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THE RELATIONSHIP BETWEEN INTESTINAL PROTECTIVE MARKERS AND SERUM ENDOTHELIN-1 CONCENTRATIONS IN LOW BIRTH WEIGHT INFANTS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

N. F. Panakhova, A. S. Hajiyeva, S. A. Huseynova *, S. S. Hasanov and N. N. Hajiyeva

Azerbaijan Medical University, K. Farajova Scientific Research Institute of Pediatry, Baku, Azerbaijan.

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Correspondence to Author:
Huseynova Saadat Arif

Ph.D
Third Pediatrics Department of Azerbaijan Medical University, AZ 1022, Bakikhanov 23, Baku, Azerbaijan.

E-mail: sadi_0105@mail.ru

ABSTRACT: Perinatal hypoxia results in poor circulation in internal organs, causing damage to the intestinal mucosa. Here, we aimed to evaluate the role of endothelial vasoconstrictor function in the formation of the intestinal mucous barrier in low-birth-weight neonates with hypoxic-ischemic encephalopathy (HIE). We comparatively analysed the concentrations of specific intestinal protective markers, *i.e.*, serum mucin 2 (MUC2), serum intestinal trefoil factor (ITF), and faecal human β-defensin 2 (HBD2), and a marker of endothelial activity, *i.e.*, serum endothelin-1 (ET-1), in early of postnatal life in 8 infants with moderate/severe HIE (group 1), 14 neonates with mild HIE (group 2), and 20 control infants using standard enzyme-linked immunosorbent assays. Markers of intestinal mucosa activity were not differentially expressed between infants in groups 1 and 2. Mean total concentrations of ITF and HBD2 were higher in groups 1 and 2 than in the control group ($p < 0.05$). In contrast, MUC2 concentrations were lower in infants of groups 1 and 2 than in the control infants. ET-1 expression was higher in group 2 than in group 1 and the control group on days 1–3 ($p < 0.05$). Spearman's rank-order correlation analysis showed that there were no significant relationships of ET-1 with MUC2 and HBD2. However, there was a significant negative correlation between ET-1 and ITF in group 1 infants. High serum ITF and faeces HBD2 levels accompanied low blood concentrations of MUC2, reflecting the depletion of Goblet cell function in response to hypoperfusion in low-birth-weight infants with HIE.

INTRODUCTION: Severe hypoxia/ischemia results in generalised endothelial dysfunction, which can lead not only to permanent brain damage but also to damage in other tissues of the body [1–3]. Endothelial activity is regulated through the actions of locally produced agents and reflects the balance of constricting and dilating factors.

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Among the vasoconstrictors, endothelin-1 (ET-1) appears to be the most important contributor to the acute regulation of vascular tone [4]. Disorders of the digestive tract are caused by haemodynamic disturbances as a result of centralisation of the bloodstream and poor circulation in the internal organs, leading to hypoxic damage to the mucosa layer of the gastrointestinal tract.

These disorders may be apparent in the first days of life as in the case of early complications in the form of paresis, motoric defects, and necrotising enterocolitis and in later complications in the form of vegeto-visceral syndrome, persistent vomiting, and regurgitation [5, 6].

Approximately 55–98% of infants with perinatal hypoxic brain injury suffer from different deviations in the gastrointestinal tract [7].

Intestinal ischemia or hypoxia initially results in mucosal damage of a part of the intestinal wall that is the most vulnerable to hypoxia. The protective function of the intestinal mucosal barrier depends on the expression and properties of mucins [8] and antimicrobial defensive factors, which are involved in the regulatory system and generate the main chain of host defence against pathogens [9]. Mucins are actively expressed in the epithelium of the gastrointestinal tract and form the high-molecular-weight viscoelastic layer, which is the protective barrier between the mucosal surface of the abdominal contents of the gastrointestinal tract, representing a nourishing environment for vital activity of commensal bacteria of the intestine [10, 11].

In addition to mucins, defensins play important roles in the formation of the gastrointestinal barrier. Defensins have broad-spectrum antimicrobial activity owing to their ability to disrupt the structure and function of bacteria and viruses and participate in the stabilisation of the mucosal protective layer through interactions with mucins [12].

