

A prospective study of Daikenchuto on superior mesenteric artery and portal venous blood flows in extremely low birthweight infants

Shunsuke Watanabe (✉ watanabe@fujita-hu.ac.jp)

Fujita Health University Hospital

Mikihiro Inoue

Fujita Health University Hospital

Masafumi Miyata

Fujita Health University Hospital

Hiroko Boda

Fujita Health University Hospital

Research Article

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Abstract

Background: Focal intestinal perforation (FIP) is a devastating complication of prematurity, and extremely low birthweight (ELBW) infants are at highest risk. The aim of this study was to evaluate the relationship between superior mesenteric artery (SMA) and portal venous (PV) blood flow velocities to investigate the association between FIP and intestinal blood flow. In addition, Daikenchuto (TJ-100) is expected to have the effect of improving intestinal blood flow disorders, so we evaluated the effect.

Methods: We conducted a prospective cohort study of 15 ELBW infants from January 2020 to August 2021.

15 infants were divided the non-surgery group (Group I; 6), the surgery group with FIP (Group II; 4), and the TJ-100 administration group (Group III; 5). Main outcome parameters included SMA blood flow velocity and PV blood flow velocity.

Results: A statistically significant difference was observed between the Group I and Group III on gestational age ($p = 0.03$). On the longitudinal evaluation of SMA and PV blood flow, statistically significant differences were found in SMA of Group I, and SMA and PV of Group III ($p < 0.01$, $p = 0.01$ and $p = 0.04$, respectively). And there was a correlation between SMA and PV in Group III ($p = 0.03$).

Conclusion: TJ-100 may increase SMA and PV blood flow, and improve intestinal blood flow in ELBW infants at the risk of FIP. Therefore, we will continue to study the effect of TJ-100.

Introduction

Complications due to the immaturity of various organs in Extremely low birthweight (ELBW < 1000 g) infants remain a major healthcare problem. Gastrointestinal dysfunction in ELBW infants is one of the most serious complications, and it is an important factor that determines the prognosis of life as it may cause intestinal perforation such as focal intestinal perforation (FIP) or Necrotizing enterocolitis (NEC). Infants with FIP have high frequency of long-term complications, high economic burden. Also, FIP present with isolated intestinal perforation, and is thought to be secondary to immaturity of the intestinal wall and ischemia [1]. There is evidence of hemorrhagic necrosis primary in the terminal ileum [2]. On the contrary, NEC has presence of a thickened abdominal wall, pneumatosis intestinal, and characterized resulting in intraluminal air by severe inflammation and bacterial translocation. The risk of FIP has early steroid use, birth trauma, indomethacin, multiple gestation, chorioamnionitis and syncytial knots [1]. Therefore, we focused on the relationship between superior mesenteric artery (SMA) blood flow and portal venous (PV) blood flow as gastrointestinal dysfunction in order to predict FIP [3, 4]. In recent, Tsumura Daikenchuto (TJ-100) is administered as treatment for intestinal blood flow disorders [5]. We investigated the effect of TJ-100 on intestinal blood flow to improve intestinal blood flow, which causes FIP in ELBW infants.

Methods

Study design

This study is a prospective cohort study of ELBW infants conducted from January 2020 to August 2021. The measurement time for each observation was 7 days after birth. Approval was obtained from the Ethics Committee of the Fujita Health University Hospital (HM19-477). The procedures used in this study adhered to the tenets of the Declaration of Helsinki.

Participants

The inclusion criteria were admission to neonatal intensive care unit (NICU) with a birth weight less than 1,000 g and use of only donor milk for enteral feeding [6]. During the study period, the donor milk dose was 0.5 ml at the start and 3 ml at the upper limit. The exclusion criterion was serious complications such as unstable circulatory status, complex cardiac malformations, and severe neonatal asphyxia. At the time of inclusion, we recorded the main clinical characteristics of the infants; appropriate for gestational age (AGA), small for gestational age (SGA), birth weight, gestational age, Apgar score at five minutes, time of initiation of oral feeding, SMA blood flow velocity, PV blood flow velocity, diastolic blood pressure, systolic blood pressure, patent ductus arteriosus (PDA) closure number, and the onset data of FIP. The diagnostic criteria for FIP were surgical or pathological findings, and the procedures were ileostomy or drainage.

