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ORIGINAL ARTICLE

Safety and efficacy of mucous fistula refeeding in low-birth-weight infants with enterostomies

Kiyoaki Yabe[1] · Katsunori Kouchi[1] · Ayako Takenouchi[1] · Aki Matsuoka[1] · Takahiro Korai[1] · Chikako Nakata[1]

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Abstract

Purpose To investigate the safety and efficacy of mucous fistula refeeding (MFR) in low-birth-weight infants.

Methods Between December 2006 and December 2018, medical records of low-birth-weight infants who underwent small bowel enterostomy formation in the neonatal period and subsequent stoma closure at our institution were retrospectively reviewed. Patients were assigned to "refeeding" (RF) and "non-refeeding" (NRF) groups, which were compared for patient characteristics and clinical outcomes. We also cultured the proximal stoma output over time in the RF group and reviewed changes in the flora to evaluate the safety of refeeding.

Results In the RF group, compared with that before refeeding, there was significantly more rapid weight gain after refeeding (17.7 vs 10.6 g/day; $P=0.002$). Median total time of parenteral nutrition (PN) was 25 and 87 days in the RF and NRF groups, respectively ($P=0.001$). The number of patients who developed PN-associated liver disease (PNALD) was smaller in the RF group ($P=0.12$). No complications of MFR were noted and no pathogenic bacteria were cultured.

Conclusion MFR was able to diminish the need for PN, which potentially decreased the incidence of PNALD, and was safe as there were no complications of the refeeding process.

Keywords Low birth weight · Neonates · Small bowel enterostomy · Stoma · Mucous fistula refeeding · Pn-associated liver disease

Introduction

Neonates can develop several acute abdominal pathologies, such as intestinal perforation, meconium ileus, and necrotizing enterocolitis, which require surgical intervention including enterostomy and mucous fistula (MF) formation [1, 2]. The presence of a proximal small bowel enterostomy typically results in poor growth and electrolyte imbalance caused by loss of enterostomy effluent, especially in low-birth-weight infants [3]. In such cases, parenteral nutrition (PN) is often needed to supplement patient growth. Since the time between stoma formation and stoma closure can be several months, PN may be required for a long period of time. However, prolonged use of PN can result in PN-associated liver disease (PNALD), which is defined as direct serum bilirubin > 2 mg/dL for a minimum of 2 weeks and for at least two consecutive measurements [4]. PNALD can lead to cholestasis, portal hypertension, progressive liver failure, and even death [4]. Premature infants are at increased risk of PNALD secondary to immature liver development and incomplete enzyme activity [5]. Along with the duration of PN, disruption of the enterohepatic circulation of bile acids plays a key role in the development of PNALD [6]. One method to reduce the dependency on PN is to enhance intestinal adaptation by means of MF refeeding (MFR). MFR involves the introduction of proximal enterostomy effluent into an MF, which theoretically can improve weight gain and reduce electrolyte imbalance and the need for PN [7]. The effects of MFR have been demonstrated in the previous studies [3, 7]; however, there is little evidence to support the safety and efficacy of this practice in low-birth-weight infants. The purpose of this retrospective cohort study was to evaluate the safety and efficacy of MFR in low-birth-weight infants.

✉ Kiyoaki Yabe
akiyb17@gmail.com

[1] Department of Pediatric Surgery, Tokyo Women's Medical University Yachiyo Medical Center, 477-96 Owadasinden, Yachiyo-shi, Chiba, Japan

Materials and methods

Study setting and population

This study was approved by the Ethics Committee of Tokyo Women's Medical University (approval number: 5219) and performed in accordance with the Declaration of Helsinki of 1964 (revised in 2013). Between December 2006 and December 2018, the medical records of low-birth-weight infants who underwent small bowel enterostomy formation with or without an MF in the neonatal period and subsequent stoma closure at a single institution were retrospectively reviewed. Since 2012, MFR has become a routine practice in neonates with an MF at our hospital. Patients who had an MF and underwent MFR were included in the "refeeding" (RF) group, while those without an MF or with an MF who did not undergo MFR owing to stricture in the MF or before MFR became a routine practice were included in the "non-refeeding" (NRF) group. Patients who started MFR, but discontinued before stoma closure for reasons other than complications associated with refeeding were excluded from this study.