The results of previous investigations have shown that different inflammatory factors may contribute to the pathogenesis of intestinal barrier injury, and most studies have focused on the pathological roles of cytokines and biologically active mediators produced by enterocytes and macrophages [13, 14]. However, the relationships between vasoregulation and the protective mechanisms of the gastrointestinal barrier have not been investigated. Therefore, in this study, we aimed to evaluate the role of endothelial function in the formation of the intestinal mucous barrier in low-birth-weight neonates with hypoxic-ischemic encephalopathy (HIE). We comparatively analysed the expression of specific intestinal protective markers, *i.e.*, mucin 2 (MUC2), intestinal trefoil factor (ITF), and human β-defensin 2 (HBD2), and a marker of endothelial activity, *i.e.*, ET-1, in early of postnatal life.

MATERIALS AND METHODS:

Patients and study design: The Problem Commission on Pediatric Research at Azerbaijan Medical University and the Azerbaijan National Committee on Bioethics and Ethics of Science and Technology approved this study. This prospective study was conducted at the neonatal intensive care unit (NICU) of the K. Farajova Pediatry Institute. Twenty-two low-birth-weight preterm infants who had moderate/severe perinatal HIE were enrolled in this study. Two patient groups were identified: group 1, infants who had moderate/severe HIE (n = 8); group 2, infants with mild HIE (n = 14). The control group included 20 low-birth-weight neonates who fulfilled all of the following criteria: an uncomplicated maternal history, a 5 min Apgar score of 7 or more, capillary or arterial cord blood pH of 7.00 or higher, a normal delivery after an uncomplicated pregnancy, no neurologic manifestations, normal cranial ultrasound, and no medication during the neonatal period.

We collected intrapartum and neonatal data prospectively and obtained obstetric data from hospital records. Data on maternal pre-eclampsia, sex, type of delivery, resuscitation measures in the delivery room, and anthropometric measurements (*e.g.*, weight, body length, head and chest circumference) were included on an individual research card for each infant. The diagnosis of asphyxia was determined according to Apgar scores (≤ 5 at 5 min of life), initial capillary or arterial pH of less than 7.00, and initial capillary or arterial lactate of greater than 7.00 mMol/L, according to the American Academy of Pediatrics guidelines [15]. Blood gases were detected within 30 min after delivery.

Gestational age was determined by the first day of the last menstrual cycle, and when possible, was confirmed or corrected by the first sonographic examination with growth measurements. Growth restriction was defined as estimated foetal anthropometric parameters [16], confirmed at birth, below the 10^{th} percentile for gestational age and sex. The severity of neonatal encephalopathy was estimated by Sarnat scoring based on abnormal neurologic signs, such as increased irritability and jitteriness, abnormal tone, abnormal primitive reflexes, altered consciousness, or convulsions, within the first 24 h of life [17]. All infants were closely monitored for gastric residuals, bilious aspirates, and abdominal distension.

Intraventricular haemorrhage (IVH) was detected by ultrasound examination, which was performed on day 3 of life using 5- and 7.5-MHz sector transducers and was classified into four grades according to the Papile description [18]. Periventricular leucomalacia (PVL) was diagnosed as an echolucent area or areas of persistent echogenicity in the periventricular region of the brain in coronal and sagittal views [19]. The diagnosis of necrotising enterocolitis (NEC) was based on clinical findings consistent with Bell's staging, confirmed by radiologic evidence of NEC [20]. The study exclusion criteria included death of the neonate within the first 3 days of life, transfer to other units, clinical or laboratory evidence of TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes infections), a proven and advanced stage of NEC, or congenital malformation.

Blood collection: Venous blood was collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes on days 1–3 and 7–10 and centrifuged for 15 min. Samples were stored in aliquots at -70 °C until analysis. No venous punctures were performed for the sole purpose of study-related analysis.

Measurement of serum MUC2, ITF, and ET-1 concentrations in peripheral blood: The plasma concentrations of MUC2, ITF (Life Science, Wuhan, China), and ET-1 (Cayman Chemical Company, Ann Arbor, MI, USA) were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits, based on a standard enzyme immunoassay procedures. The specimens were diluted according to the manufacturer's instructions for the ELISA kits to obtain the optimal density. The expression levels of MUC2 and ITF are reported in ng/mL, whereas that of ET-1 is reported in pg/mL.