Sixteen ELBW infants were admitted to the NICU. Of the 16 infants, 15 (male-to-female ratio [M:F] = 6:9) met the eligibility criteria, and one infant was excluded due to complex cardiac malformations. All infants were on pressure-raising drugs (dopamine and dopamine), and steroids were administered to them to prevent chronic lung injury. Indomethacin was administered at low dose to prevent cerebral hemorrhage, regardless of the status of the ductus arteriosus (i.e., open or closed). Of the 15 included ELBW infants, six patients (M:F = 1:5) had the non-surgery group (Group I). Four patients (M:F = 3:1) who developed FIP and underwent surgery had the surgery group (Group II). Five patients (M:F = 2:3) had been administered TJ-100 (Group III), and there were no surgical cases in Group 3. No infections were seen during the observation period.

Doppler Flowmetry

The ultrasonic pulse Doppler method was used in this study. Ultrasonic waves were generated using the PHILIPS iE33 imaging system, and the linear S12 ultrasound probe was used. The examination was performed by a neonatologist. The infants were placed in supine position, and measurements were taken at about the same time. If an infant was on enteral feeding, examination was performed before light enteral feeding. Warm gel was used to reduce movement, minimize discomfort, and maintain respiration rate and heart rate, thereby avoiding blood circulation changes. To measure SMA blood flow velocity, the

Doppler window was positioned such that the SMA is centered, and peak systolic velocity, which was measured at least three times, was used to determine absolute indexes. To measure PV blood flow velocity, the hilar region and the portal trunk were identified.

Treatment

TJ-100 was randomly administered. A dose of 0.2 g/kg of TJ-100 was administered through the anus using a tube twice a day. The administration of TJ-100 was started within 12 hours after the start of oral administration.

Outcomes

Longitudinal evaluation of SMA blood flow and PV blood flow, which were measured using the ultrasound pulsed Doppler method, was performed to investigate their relationship with surgery. The relationship between SMA blood flow and PV blood flow following TJ-100 administration was also evaluated.

Statistical analysis

Steel-Dwass test was used to multiple compare continuous variables between groups. All measurement values were presented as average \pm standard deviation. Regression analysis was also performed to compare variables. The Mahalanobis squared distance was used to detect outliers. P values ≤ 0.05 were considered statistically significant. Statistical tests were carried out using JMP12.2 (SAS Institute Inc, Cary, NC, USA).

Results

Table 1 shows the characteristics (AGA number, SGA number, birth weight, gestational age, Apgar score at five minutes, time of initiation of oral feeding, and PDA close number, the onset data of FIP). There was one case each in Group I and II without PDA closure during the observation period. In Group II, three patients had undergone ileostomy, one drainage. All perforations were near the terminal ileum. By Steel-Dwass test, a statistically significant difference was observed between the Group I and III on gestational age ($p = 0.03$) (Table 1b). No statistically significant differences in systolic and diastolic blood pressures were observed between the surgery and non-surgery groups (Fig. 1a).

Table 1
a. Characteristics of the Group I, Group II, and Group III.

	Group I	Group II	Group III
	(M: F = 1:5)	(M: F = 3:1)	(M: F = 2:3)
AGA: SGA	6:0	4:0	1:4
Birth weight (g)	710.3 ± 16.6	678.3 ± 13.4	807.7 ± 18.1
Gestational age (day)	173.8 ± 0.8	171.3 ± 0.9	212.7 ± 2.6
Apgar score at five minutes	6.2 ± 0.4	7.3 ± 0.2	9.0 ± 0.3
Time of initiation of oral feeding (day)	1.0 ± 0.1	1.3 ± 0.2	1.0 ± 0.2
PDA closure number	5	3	5
The onset data of FIP	N/A	8.8 ± 1.0	N/A

Table 1b. The Steel–Dwass test between the Group I, Group II, and Group III.

	Comparison	Difference in mean value	t value	p value
Birth weight	Group I- Group II	-1.04	-0.53	0.86
	Group I- Group III	2.38	1.19	0.46
	Group II- Group III	3.83	2.08	0.09
Gestational age	Group I- Group II	-0.63	-0.33	0.94
	Group 1- Group III	4.95	2.49	0.03
	Group II- Group III	4.28	2.34	0.05
Apgar score at five minutes	Group I- Group II	0.83	0.45	0.90
	Group I- Group III	3.48	1.78	0.18
	Group II- Group III	2.48	1.41	0.33
Time of initiation of oral feeding	Group I- Group II	0	0	1.0
	Group I- Group III	-1.65	-0.88	0.65
	Group II- Group III	-1.35	-0.78	0.71

