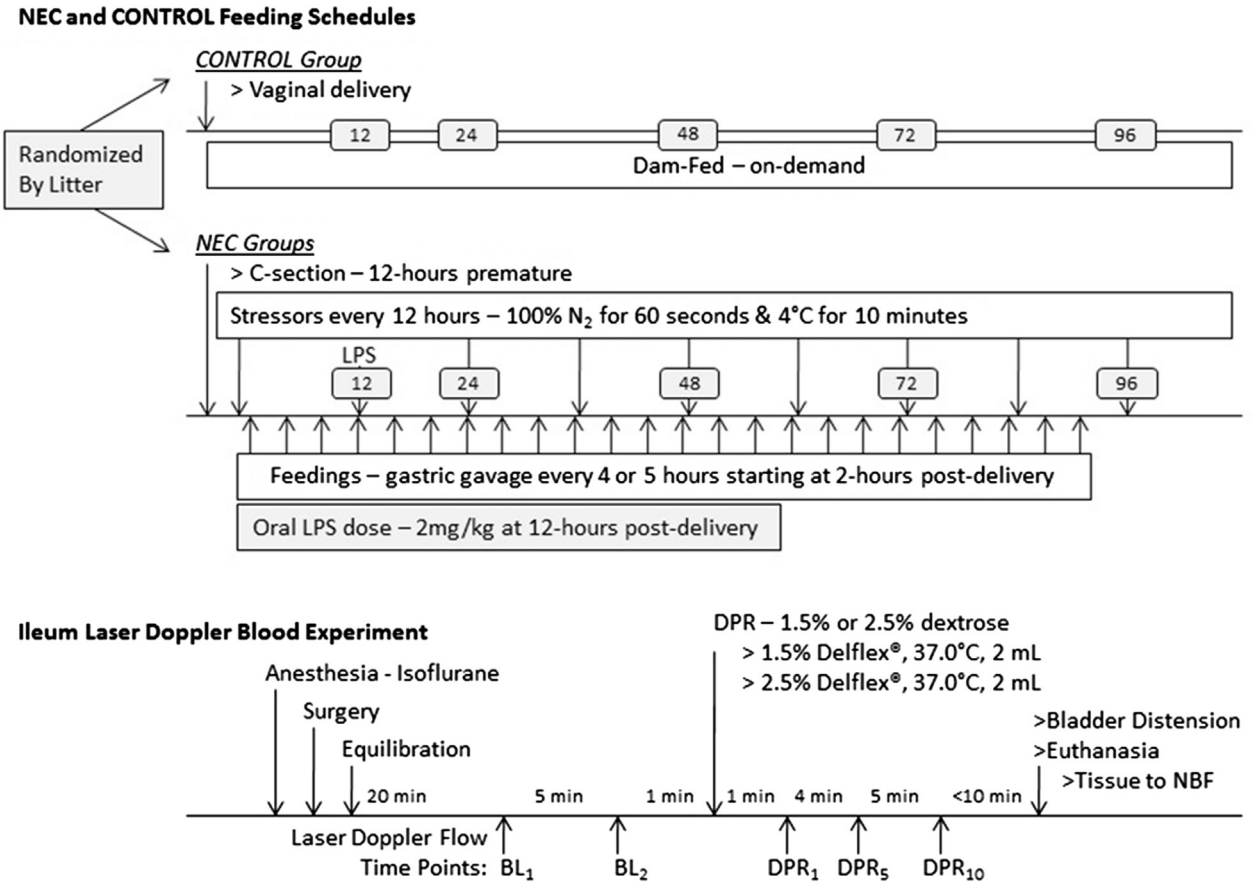

Fig. 1 – Experimental timeline. We randomized pups to feeding protocol by litter to the control group, which were delivered vaginally and dam-fed, or to the NEC group, which were delivered by caesarian at 12 h prematurity and underwent gastric gavage feedings and stressors every 12 h. Pups were anesthetized by inhaled isoflurane and underwent ileum laser Doppler flow studies at 12, 24, 48, 72, or 96 h post-birth. We recorded baseline blood flow over 5 min and then topically applied 1.5% or 2.5% Delflex to the ileum and recorded blood flow 1, 5, and 10 min later. C-section = caesarian delivery; N_2 = nitrogen gas; NBF = 10% neutral-buffered formalin for histopathology samples; BL = baseline laser Doppler blood flow.

with NEC include prematurity, low birth weight, and formula feeds [3,6–11]. Studies suggest that the intestinal ischemia seen in NEC is the result of nitric oxide (NO) and endothelin-1 dysregulation [12,13]. Decreased endothelial NO synthase activity and a resultant decrease in NO production have also been demonstrated in neonates with NEC [14]. Our laboratory has previously demonstrated that vasoconstriction is a key step in the development of NEC [15]. Thus, interventions that improve newborn intestinal blood flow may prove effective in the treatment of NEC.

We have previously shown that direct peritoneal resuscitation (DPR), in which commercially available peritoneal dialysis solution is topically applied to the intestine as an adjunct to conventional resuscitation, improves intestinal blood flow in a hemorrhagic shock rat model and improves outcomes in humans undergoing damage control laparotomy for trauma [16,17]. In translating this treatment to neonates, we have also demonstrated that DPR using a buffered 2.5% dextrose peritoneal dialysis solution (2.5% Delflex; Fresenius USA, Ogden, UT) improves intestinal hypoperfusion seen in experimental NEC [18]. Because of concerns regarding hyperglycemia and hypovolemia with use of a hyperosmolar solution in the peritoneum, we hypothesized that buffered 1.5% Delflex would similarly increase intestinal blood flow in an animal model of NEC, but cause less hyperglycemia than 2.5% Delflex solution.

2. Methods

All studies were conducted at the Robley Rex Veterans Affairs Medical Center in Louisville, Kentucky, and were approved by the Institutional Animal Care and Use Committee and Research Safety Committee before the initiation of experiments. Timed-pregnant Sprague-Dawley rat dams (Harlan, Indianapolis, IN) were housed in the Association for Assessment and Accreditation of Laboratory Animal Care International–accredited Veterinary Medical Unit for at least 1 wk before the study and were allowed *ad libitum* access to water and commercial rat diet (LabDiet 5001; PMI Nutrition International, LLC, Brentwood, MO). Litters were randomized to caesarian delivery under carbon dioxide anesthesia 24 h before the expected date of delivery or vaginal delivery. We