Measurement of HBD2 concentrations in faeces: HBD2 levels were determined using a standard enzyme immunoassay kit (Immundiagnostik, Bensheym, Germany). Faecal samples were diluted in extraction buffer at a ratio of 1:50. Before standard ELISA, homogenates were centrifuged and dissolved in solution buffer. The concentrations of HBD2 in faeces are expressed in ng/g.

Statistical analysis: Data were tested for normal distributions and found to be nonparametric. Significant differences between groups were determined using the Mann-Whitney *U*-test to assess differences in the production of protective markers of the intestinal barrier and endothelial function. Qualitative variables, such as sex, maternal pre-eclampsia, caesarean section, resuscitation measures in the delivery room, and the degree of HIE and IVH were compared using Fisher's exact test. Spearman rank-order correlation coefficients were used to determine the associations between appropriate variables. In all instances, significance was established at $p < 0.05$.

RESULTS: As demonstrated in **Table 1**, there were no significant differences in mode of delivery or in maternal characteristics between groups 1 and 2, including factors that may have contributed to uteroplacental insufficiency (anaemia, pre-eclampsia).

TABLE 1: MATERNAL CHARACTERISTICS OF THE STUDY GROUPS

	Group 1 (n = 8)	Group 2 (n = 14)
Age	25.2 (19–31)	26.4 (19–34)
Gravidy	2.3 (1–7)	2.1 (1–5)
Premature rupture of membranes	2 (25)	3 (21.43)
Preeclampsia	2 (25)	2 (14.28)
Anaemia	4 (50)	6 (42.86)
Caesarean section	2 (25)	4 (28.57)

Data are shown as the mean (range) or n (%)

The neonatal characteristics of infants included in the study groups are presented in **Table 2**. The groups were similar in baseline neonatal characteristics, including gestational age, Apgar scores, and small for gestational age data. The majority of infants with severe/moderate HIE had a high incidence of seizures compared with that in group 2 ($p < 0.05$). The incidences of PVL and IVH grades II–III were also higher in infants with severe/moderate HIE compared with those in group 2 ($p < 0.05$).

The frequency of total parenteral nutrition (TPN) was similar in groups 1 and 2 during the first postnatal days. Group 1 infants reached well-sustained feeding at a significantly later age than group 2 infants ($p < 0.05$). Although the frequency of gastrointestinal disorders was also higher in infants in group 1 than in infants in group 2, this difference was not statistically significant ($p > 0.05$).

TABLE 2: NEONATAL CHARACTERISTICS OF THE STUDY GROUPS

	Group 1 (n = 8)	Group 2 (n = 14)
Gestational age, weeks	31.4 (28–34)	31.9 (28–33)
Birth weight, g	1345 (980–1480)	1398 (1100–1450)
Small for gestational age	2 (25)	4 (28.57)
Apgar 1 min	4.2 (3–6)	5.5 (4–7)
Apgar 5 min	6.3 (4–6)	6.2 (4–7)
pH	7.15 (6.85–7.29)	7.21 (6.98–7.32)
RDS	3 (50)	6 (42.86)
Gastrointestinal disorders	5 (62.5)	6 (42.86)
NEC	-	1 (7.14)
TPN ≥ 7 days	5 (62.5)*	4 (28.57)
Seizures	6 (75)¶	5 (35.71)
Moderate HIE	3 (37.5)	8 (57.14)
Severe HIE	5 (62.5)	6 (42.86)
IVH, grade I	1 (12.5)	3 (21.43)
IVH, grades II–III	4 (50)	6 (42.86)

Data are shown as the mean (range) or n (%), $^{*}p < 0.05$.

Fig. 1 shows comparisons of the plasma concentrations of MUC2, ITF, and ET-1 and faecal concentrations of HBD2 in the study groups. The markers of intestinal mucosa activity were not significantly different between groups 1 and 2.