Patient characteristics, operative data, postoperative diagnosis, laboratory values, timing of enteral feeding, timing of MFR, total time from start of enteral feeding to volume of enteral feeds > 150 mL/kg/day, age and body weight at stoma closure, histopathological findings, and complications associated with refeeding were collected. Primary outcomes included total time of PN from start of enteral feeding to stoma closure and incidence of PNALD. Secondary outcomes included average weight gain from start of enteral feeding to stoma closure and complications relating to refeeding. In addition, in three cases in the RF group, we cultured the proximal stoma output over time (immediately, 1 h, 2 h, and 3 h after the output pooled in the pouch) after starting MFR and reviewed changes in the flora to evaluate the safety of refeeding, whether bacteria overgrowth occurred, and whether pathogenic bacteria causing enteritis were cultured in the time course.

MFR

At our institution, we started enteral feeding as soon as the patient's condition allowed following enterostomy formation. MFR was started after sufficient proximal stoma output was obtained. NICU nurses collected the proximal stoma output pooled in the pouches of patients every 3 h and manually delivered the output into the distal MF through a 7-French catheter for 5–10 min (Fig. 1). Unlike in the previous reports [3, 7], the catheter was not placed constantly, but nurses inserted and subsequently removed the catheter for each infusion. The infusion volume was started at a small amount to ensure patency of the distal bowel, and a distal loopogram was performed to confirm patency, if necessary. Once patency was established and stool was obtained from the patient's anus, the infusion volume was gradually increased until it matched the total proximal stoma output. MFR continued until just before stoma closure.

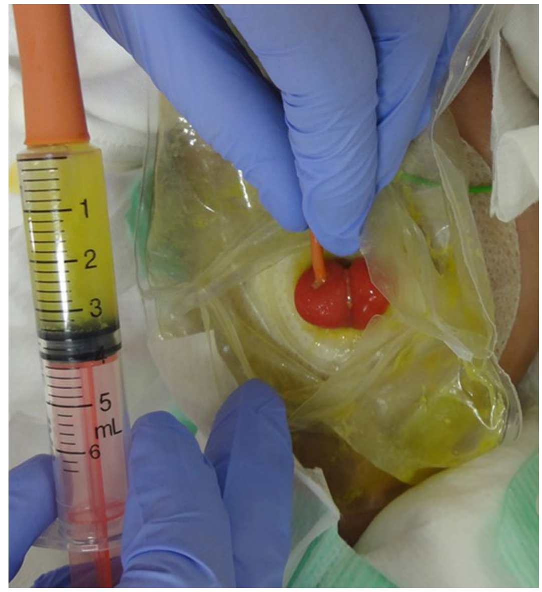


Fig. 1 Nurses manually deliver proximal stoma output into the distal mucous fistula through a 7-French catheter

PN

In this study, PN was initiated on postoperative day 0 and adjusted daily. After the patient's general condition was stabilized and peritonitis was improved, enteral nutrition (EN) was initiated as soon as possible. Breast milk, formula milk, and elemental diet (Elental P; EA Pharma, Tokyo, Japan) were used for EN. Oral probiotics were prescribed as necessary. PN was discontinued when a patient was tolerating approximately 120–150 mL/kg/day of enteral feeds to achieve weight gain without requiring supplementation of PN. PN was continued if the patient demonstrated feeding intolerance or failure to thrive despite receiving sufficient supplementation of EN.

Statistical analyses

Continuous variables are expressed as median (range). Differences between groups were examined using the Wilcoxon rank-sum test for non-parametric variables and the Fisher exact test for categorical variables. All P values (2 sided) < 0.05 were considered statistically significant.

Statistical analysis was performed using JMP Pro version 14.0.0 software (SAS Institute Inc).

