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Beneficial effects of mucous fistula refeeding in necrotizing enterocolitis neonates with enterostomies

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ABSTRACT

Background: Necrotizing enterocolitis in premature neonates often results in bowel resection and stoma formation. One way to promote bowel adaptation before stoma closure is to introduce proximal loop effluents into the mucous fistula. In this study, we reviewed our experience with distal loop refeeding with respect to control group.
Methods: All patients with necrotizing enterocolitis between 2000 and 2014 necessitating initial diverting enterostomies and subsequent stoma closure in a tertiary referral center were included. Medical records were retrospectively reviewed. Demographic data, surgical procedures, and postoperative outcomes were analyzed.
Results: 92 patients were identified, with 77 patients receiving mucous fistula refeeding. The refeeding group showed less bowel ends size discrepancy (25 vs 53%, $p = 0.034$) and less postoperative anastomotic leakage (3 vs 20%, $p = 0.029$). Fewer refeeding group patients developed parenteral nutrition related cholestasis (42 vs 73%, $p = 0.045$) and required shorter parenteral nutrition support (47 vs 135 days, $p = 0.002$). The mean peak bilirubin level was higher in the non-refeeding group (155 vs 275 μmol/L, $p < 0.001$). No major complication was associated with refeeding.
Conclusions: Mucous fistula refeeding is safe and can decrease risk of anastomotic complication and parental nutrition related cholestasis. It provides both diagnostic and therapeutic value preoperatively and its use should be advocated.
Level III Treatment Study in a Case Control Manner.

Necrotizing enterocolitis is one of the most common neonatal condition that requires surgical intervention with the formation of enterostomy and mucous fistula [1]. Most of these patients are premature neonates with complex nutritional need. They are prone to fluid and electrolyte imbalance especially in those proximally placed enterostomies with high output. The fragile physiological balance may be further complicated by the presence of short bowel syndrome. As a result these patients often require parenteral nutritional support, either on short- or on long-term basis.

With advances in parenteral nutrition preparation, including the use of omega-3-fatty acid, metabolic complications are becoming less common [2]. Prolonged use of parenteral nutrition nevertheless can be associated with cholestatic jaundice, central venous catheter related sepsis and thrombosis, with preterm babies particularly at risk. One method to reduce cholestasis and dependency on parenteral nutrition is to encourage intestinal adaptation by means of mucous fistula refeeding. It involves the introduction of proximal enterostomy effluent into the mucous fistula (distal loop), so as to mimic the complete physiological pathway that normal intestinal content will go through.

Effects of mucous fistula refeeding have been demonstrated in previous studies [3–8]. However these are all small case series with no control group as comparison. Here we present our experience in this case controlled study to elucidate its safety and efficacy.

1. Methods

A retrospective study of all patients with the diagnosis of necrotizing enterocolitis admitted between 2000 and 2014 was performed. Patients who had undergone surgery for the formation of stoma with mucous fistula and later stoma closure were included into the study. Patients with contraindication for mucous fistula refeeding such as stricture in the distal loop were excluded from the study. Medical records were reviewed with data extracted. Demographic and clinical outcome data including gender, maturity at birth, birth weight, severity of illness, indication for operation, operation performed, residual bowel length, duration of parenteral nutrition used, duration of mucous fistula refeeding, presence of cholestasis (bilirubin level > 20 μmol/L persistently), postoperative complications, duration of neonatal intensive care unit (NICU) and hospital stay were collected.

Since 2000, distal loop refeeding has gradually become a routine in neonates with mucous fistula. These patients received parenteral nutrition soon after operation. Enteral feeding was started once condition was stabilized. A distal loopogram using water soluble contrast was

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performed to confirm distal bowel patency. Mucous fistula refeeding was commenced if no stricture was identified. An Fr8 infant feeding tube was inserted to the mucous fistula and secured to skin using adhesive tape. Proximal enterostomy effluent was collected every 4 h and subsequently infused in a continuous manner to the mucous fistula using a syringe pump. The infusion rate was gradually stepped up until it matched the total proximal stoma output. When patients reached reasonable body size with good bowel opening per rectum, closure of enterostomy was arranged. Bilirubin levels were regularly monitored.

Data of the two groups of patients were statistically compared and analyzed using SPSS (version 17; SPSS, Chicago, IL). Continuous variables were studied using Student's t test, while ordinal variables used Mann–Whitney U test and categorical variables used Chi-square test respectively. Data were presented as mean ± standard error of mean and range. $p < 0.05$ was considered statistically significant.