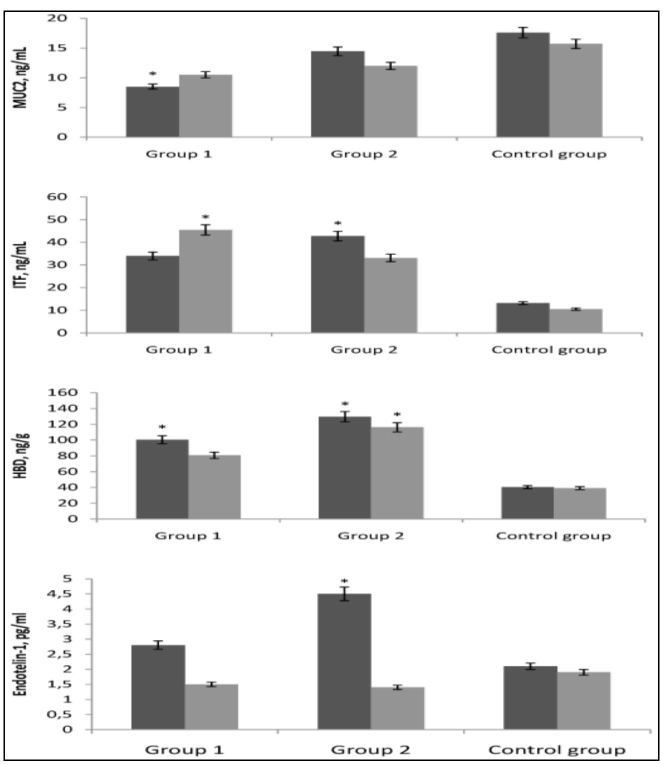

FIG. 1: MEAN TOTAL MUC2, ITF, HBD, AND ET-1 CONCENTRATIONS IN THE STUDY GROUPS. BLACK BARS INDICATE DAYS 1–3, AND GREY BARS INDICATE DAYS 7–10. *P < 0.05 VERSUS THE CONTROL GROUP

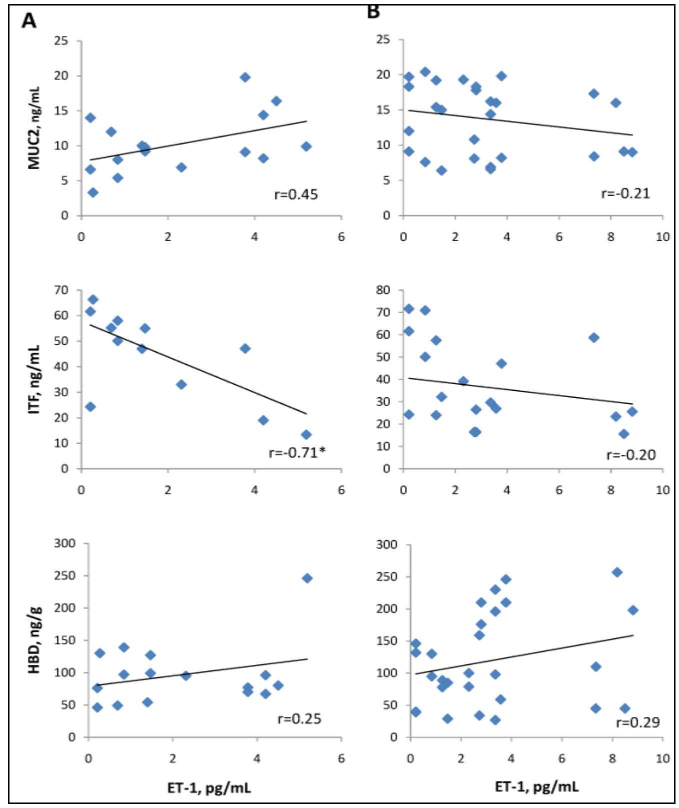

FIG. 2: SPEARMEN'S RANK-ORDER CORRELATION BETWEEN ET-1 EXPRESSION AND INTESTINAL MUCOSA MARKERS IN PRETERM INFANTS WITH HIE. EACH CORRELATION ANALYSIS INCLUDES BOTH PARAMETERS OF DAYS 1–3 AND DAYS 7–10 IN APPROPRIATE STUDY GROUPS (*p < 0.05). COLUMN A SHOWS GROUP 1 DATA, AND COLUMN B SHOWS GROUP 2 DATA

Plasma MUC2 concentrations were lower in infants in both HIE groups compared with those in the control group, whereas only the mean MUC2 levels on days 1–3 were significantly different between group 1 and the control group ($p < 0.05$). Mean total ITF concentrations increased during the early postnatal days in infants with severe/moderate HIE but decreased in infants with mild HIE. ITF levels were also significantly higher on days 7–10 in group 1 and on days 1–3 in group 2 compared with those in the control group ($p < 0.05$). Decreased faecal HBD levels during the neonatal period were also observed in infants in both HIE groups compared with those in the control group ($p < 0.05$). There were slight differences in ET-1 concentrations between group 1 and the control group. However, ET-1 levels were considerably higher in group 2 than in group 1 and control group, and only the difference on days 1–3 was significant compared with the control group ($p < 0.05$).