Results

During the study period, ten neonates managed with MFR were identified (RF group). Three neonates underwent enterostomy formation without MF creation and three neonates had an MF created, but did not undergo MFR (NRF group). Tables 1 and 2 present the patient and postoperative characteristics, respectively. The median gestational age, birth weight, and age at stoma formation were not significantly different between the RF and NRF groups ($P > 0.05$). In the RF group, postoperative diagnoses included meconium ileus (6 cases), focal intestinal perforation (3 cases), and inner hernia (1 case). In the NRF group, postoperative diagnoses included a variety of pathologies. Four cases were included in the NRF group, because they occurred before MFR became a routine practice. After MFR became a routine practice, one case with an MF who did not undergo MFR owing to stricture in the MF, and one case without an MF were included in the NRF group. The number of patients who underwent jejunostomy was the same between the RF and NRF groups (Table 1), and the position of the jejunostomy from the Treitz ligament was 30 and 45 cm in the RF group and 25 and 40 cm in the NRF group. All other patients underwent ileostomy, and the small bowel length from the distal enterostomy to the terminal ileum was within 30 cm in all cases. The median C-reactive protein level at stoma formation was higher in the NRF group than in the RF group, but without significance ($P = 0.07$). The median postoperative day of starting enteral feeding was significantly delayed in the NRF group ($P = 0.002$). The type of postoperative enteral feeding and number of patients who received probiotics were not different between groups. The median time from start of enteral feeding to volume of enteral feeds > 150 mL/kg/day, age at stoma closure, and

Table 1 Patient characteristics

	Refeeding group	Non-refeeding group	*P* value
No. of patients	10	6	
Male, *n* (%)	6 (60)	4 (67)	
Gestational age, median (range), weeks	28 (23–33)	27 (23–37)	0.93
Birth weight, median (range), g	925 (502–1206)	976 (560–2366)	0.64
Age at stoma formation, median (range), day	5 (1–15)	9 (1–22)	0.19
Diagnosis, *n*			
Meconium ileus	6	1	
Focal intestinal perforation	3	1	
Inner hernia	1	1	
Intussusception	0	1	
Necrotizing enterocolitis	0	1	
Gastroschisis	0	1	
Jejunostomy, *n* (%)	2 (20)	2 (33)	

Table 2 Postoperative characteristics

	Refeeding group	Non-refeeding group	*P* value
C-reactive protein level at stoma formation, median (range), mg/dL	0.11 (0.02–11.9)	4.9 (1.9–12.4)	0.07
Postoperative day of starting enteral feeding, median (range)	3.5 (3–6)	9 (5–14)	0.002
Type of postoperative enteral feeding, *n*			
Breast milk	2	1	
Formula milk	0	0	
Breast milk and formula milk	2	1	
Elemental diet	5	3	
Breast milk and elemental diet	1	1	
Probiotics, *n* (%)	7 (70)	4 (67)	
Time to volume of enteral feeds > 150 mL/kg/day, median (range), days	14.5 (8–26)	20.5 (9–42)	0.25
Age at stoma closure, median (range), days	84 (68–216)	155 (76–254)	0.15
Body weight at stoma closure, median (range), g	2100 (1580–4842)	2645 (2246–3082)	0.12

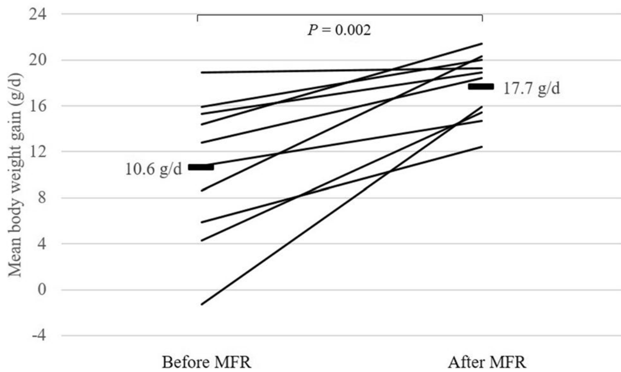


Fig. 2 Effect of mucous fistula refeeding (MFR) on mean weight gain of infants in the refeeding group

