Clinical Characteristics and Outcome of Very Low Birth Weight Infants with Surgical Meconium Related Ileus

Objective: Meconium related ileus (MRI) was defined as functional ileus in neonates characterized by impaired meconium excretion with preferential occurrence in very low birth weight (VLBW) infants. The aim of this study was to investigate the clinical characteristics and outcome of VLBW infants who underwent surgical treatment, especially exploratory laparotomy and ileostomy, due to MRI.

Methods: This retrospective study included VLBW infants born in our hospital between January 2010 and December 2018. Infants were included if they were diagnosed with MRI and underwent exploratory laparotomy. In order to compare the clinical characteristics, matched controls for each subject were chosen.

Results: Among the 178 VLBW infants delivered during the study period, total 19 cases and 19 controls were identified. The mean GA and birth weight in the MRI group were 27.6±1.9 weeks and 966±233 g, respectively, and 28.7±2.2 weeks and 1,005±198 g, respectively, in the control group. There was no significant difference between the both groups in perinatal, maternal and neonatal characteristics such as respiratory distress syndrome (RDS). Day of full enteral feeding and hospitalization were significantly longer in MRI group compared to control group. The proportion of less than 3 percentile for postmenstrual age at discharge were significantly higher in MRI group (73% vs. 21%, \(P=0.001\)).

Conclusion: The results of our study showed that delayed treatment of MRI lead to longer hospital stay and lower weight at discharge. Early treatment including exploratory laparotomy should be considered to improve outcome when the baby was suspected MRI with risk factors.

Key Words: Ileostomy, Meconium related ileus, Very low birth weight infant

Introduction

The concept of each type of meconium obstruction is still not definitive, although several types of meconium obstruction have been described.\(^1\) The term of meconium ileus is a disease of bowel obstruction due to inspissated meconium in cystic fibrosis patients.\(^1\) The other terms of meconium plug syndrome (MPS) or meconium disease (MD) refer to meconium obstruction in patients without cystic fibrosis. Especially, MD is frequently associated to severe prematurity and low birth weight and results from combination of highly viscous meconium and poor intestinal motility.\(^2,3\) Since Kubota et al.\(^4\) first used the them meconium related ileus (MRD) in 1999, the term MRI has described both MPS and MD because there is no rationale to differentiate MPS and MD.

MRI was defined as functional ileus in neonates characterized by impaired meconium excretion with preferential occurrence in premature infants.\(^5\) The etiology is thought to be a combination of the highly viscous meconium of prematurity and the poor motility of the premature gut.\(^5\) Despite recent advancements in neonatal care, the incidence of MRI could also increase and the management of MRI is often challenging.\(^4,6\)
Perinatology

The aim of this study was to investigate the clinical characteristics of very low birth weight (VLBW) infants who underwent surgical treatment, especially exploratory laparotomy and ileostomy, due to MRI, which did not respond to conservative treatment.

Methods

1. Patients

A retrospective study was conducted on VLBW infants born between January 2010 and December 2018 in Pusan National University Hospital. In this study, MRI was defined if the preterm infants showed 1) micro or small sized colon extending to the distal ileum on contrast enema with or without filling defects, 2) a distended abdomen, bilious or nonbilious vomiting and/or gastric residual volume of more than 50% of the previous feeding volume clinically and 3) fixed distended bowel loops without air fluid level or pneumatosis interstitialis.

In our neonatal intensive care unit, trophic feeding was started within 48 hours after birth, if the vital signs were stabilized in VLBW infants. A glycerin (2 mL/kg) enemas was given once or twice daily as a routine procedure for 1 week after birth. If the patient showed presumed MRI symptoms, four-fold diluted gastrografin enema (5 mL/kg) was given once or twice daily until the symptoms began to resolve. After 2 weeks of life, gastrografin enema of 10 mL/kg was given once or twice daily. Exploratory laparotomy was considered if the symptoms were not improved and failed with conservative treatment.

Infants were included if they were presumed MRI and needed finally surgical treatment including exploratory laparotomy. Infants were excluded if they had any of the following: 1) infants who had major congenital anomalies and/or chromosomal abnormality, 2) infants whose final diagnosis were not MRI postoperatively and 3) infants died during hospitalization. For the purpose of this study, this patient was named as surgical MRI group. In order to compare the clinical characteristics, infants of surgical MRI group were strictly matched to 1 to 1 control infants based on same sex, gestational age (GA) (±3 days) and birth weight (BW) (±50 g) among the infants without undergoing any other abdominal surgery.