Group I: the non-surgery group, Group II: the surgery group, Group III: the Tsumura Daikenchuto (TJ-100) administration group, AGA: Appropriate for gestational age, SGA: Small for gestational age, FIP: Focal intestinal perforation, M: Male, F: Female, PDA: Patent ductus arteriosus

Regression analysis was used for longitudinal evaluation of SMA and PV blood flow. In Group I, SMA blood flow was not statistically significant (coefficient of determination [R²] = 0.12, p = 0.40), while PV blood flow was statistically significant (R² = 0.82, p < 0.01). In Group II, SMA and PV blood flows were not statistically significant (R² = 0.19, p = 0.90; R² = 0.10, p = 0.23). Outlier detection based on Mahalanobis squared distance was used to study the PV blood flow of Group I and Group II. Outliers for Group II were 6 and 7 days after birth. In Group III, SMA and PV blood flows were statistically significant (R² = 0.68, p = 0.01; R² = 0.46, p = 0.04).

Furthermore, regression analysis was performed to determine the relationship between SMA and PV blood flows (Fig. 1b). In Group I and Group II, no statistically significant differences were observed (p = 0.46 and p = 0.74, respectively). In Group III, statistically significant difference was observed (R² = 0.52, p = 0.03).

Discussion

In addition to immature gastrointestinal motility and poorly functioning gastrointestinal enzymes, ELBW infants have inadequate nutritional reserves at birth and are deficient in various nutrients [7–9].

In utero, the fetus digests amniotic fluid, which promotes gastrointestinal growth [10]. Postnatal fasting results in decreased villus number, gastrointestinal enzyme activity, and barrier function [11]. Early onset of enteral nutrition has been reported because prolonged fasting after birth has a negative effect including FIP [1]. In this study, the mortality rate of FIP patients was 20.6% in Japan [12], but none of the patients with FIP (0.26%) died. Recent advances in neonatal care may have improved survival rates for ELBW infants. Nevertheless, FIP was considered to be due to the fragility of the intestinal wall and blood flow problems in ELBW infants. Ischemia associated with gastrointestinal dysfunction causes gastrointestinal perforation by decreasing PV blood flow [3], and SMA blood flow is involved in intestinal motility [4]. SMA and PV blood flow velocities were measured to evaluate intestinal blood flow. The results in Group I were considered as follows. The PDA closure numbers during the observation period was 5 of 6. PDA patency steals SMA blood flow and SMA blood flow may have decreased. PV consists of gastrointestinal blood flow including the ileocecal region. The absorption of nutrients around the ileocecal region increases blood flow, and PV blood flow may have increased over time. In Group II, PV blood flow may be involved in the case of FIP. Since the perforations were near the terminal ileum, it is possible that an ischemic region was formed in the ileocecal region and secondary peristaltic disorders caused FIP at the timing to increased intestinal pressure. The timing to increased intestinal pressure may be more likely to occur after the 5th day of life. The cause of the increased intestinal pressure may be related to immature intestinal function and nutrient absorption in the ileocecal region, but this study did not reveal it. PV blood flow velocity may be useful for the prediction of FIP in ELBW infants.

TJ-100 is a Japanese traditional herbal medicine consisting of four crude drugs: ginseng, sansho, kankyo, and koui [13]. It was reported that TJ-100 may increase microvascular dilation and blood flow in the intestine by the gastrointestinal transient receptor potential (TRP) channels [5]. In fact, TJ-100 was reported to increase SMA and PV blood flows in adults [14–16]. We for the first time found that the correlation between SMA and PV blood flow may be due to the effects of TJ-100 in Group III. And SGA may generally have more problems with intestinal blood flow than AGA on ELBW [17, 18], but no FIP was found in Group III containing a large amount of SGA. SGA infants have a higher PDA patency rate than AGA [19]. TJ-100 increases SMA blood flow, and may have prevented blood stealing due to PDA patency. Therefore, we posit that TJ-100 may modulate SMA and PV blood flows by acting on intestinal microvessels and that modulation of SMA and PV blood flows may prevent FIP in ELBW infants by improving intestinal blood flow disorders.

Limitations

There are some limitations in this study. First, the surgery group included only ELBW infants with FIP. Second, there may be a random but selection bias associated with TJ-100 administration.

Conclusions

In this study, we found that PV blood flow velocity may be used to screen for FIP in ELBW infants. We believe that TJ-100 increase SMA and PV blood flow, and improve intestinal blood flow disorders in ELBW infants at the risk of FIP. Therefore, we will continue to study the effect of TJ-100.