2. Results

A total of 92 patients were identified during the study period. 54 of them were males and 38 were females. The mean gestational age was 30.7 ± 0.45 weeks and mean birth weight was 1.57 ± 0.08 kg. 77 patients received mucous fistula refeeding. The other 15 patients did not receive mucous fistula refeeding owing to parent's preference. All patients had distal loop patency confirmed with loopogram before stoma closure.

Statistical analysis between the refeeding group (n = 77) and nonrefeeding group (n = 15) was performed. The demographic characteristics including sex distribution, gestational age and birth weight were similar (Table 1). 45% (n = 35) and 33% (n = 5) of patients had pneumoperitoneum before the operation in the refeeding and nonrefeeding group respectively ($p > 0.05$). More patients (60%, n = 45) in the refeeding group were noted to have bowel perforation during the operation, but it was not statistically different from the nonrefeeding group. The percentages of ileocecal valve and small bowel length preserved were similar in the 2 groups (Table 2).

For the refeeding group, the mean time between surgery and the start of refeeding was 28.7 ± 8.7 days (range 15–140 days). The mean duration of refeeding before closure of stoma was 76.5 ± 5.5 days (range 13–236 days). When compared to the nonrefeeding group, the refeeding group had significantly lower incidence of size discrepancy between the bowel ends at closure, which is defined as >50% difference in bowel diameter (25 vs 53%, $p = 0.034$). Higher proportion of patients in the nonrefeeding group developed postclosure anastomotic leakage (3 vs 20%, $p = 0.029$). However, the anastomotic stricture rate was not different between the 2 groups (4 vs 7%, $p = 0.52$). 42% of patients with refeeding developed parental nutrition related cholestasis compared to 73% in the nonrefeeding group ($p = 0.045$). In addition, the mean peak bilirubin level was much higher in the nonrefeeding group (155.37 vs 275.42 μmol/L, $p < 0.001$). The refeeding group was able to wean from parental nutritional support in a significantly shorter time (47.7 vs 135.8 days, $p = 0.002$). The average NICU and hospital stay was 75 and 83 days shorter in the refeeding group, but the difference was not statistically significant ($p = 0.16$ and 0.33 respectively) (Table 3).

Table 1
Patient demographics.

	Refeeding group	Nonrefeeding group	p
Numbers	77	15	
Sex: male (no.)	44 (57%)	10 (67%)	NS
Mean gestational age (weeks)	30.79 ± 0.51 (23–41)	30.53 ± 1.10 (24–38)	NS
Mean birth weight (kg)	1.58 ± 0.09 (0.57–3.78)	1.53 ± 0.79 (0.71–2.95)	NS
Birth weight by category (no.)			
Normal (>2.5 kg)	11	2	
Low (1.5–2.5 kg)	26	5	
Very low (1.0–1.5 kg)	19	4	
Extremely low (<1.0 kg)	21	4	

NS indicates not significant.

Table 2
Clinical characteristics.

	Refeeding group	Nonrefeeding group	p
Pneumoperitoneum (no.)	35 (45%)	5 (33%)	NS
Perforation (no.)	46 (60%)	5 (33%)	NS
Ileocecal valve preserved (no.)	53 (69%)	12 (80%)	NS
Mean small bowel length preserved (cm)	67.79 ± 4.23 (10–185)	78.67 ± 10.14 (7–120)	NS

NS indicates not significant.

No major complication was noted with all the refeeding process. The minor clinical problems encountered were occasional back flow of refeeding contents and slip out of refeeding tubes in some patients. These problems were solved by refeeding the refluxed content and reinsertion of refeeding tubes respectively. All patients in both groups survived until discharge from hospital.

3. Discussion

Necrotizing enterocolitis remains a challenging neonatal condition for pediatric surgeons to manage. Short bowel syndrome is one of the most dreadful long-term complications in this aforementioned condition when bowel resection is necessary. In patients with short bowel syndrome, their intestinal absorptive function is not sufficient to maintain the need for growth and development, therefore most of them would require prolonged use of parenteral nutrition. This in turn may lead to other complications including metabolic disturbance, line sepsis and parenteral nutrition associated liver disease [9]. Even in the majority of patients who do not suffer from short bowel syndrome, most of them nevertheless require the support of parenteral nutrition to tie over the postoperative ileus, and they are still at risk of cholestatic liver disease since premature babies are particularly vulnerable. Among different strategies to improve bowel function and reduce parenteral nutrition associated liver disease, mucous fistula refeeding has gained increasing attention as a potential adjunct [10,11].