2. Data collection

The data including clinical characteristics and morbidities were reviewed retrospectively. The perinatal data were collected from the medical chart of infants and included the following parameters: GA, BW, intrauterine growth retardation (defined as a weight below the 10th percentile for the gestational age), gender, 1 minute and 5 minutes Apgar, and mode of delivery.

The maternal data were collected from the medical chart of mothers and included the following parameters: premature rupture of membranes (PROM, defined as duration >18 hours after membrane rupture), preeclampsia, oligohydramnios, antenatal fever, antenatal steroid medication, antenatal magnesium medication, gestational diabetes mellitus.

The neonatal characteristics were reviewed including respiratory distress syndrome (RDS); patent ductus arteriosus (PDA, defined as the need for ibuprofen medication or surgical ligation); chronic lung disease (CLD, defined as moderate and severe bronchopulmonary dysplasia by Jobe and Bancalari); postnatal steroid medication; intraventricular hemorrhage (defined as grade 3 and above by Papile criteria); retinopathy of prematurity (ROP, defined as stage 2 and above). Immediate postoperative clinical course was assessed by postoperative diagnosis, ileostomy site, clinical outcome and complication.

3. Standard protocol approval

Ethical approval for this study was granted by the institutional review board of Pusan National University Hospital (2006-006-091).

4. Statistical analysis

Data were stored in a dedicated access database and verified for accuracy. Statistical analyses were performed with SPSS 22.0 (IBM Corp., Chicago, IL, USA) software using raw scores. Analyses presented here focus on the comparisons between the two groups (surgical MRI group and control groups). Statistical comparison of the continuous and categorical variables was tested by means of t-test and chi-square test as appropriate for the data. In addition to univariate non-parametric statistical tests, the results of the t-test and chi-square tests were confirmed with the Mann-Whitney test and the Fisher’s exact test. Pearson correlation analysis was used to relationship between the days of exploratory laparotomy and the outcomes...
of surgery. A $P$-value $<0.05$ was regarded as statistically significant.

**Results**

During the study period, 178 VLBW infants delivered at our hospital. Total 19 cases and 19 controls were identified. The demographic and clinical characteristics of both groups are shown in Table 1. The mean gestational age and birth weight were 27.6±1.9 weeks and 966±233 g, respectively, in the surgical MRI group. In the control group, the mean gestational age was 28.7±2.2 weeks and the mean birth weight was 1,005±198 g. There was no significant difference between the surgical MRI group and the control group in perinatal characteristics including gestational age, birth weight and Apgar score. Of the 19 infants in surgical MRI group, 26% had a history of preeclampsia and 42% had premature rupture of the membranes (Table 2). There was no difference in maternal characteristics between the two groups.

Table 3 reports comparison of neonatal morbidities between both groups. The prevalences of RDS, PDA and CLD in preterm infants of surgical MRI were 94%, 52% and 74%, respectively. Day of full enteral feeding and hospitalization were significantly longer in surgical MRI group compared to control group (57.8±18.3 vs. 32.2±11.7 days, $P<0.001$; 124.9±7.6 vs. 78.5±18.5 days, $P<0.001$; respectively). Pearson correlation demonstrated a positive correlation between the mean days (age) of exploratory laparotomy and mean duration of hospitalization in surgical MRI group ($r=0.41$, $P=0.002$, data was not shown). Although body weight per se at discharge were not statistically different, the proportion of less than 3 percentile for postmenstrual age at discharge were significantly higher in surgical MRI group (73% vs. 21%, $P<0.001$). The mean age of exploratory laparotomy was 32.7±14.6 days and mean body weight was 1,460±443 g. The mean postmenstrual age at surgery was 32.0±3.1 week (Table 4).