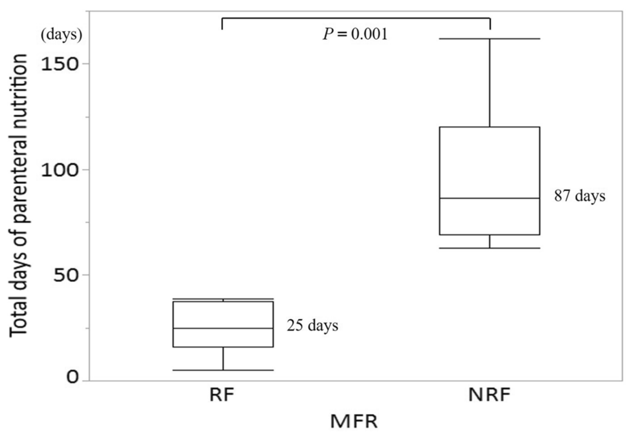


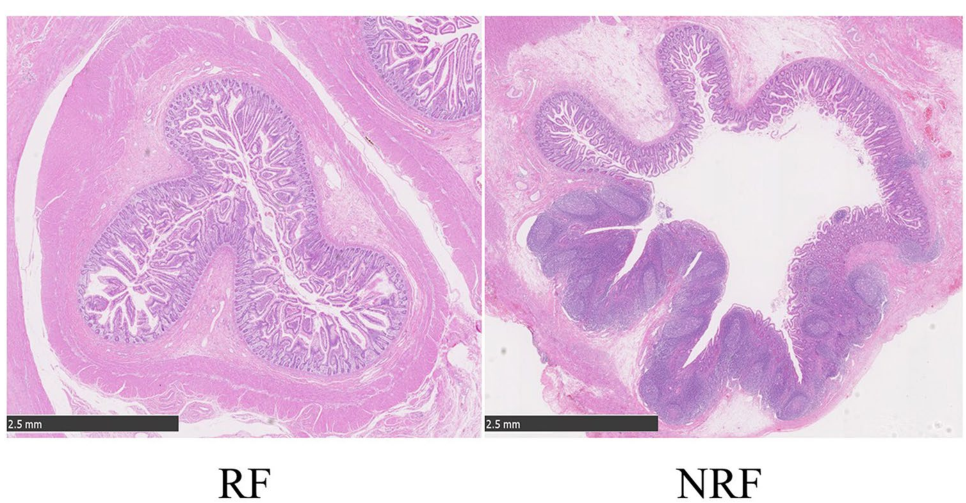
Fig. 3 Effect of mucous fistula refeeding (MFR) on total days of parenteral nutrition from start of enteral feeding to stoma closure. RF, refeeding; NRF, non-refeeding

body weight at stoma closure were not significantly different between the RF and NRF groups ($P > 0.05$) (Table 2). In the RF group, the mean body weight gain before and after MFR is depicted in Fig. 2. Compared with that before refeeding, there was significantly more rapid weight gain after refeeding (17.7 ± 2.9 vs 10.6 ± 6.2 g/day; $P = 0.002$). However, there was no significant difference in the mean body weight gain from start of enteral feeding to stoma closure between the two groups. The median total time of PN from start of enteral feeding to stoma closure was 25 days (range 5–88 days) in the RF group and 87 days (range 63–162 days) in the NRF group ($P = 0.001$) (Fig. 3). Thus, RF patients were able to have PN discontinued significantly earlier. Only one of ten patients developed PNALD in the RF group, whereas three of six patients developed PNALD in the NRF group ($P = 0.12$). The number of patients who developed PNALD was smaller in the RF group, but there was no significant difference between the two groups.

According to the histopathological findings, the RF group showed increased mucosal thickness and maintained villous structure of the distal ileum at stoma closure. On the other hand, the NRF group showed loss of villous structure and increased lymphoid follicle of the mucous membrane, which is associated with chronic inflammation and mucosal atrophy (Fig. 4).

No complications, such as perforation or bleeding, were noted with the refeeding process. One case in the NRF group died of chronic heart failure after stoma closure, but all the others survived until discharge from the hospital. In the RF group, we cultured the proximal stoma output over time in three cases. Each bacterial count sequentially changed and new bacterial flora, such as intestinal bacteria in case 1, methicillin-susceptible *Staphylococcus aureus* in case 2, and *Enterococcus faecalis* in case 3, were cultured (Fig. 5). No pathogenic bacteria, such as methicillin-resistant *S. aureus*

Fig. 4 Photomicrographs comparing mucosal membrane structure of the distal ileum at stoma closure. The refeeding (RF) group showed increased mucosal thickness and maintained villous structure. On the other hand, the non-refeeding (NRF) group showed loss of villous structure and increased lymphoid follicle of the mucous membrane (hematoxylin and eosin staining)