Spearman's rank-order correlation analysis showed that ET-1 and intestinal mucosa defence marker results differed among groups 1 and 2 (**Fig. 2**). The relationship between MUC2 and ET-1 tended to be positive in group 1 infants, and HBD2 was positively correlated in both groups of newborns. In contrast, ET-1 was not significantly related to MUC2 and HBD2. There was a significant negative correlation between ET-1 and ITF in group 1 infants with moderate/severe HIE.

DISCUSSION: Hypoxic and ischemic complications during the pre- and perinatal period cause acquired neonatal brain damage associated with different grades of poliorgan insufficiency [21]. Although the neonatal brain is one of the most vulnerable organs due to its high energy and oxygen consumption, hypoxic ischemia has been implicated in the breakdown of the intestinal epithelial barrier, which can lead to bacterial translocation [22, 23]. In the present study, decreased MUC2 expression was associated with increased ITF and HBD2 concentrations in the two HIE groups compared with those in the control group. MUC2, the major colonic gel-forming protein, is known to be a critical factor for establishment of goblet cell morphology [24] and plays an important role in mucosal protection by preventing bacterial pathogens from gaining access to the epithelium [25, 26]. According previous study, MUC2-knockout mice show increased susceptibility to the development of inflammatory bowel diseases, suggesting a potential role for mucins in epithelial protection [27].

These findings suggest that defective mucus coat production could contribute to the pathogenesis of intestinal injury. We speculate that systemic hypoperfusion and severe hypoxic-ischemic injury in group 1 infants was associated with more serious alterations in goblet cell function, leading to significant reduction of MUC2 compared with that in control infants. Considering the possibility of intestinal injury as a result of an imbalance between vasoconstriction and vasodilatation, low ET-1 levels may cause systemic hypoperfusion and different structural and pathological changes in the gastrointestinal tract of infants with severe/ moderate HIE. According to the literature, brain injury can induce significant damage to gut structures and impairment of barrier function due to relative hypoperfusion and interactions of inflammatory mediators with their receptors located on gut epithelial cells [28, 29]. Increased ET-1 concentrations in infants with mild HIE may compensate for centralisation of blood circulation.

In our study, increased expression of peripheral blood ITF peptide and faecal HBD in the background of weakened colonic mucosal defence early after birth suggested the activation of acute repair mechanisms at the site of injury. Hypoxia has been reported to increase ITF and HBD expression in intestinal epithelial cells in previous studies; Furuta interpreted this process as the mechanism for maintenance of barrier function when oxygen levels are low [30, 31]. Xu *et al.*, demonstrated that ITF expression in the intestines of rats exposed to intrauterine asphyxia increased 72 h after birth [32], followed by rapid proliferation of the mucosa with the recovery of intestinal function.

In the context of broad investigations confirming the significant effects of nitric oxide (NO) and ET-1 on the physiology and pathology of vascular homeostasis [33, 34], the role of endothelial dysfunction markers in the pathogenesis of epithelial injury of the intestinal tract has not been investigated completely. According to the results of correlation analysis in the present study, we hypothesised that decreased ET-1 levels in peripheral blood were a precursor for systemic hypoperfusion and may alter the protective functions of the intestinal mucosa, manifesting as decreased serum MUC2 and faecal HBD2 concentrations and increased ITF concentrations. However, further studies with more patients are needed to support the results of correlation and comparative analyses. We were also unable to detect the relationship between constricting/dilating markers and the functional activity of the intestinal mucosa, which would help to confirm our hypothesis.

In conclusion, we found that vasoconstrictor activity of the vascular endothelium played an important role in mediating the functional activity of the gut mucosa through maintenance of intestinal blood circulation. High serum ITF and faecal HBD2 levels accompanied by low blood concentrations of MUC2 may reflect the depletion of goblet cell function in response to hypoxic inflammation. Imbalances between these two main products of goblet cells may reflect disruption of the regulatory effects of trefoil peptides on the expression and protective properties of mucins in infants with severe and moderate HIE.

CONFLICT OF INTERESTS: The authors declare that they have no competing interests.

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