### Table 1. Comparison of Perinatal Characteristics between Surgical MRI Group and Control Group

|                          | Surgical MRI group (n=19) | Control group (n=19) | $P$-value |
|--------------------------|--------------------------|----------------------|-----------|
| Gestational age (weeks)  | 27.6±1.9                 | 28.7±2.2             | 0.455     |
| Birth weight (g)         | 966±233                  | 1,005±198            | 0.754     |
| Sex (male)               | 10 (52)                  | 13 (68)              | 0.319     |
| IUGR                     | 5 (26)                   | 4 (21)               | 0.573     |
| Cesarean section         | 17 (85)                  | 14 (73)              | 0.209     |
| Twin                     | 8 (42)                   | 7 (36)               | 0.739     |
| Apgar score at 1 minute  | 2.9±0.9                  | 3.2±0.5              | 0.346     |
| Apgar score at 5 minutes | 5.3±1.1                  | 5.7±0.5              | 0.195     |

Values are presented as mean±standard deviation or number (%). Abbreviations: MRI, Meconium related ileus; IUGR, intrauterine growth restriction.

### Table 2. Comparison of Maternal Characteristics between Surgical MRI Group and Control Group

|                          | Surgical MRI group (n=19) | Control group (n=19) | $P$-value |
|--------------------------|--------------------------|----------------------|-----------|
| Maternal age (years)     | 33.2±3.2                 | 33.8±5.4             | 0.415     |
| IVF                      | 6 (31)                   | 5 (28)               | 0.720     |
| Preeclampsia             | 5 (26)                   | 4 (21)               | 0.702     |
| PROM                     | 8 (42)                   | 7 (36)               | 0.739     |
| Oligohydramnios          | 7 (36)                   | 5 (26)               | 0.485     |
| Antenatal steroid        | 14 (73)                  | 18 (94)              | 0.075     |
| Antenatal magnesium      | 12 (63)                  | 11 (57)              | 0.739     |
| Fever                    | 2 (10)                   | 1 (5)                | 0.547     |
| Gestational DM           | 3 (15)                   | 4 (21)               | 0.675     |

Values are presented as mean±standard deviation or number (%). Abbreviations: MRI, Meconium related ileus; IVF, in vitro fertilization; PROM, premature rupture of membrane; DM, diabetes mellitus.

### Table 3. Comparison of Neonatal Morbidities between Surgical MRI Group and Control Group

|                          | Surgical MRI group (n=19) | Control group (n=19) | $P$-value |
|--------------------------|--------------------------|----------------------|-----------|
| RDS                      | 18 (94)                  | 17 (89)              | 0.547     |
| PDA                      | 10 (52)                  | 9 (47)               | 0.745     |
| CLD                      | 14 (74)                  | 13 (68)              | 0.721     |
| Postnatal steroid        | 10 (52)                  | 8 (42)               | 0.515     |
| IVH                      | 3 (15)                   | 1 (5)                | 0.290     |
| ROP                      | 9 (47)                   | 6 (31)               | 0.319     |
| Day of reaching full enteral feeding (>120 mL/kg) | 57.8±18.3 | 32.2±11.7 | <0.001 |
| Day of hospitalization   | 124.9±7.6                | 78.5±18.5            | <0.001    |
| Postmenstrual age to discharge | 45.6±4.4            | 38.5±3.5             | <0.001    |
| Body weight to discharge | 3.3±0.7                  | 3.1±0.5              | 0.437     |
| <3 percentile of body weight for GA at discharge | 14 (73) | 4 (21) | 0.001 |

Values are presented as mean±standard deviation or number (%). Abbreviations: MRI, Meconium related ileus; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; CLD, chronic lung disease; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.
In the neonatal morbidities of our study, majority of diseases including RDS, PDA and ROP were not different in both groups. However, day of full enteral feeding and hospitalization were significantly longer in surgical MRI group. In our study, the mean age of exploratory laparotomy was 32.7 days. And mean durations of hospitalization in both groups were 114.9 and 78.5 days respectively and the difference between both groups was 36.4 days. As a result, it could be seen that the length of hospital days was increased by the period until the surgery was decided. Pearson correlation demonstrated a positive correlation between the mean days (age) of exploratory laparotomy and mean duration of hospitalization. Therefore, delay in decision for surgery might lead to prolonged hospital stay. And the rate of less than 3 percentile of weight for postmenstrual age was much higher at discharge, which might be due to poor enteral nutrition before surgery.

Many previous reports have mentioned that a delay in the initiation of therapy leads to decreased chance of avoiding surgery.\cite{1,9} Emil et al.\cite{9} indicated that a 10-day duration of obstruction is the limit for which an enema is effective.\cite{8} Hatanaka et al.\cite{1} concluded that for extremely low birth weight (ELBW) neonates with bowel obstruction of unclear etiology, mainly MRI, the early and frequent administration of a gastrografin enema is reasonable and surgery should be considered if the obstruction lasts beyond approximately 14 days after birth. Those were quite shorter than our report, in which surgery was done median 32 days after birth.