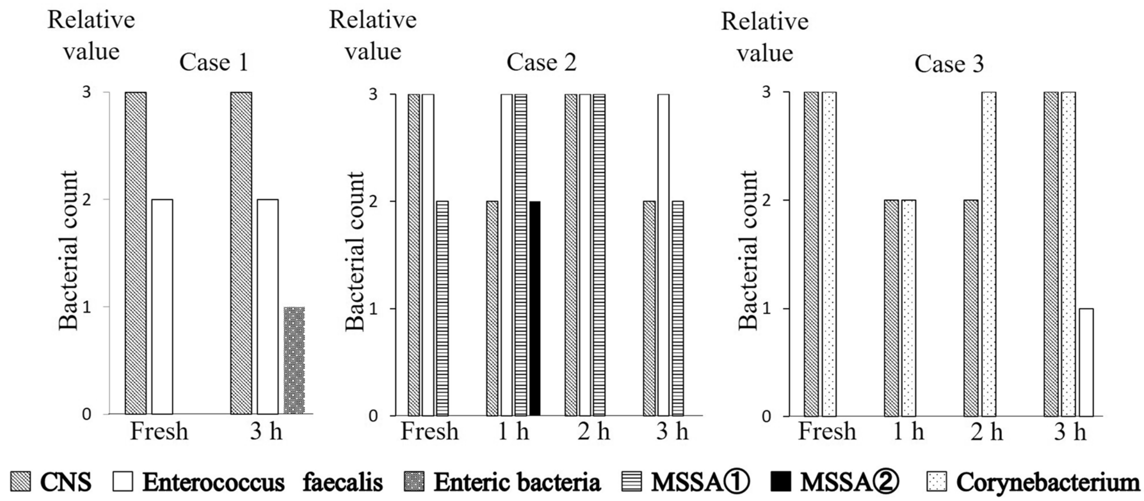


Fig. 5 Vertical line shows the relative value of bacterial count, while the horizontal line shows the time course after the proximal stoma output pooled in the pouch. Each bacterial count sequentially changed and new bacterial flora were cultured in all cases, but no pathogenic bacteria, such as methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa,* were cultured. CNS, coagulase-negative *Staphylococcus*; MSSA, methicillin-susceptible *Staphylococcus aureus*

or *Pseudomonas aeruginosa*, were cultured, and no enteritis occurred related to MFR.

Discussion

In the current study, we found that MFR was able to diminish the need for PN, which potentially decreased the incidence of PNALD. Moreover, we found that MFR was safe in that there were no complications of the refeeding process, and no pathogenic bacteria were cultured in the proximal stoma output.

The percentage of low-birth-weight infants with acute abdominal pathologies, such as intestinal perforation, meconium ileus, and necrotizing enterocolitis, has increased [8, 9]. In such infants, primary anastomosis can lead to complications due to the thin and vulnerable intestinal wall [9-11]; thus, they often necessitate partial resection of the small bowel combined with enterostomy formation. Because the presence of a proximal small bowel enterostomy can lead to dehydration, electrolyte imbalance, and poor growth [3, 12], the neonate is usually dependent on PN until intestinal adaptation occurs. In this study, the most common cause of enterostomy formation was meconium ileus in the RF group, whereas there were a wide variety of causes in the NRF group. There was no significant difference in the number of patients who underwent jejunostomy and the position of enterostomy between the two groups, and all cases required PN from the first day of enterostomy formation.

PN is associated with significant risk of central line-related sepsis, thrombosis, cholestasis, and hepatic failure [13]. In fact, up to 50% of premature infants and neonates with enterostomy develop cholestasis, particularly in combination with PN [12]. Surgical restoration of intestinal continuity may take several months; thus, the refeeding technique is used to promote intestinal adaptation [7]. The concept of MFR was initially reported by Levy et al. [14]. Since Puppala et al. reported his initial experience of MFR in neonates with short bowel syndrome [15], this method has been employed to theoretically improve weight gain and reduce electrolyte imbalance and avoid reliance on PN. Wong et al. reported that MFR increased absorptive function from the added length of intestine and promoted better weight gain [16], while Richardson et al. also reported MFR improved weight gain in infants with short bowel syndrome [17]. In accordance with these previous studies, we found that patients who underwent MFR achieved better weight gain after MFR than before MFR. However, between the RF and NRF groups, there was no significant difference in the mean body weight gain from start of enteral feeding to stoma closure. In the NRF group, to compensate for the loss of proximal output, the patient required more supplementation of EN, and then, further loss of proximal stoma output led to "a cat-and-mouse game." Feeding intolerance or failure to thrive required supplementation of PN, and patients in the NRF group achieved body weight gain by benefit of PN to a certain extent.