Declarations

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript

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Data, Material and/or Code availability

All data generated or analysed during this study are included in this published article.

Ethics approval/ Informed Consent

Approval was obtained from the Ethics Committee of the Fujita Health University Hospital. The procedures used in this study adhered to the tenets of the Declaration of Helsinki.

Authors' contribution statements. CRediT taxonomy:

Conceptualization: Shunsuke Watanabe, Mikihiro Inoue

Methodology: Shunsuke Watanabe

Formal analysis and investigation: Shunsuke Watanabe, Masafumi Miyata, Hiroko Boda

Writing - original draft preparation: Shunsuke Watanabe

Writing - review and editing: Mikihiro Inoue

Funding acquisition: no

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Declaration of interest none

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Figures

Fig 1a.

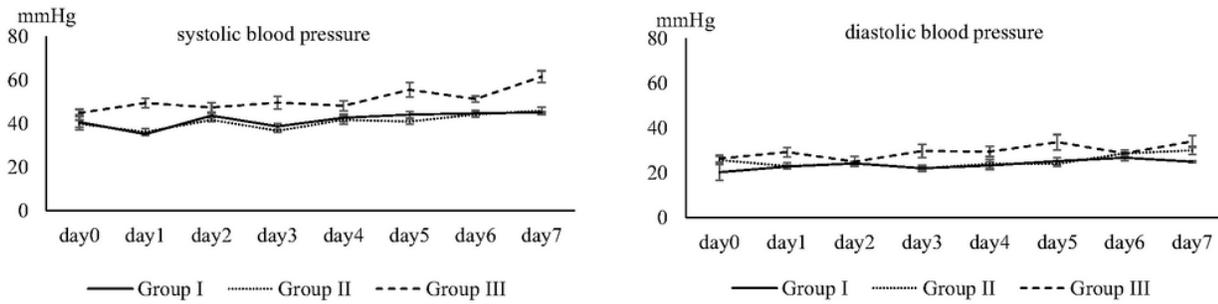


Fig 1b.

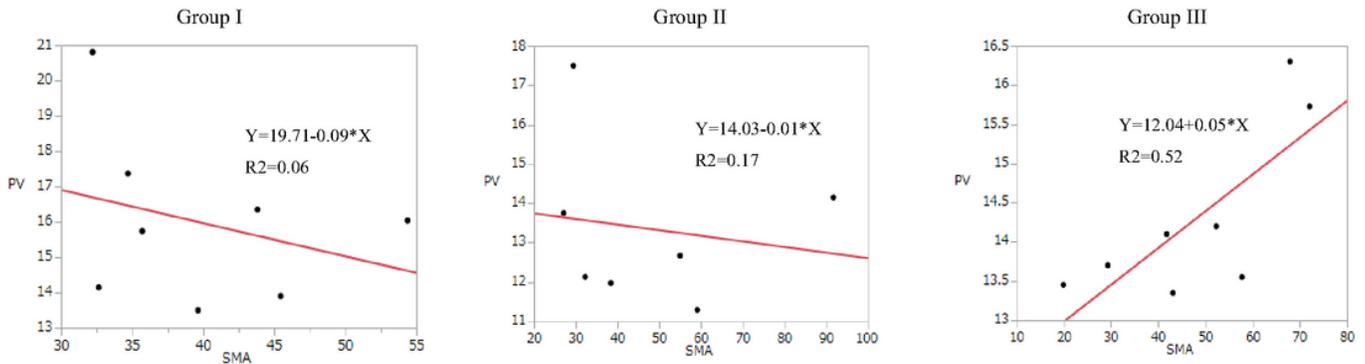


Figure 1

a. Changes of systolic blood pressure and diastolic blood pressure.

No statistically significant differences in systolic and diastolic blood pressures were observed between the Group I, Group II, and Group III. P values ≤ 0.05 were considered statistically significant.

b. The relationship between SMA and PV blood flows on regression analysis.

A scatter plot and the corresponding regression line and regression equation for the relationship between the dependent variable PV (cm/s) and the independent variable SMA (cm/s). R2 = coefficient of determination.

Group I: the non-surgery group, Group II: the surgery group, Group III: the Tsumura Daikenchuto (TJ-100) administration group, AGA: appropriate for gestational age, F: Female, M: Men, PV: portal venous,

SGA: small for gestational age, SMA: superior mesenteric artery.