The concept of mucous fistula refeeding was first introduced by Levy et al. in 1983 [12]. This study demonstrated the inhibitory effect of refeeding on proximal stoma output, as well as the ability to recruit residual bowel absorptive capacity for better fluid and electrolyte balance in adult patients. Puppala et al. took a step further and reported his initial experience of refeeding in neonates with short bowel syndromes [8]. The rationale behind mucous fistula refeeding in neonates took advantage of their strong intestinal adaptation. With refeeding, the previously nonfunctional distal loop is put into use so the total absorptive intestinal surface for fluid and electrolyte is much increased. Strong intestinal growth stimulants including intestinal peptides and nutrient substances, which are present in high concentration in the proximal enterostomy effluent, induce substantial bowel lengthening and hypertrophy. Growth of intestinal mucosa is stimulated with cellular hyperplasia and increase in height of villi. Disuse atrophy of distal loop can thus be prevented. Functionally the bowel peristalsis is improved with increase in overall absorptive power [11].

Although most authors focused on the effect of refeeding in patients with short bowel syndrome, its beneficial effects in patients with normal bowel length should not be underestimated [3,5–8]. Similar to other studies, owing to the increase in anatomical and functional capacity of the bowel, patients in our study were able to achieve enteral independence earlier with reduced parenteral nutrition requirement when compared to those without refeeding. As a result they can be weaned off from parenteral nutrition in a shorter period of time with less incidence of cholestasis and lower serum bilirubin level. The involvement of the mucous fistula also helps to eliminate cholestasis by improving enterohepatic recirculation. Although metabolic complications such as

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Table 3
Postoperative outcomes.

	Refeeding group	Nonrefeeding group	*p*
Bowel ends size discrepancy (no.)	19 (25%)	8 (53%)	0.034
Anastomotic leak (no.)	2 (3%)	3 (20%)	0.029
Anastomotic stricture (no.)	3 (4%)	1 (7%)	NS
Cholestasis (no.)	32 (42%)	11 (73%)	0.045
Mean peak bilirubin level (μmol/L)	155.37 ± 9.36 (8–364)	275.42 ± 60.30 (60–916)	<0.001
Mean duration of parenteral nutrition (days)	47.68 ± 5.84 (7–236)	135.80 ± 58.40 (4–360)	0.002
Mean duration of NICU stay (days)	125.70 ± 20.18 (10–268)	200.20 ± 63.28 (11–393)	NS
Mean hospitalization period (days)	179.30 ± 33.09 (22–748)	262.90 ± 95.00 (11–423)	NS

NS indicates not significant.

cholestasis and parenteral nutrition associated liver disease are becoming less common with improved formula, surgical complication is another area that requires special attention. In our refeeding group of patients, less size discrepancy between the proximal and distal bowel ends was observed during stoma closure. This was because of the increase in the distal intestinal caliber as a consequence of the trophic effect exerted by mucous fistula refeeding. The better matched bowel ends and easier anastomosis could explain the lower incidence of anastomotic complications such as leakage or stricture. All these factors ultimately translated into shorter NICU stay and hospitalization with significant reduction in overall healthcare cost.

Haddock et al. have recently reported their experience of mucous fistula refeeding associated major complications in 17% of patients [3]. 3 patients had bowel perforations, one had severe bleeding which required blood transfusion and one mortality was directly associated with refeeding. This was in contrast to our study where no major complication or mortality was observed. One possible explanation may be because all refeeding tubes at our center were inserted solely by surgeons who have good understanding of the patients' anatomy after surgery but not by other medical personnel. In addition, the maximum size of catheters we used was only Fr8 infant feeding tube, comparing to as big as Fr12 gastrostomy tube as in Haddock's study. Moreover Haddock's patient cohort received refeeding rate up to 23 ml/h with a mean maximum rate of 10.5 ml/h, but in our patients the rate never exceeded 6 ml/h. We hypothesize that these measures help to maintain the mucous fistula with sufficient stimulation yet at the same time avoid overloading it. Interestingly we have seen an improving survival trend in our population of patients with necrotizing enterocolitis after starting the refeeding program. To the best of our knowledge, this is the only retrospective case-controlled study of mucous fistula refeeding in neonates with necrotizing enterocolitis. We acknowledge that our study may create potential bias owing to the small sample size in the nonrefeeding group. The limitation of a retrospective study was also obvious. In addition, the decision to start distal loop refeeding was not randomized. A randomized controlled prospective study with larger and more even sample size is warranted to confirm these retrospective findings.

Nonetheless, we can conclude that mucous fistula refeeding is safe, and can decrease the risk of anastomotic complication and parental nutrition related cholestasis. It provides both diagnostic and therapeutic value and its use should be advocated.

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