The advent of PN has dramatically improved the life expectancy of children with intestinal failure [18], but patients receiving long-term PN are at risk of cholestasis and PNALD. In this study, RF patients were able to start enteral feeding significantly earlier than NRF patients, which may be because peritonitis was milder in the RF group, as shown by the C-reactive protein levels at stoma formation.

However, there was no significant difference in the proceeding of EN from start of enteral feeding to volume of enteral feeds > 150 mL/kg/day between the two groups. RF patients were also able to have PN discontinued significantly earlier than NRF patients and had a lower incidence of PNALD. Owing to the increase in anatomical and functional capacity of the bowel, the RF group was able to achieve enteral independence earlier with reduced PN need than the NRF group, while refeeding in the distal bowel also stimulated enterohepatic circulation [7]. As a result, the RF group could be weaned off PN in a shorter period.

Although there was no significant difference between the RF and NRF groups, age and body weight at stoma closure in the RF group were lower than those in the NRF group. These data show that we tended to close the stoma earlier in the RF group. Although the timing of stoma closure varied depending on the primary diagnosis, MFR could confirm patency of the distal bowel and assure us that the patient's intestinal function had improved. Thus, MFR was useful to determine the timing of stoma closure earlier in the RF group.

According to the histopathological findings in this study, the RF group showed increased mucosal thickness and maintained villous structure of the distal ileum in comparison to the NRF group. Gause et al. reported that intestinal maturation is highly dependent on exposure to enteral nutrition and associated enterotrophic factors secreted by the proximal intestine [5]. Similarly, we also believe that the introduction of enteral feeds to the distal small bowel by MFR avoided disuse atrophy while promoting intestinal maturation, which led to improved nutrient absorption.

In our study, no complications of the refeeding process were observed. However, Haddock et al. recently reported that MFR was associated with major complications, such as perforation or bleeding, in 17% of patients [19]. They inserted several different sizes of MFR catheter into the MF and the catheter was placed constantly. Lau et al. noted that the maximum size of the catheters in Haddock's study was 12-French and hypothesized that using bigger-size catheters could cause complications [7]. In addition to the maximum size of the catheter, we suppose that an indwelling catheter could also cause complications due to increased physical contact with the MF. In our study, the maximum size of the catheters was only 7-French, and NICU nurses manually inserted the refeeding tube into the MF for each infusion by feeling for any resistance of injection. Manually feeling for resistance may help to avoid complications of MFR.

Pataki et al. reported that recycling of stoma content after 1.5 h in the bag might be dangerous, because the number of colony-forming units of bacteria approached 10^5/mL, which was defined as bacteria overgrowth in the proximal small bowel [13]. In our study, each bacterial count sequentially changed and new bacterial flora were cultured, but no pathogenic bacteria were cultured in the proximal stoma output after 3 h in the pouch. The fact that no enteritis was caused by MFR in our study indicates that proximal stoma output refeeding every 3 h might be a safe time for refeeding.

The current study has some limitations. First, it was a retrospective, single-center study. Therefore, the possibility of unintentional selection bias in the selection of patients could not be fully excluded. Second, the sample size was small, also creating potential bias. In addition, the primary diagnoses in the NRF group were miscellaneous and different from those in the RF group. Since 2012, MFR has become a routine practice at our hospital, but patients without an MF or with an MF who did not undergo MFR owing to problems in the MF were included in the NRF group. Consequently, the pathological conditions in the NRF group might be different from those in the RF group. Therefore, our results need to be confirmed by a prospective study with a larger sample size.

In conclusion, we found that MFR was able to diminish the need for PN, which potentially decreased the incidence of PNALD, and was able to obtain better weight gain without supplementation of PN. In addition, MFR was safe, without complications related to the procedure, and there were no pathogenic bacteria in the proximal stoma output. Thus, the use of MFR should be recommended, although future prospective studies are needed to confirm our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki of 1964 (revised in 2013). This retrospective study was approved by the Ethics Committee of Tokyo Women's Medical University.

Informed consent For this type of study, informed consent was not required.

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