On the contrary, we should consider the risks of surgery. In our study, there were no severe complications of surgical treatment except minor complications such as bowel prolapse and bowel bleeding that were resolved spontaneously without any other interventions. Emil et al.\cite{9} suggested that surgical therapy in uncomplicated MRI cases that have failed medical management should be minimally aggressive and surgical treatment including enterotomy and evacuation of the plug suffice was quite safe and simple to perform.

Although the MRI has been increasingly described in the last 20 years, there has been no agreement on medical management.\cite{11} We could know that the previous studies reported that they used the enema at an earlier age and in a more frequent manner. Emil et al.\cite{9} used 10 mL/kg of saline rectal irrigations every 6 hours daily in patients who were obstructed for 10 days

### Discussion

We tried to investigate clinical characteristics and outcome of preterm infants clinically diagnosed MRI and failed with conservative treatment such as contrast enemas of gastrografin or glycerin, that required eventually exploratory laparotomy. The results of this study showed that the clinical characteristics, including perinatal and maternal history of VLBW infants in surgical MRI group were not different from those in the control group.

Regarding risk factors of MRI, several factors including cesarean section, maternal hypertension, maternal magnesium therapy and maternal diabetes have been identified, based on small cohort studies.\cite{7,9} Okuyama et al.\cite{7} reported that twin pregnancy and premature rupture of membrane is significantly associated with the development of MRI in VLBW infants, which required surgical treatment.\cite{6} In that study, maternal steroid treatment was found to be protective to development of MRI. Recently, Byun et al.\cite{10} reported that male gender and low birth weight were associated with surgical MRI compared with medically treated MRI. However, we did not find any differences of maternal history in the surgical MRI groups compared with control group.

### Table 4. Postoperative Clinical Course of Surgical MRI Group

|                          | Surgical MRI group (n=19) |
|--------------------------|----------------------------|
| **Ileostomy site**       |                            |
| <20 cm from ileocecal valve | 12 (64)                   |
| >20 cm from ileocecal valve | 3 (15)                    |
| Unknown                  | 4 (21)                     |
| **Outcome of ileostomy** |                            |
| Postnatal age at ileostomy (days) | 32.7±14.6               |
| Bodyweight at ileostomy (g) | 1,460±443                 |
| Postmenstrual age at ileostomy (weeks) | 32.0±3.1             |
| Day of full feeding (days) | 22.5±6.3                   |
| Interval of repair of ileostomy (days) | 55.5±12.4            |
| Body weight at repair of ileostomy (g) | 2,809±566               |
| Postmenstrual age at repair of ileostomy (weeks) | 40.5±6.7            |
| **Presence of ileostomy complication** |                       |
| Bowel bleeding | 1 (5)                     |
| Bowel prolapse | 2 (10)                     |

Values are presented as mean±standard deviation or number (%).

Abbreviations: MRI, meconium related ileus; NEC, necrotizing enterocolitis; FIP, focal intestinal perforation.
after birth. And Hatanaka et al. started gastrografin enema of 10 mL/kg initially and increased amount up to 15 mL/kg.

However, Amodio et al. reported colonic and ileal perforations secondary to a contrast enema in a premature baby. Caniano and Beaver reported a 13% complication rate after therapeutic enemas for meconium ileus. Therefore, management of MRI in premature infants, especially ELBW infants, should be need more cautions. We had followed a somewhat passive enema method because of the fear of intestinal perforation by the enema. Promptly recognition associated to an early and aggressive conservative management is essential to prevent complications and spare surgical interventions. However, if not improved despite aggressive conservative treatment, surgical treatment should be considered after 10 to 14 days after birth.

Our study has several limitations. First, the small number of case patients were included. And also, we were not able to inroll the control group as 1 to more than 2 match manner. Second, there are the limitations inherent to retrospective review study. Further studies with adequate sample size and prospective studies are needed.

Despites of these limitations, our study has been speculated that delayed decision of surgery in treatment of MRI might prolong the hospitalization and adversely affect growth in VLBW infants. Therefore, early treatment including exploratory laparotomy should be considered to improve outcome when especially the baby has more than one of risk factors including male gender and low birth weight.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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