






A case of successful treatment of an extremely preterm infant with necrotic enterocolitis complicated by sepsis of bacterial and fungal etiology

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words:
necrotizing
enterocolitis,
peritonitis, sepsis,
premature infant.

Pathologia
2022; 19 (1), 84-88

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The aim. To acquaint medical practitioners with the case of successful surgical treatment and intensive care of a extremely preterm infant with necrotic enterocolitis, complicated with intestinal perforation and sepsis of mixed bacterial and fungal etiology.

Materials and methods. The child was treated in the Neonatal Anesthesiology and Intensive Care Department of Communal Non-commercial Enterprise “City Children’s Hospital No. 5” of Zaporizhzhia City Council. Blood analyses, microbiological, X-ray and ultrasound examinations were performed by indications using the hospital equipment.

Results. An extremely preterm, very low birth weight infant underwent nine traumatic surgical interventions for NEC with gastric and intestinal perforation, diffuse peritonitis, and adhesive intestinal obstruction. The child’s condition was complicated by sepsis of mixed bacterial and fungal etiology. Preoperative preparation included antibacterial therapy, infusion therapy with modern balanced polyionic solutions, and inotropic support.

During and after surgical interventions, the child underwent multimodal combined anti-stress anesthesia with the use of neuroaxial blocks, prolonged MLV, antibacterial therapy with modern drugs according to the de-escalation principle and microbiological peculiarities of the department, antifungal therapy with reserve drugs, immune replacement therapy, parenteral nutrition and infusion program using blood products according to indications. Despite the child’s critically severe condition and morphofunctional immaturity, the child has survived, has no neurological deficit, and has gained four times his initial body weight.

Conclusions. The use of multimodal combined anesthesia with caudal-epidural blocks in the intra- and postoperative periods, adequate respiratory and hemodynamic support, parenteral and early enteral feeding in a deeply premature baby with NEC probably contributed to antinociceptive protection and positive treatment outcome after 9 urgent operations. The reserve antibiotics and antifungal drugs prescription according to de-escalation principle, considering the sensitivity of the bacterial flora to them, bacteriological monitoring and immune replacement therapy, had a positive result in the treatment of sepsis, which complicated the course of NEC in the newborn baby.

Ключові слова:
некротичний
ентероколіт,
перитоніт, сепсис,
недоношена
дитина.

Патологія. 2022.
Т. 19, № 1(54).
С. 84-88

Випадок успішного лікування глибоконедоношеної дитини з некротичним ентероколітом, що ускладнений сепсисом бактеріально-грибкової етіології

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Мета роботи – ознайомити лікарів-практиків з випадком успішного хірургічного лікування та інтенсивної терапії глибоконедоношеної дитини з некротичним ентероколітом (НЕК), що ускладнений перфорацією кишечника та сепсисом змішаної бактеріально-грибкової етіології.

Матеріали та методи. Дитина перебувала на лікуванні у відділенні анестезіології та інтенсивної терапії новонароджених КНП «Міська дитяча лікарня № 5» ЗМР. Дитині виконали клінічні та біохімічні аналізи крові, мікробіологічні, рентгенологічні та ультразвукові дослідження на обладнанні лікарні.

Результати. Глибоконедоношена дитина з дуже низькою масою тіла перенесла дев’ять травматичних оперативних втручань з приводу НЕК з перфорацією шлунка та кишківника, розлитого перитоніту, спайкової кишкової непрохідності. Стан дитини ускладнився сепсисом змішаної бактеріально-грибкової етіології. Передопераційна підготовка передбачала антибактеріальну терапію, інфузійну терапію з включенням сучасних збалансованих полііонних розчинів, інотропну підтримку.

Під час і після оперативних втручань дитині призначали мультимодальні комбіновані антистресові анестезії з використанням нейроаксіальних блоkad, подовжену штучну вентиляцію легень, антибактеріальну терапію сучасними препаратами за деескалаційним принципом, враховуючи висіві дитини та мікробіологічні особливості відділення, протигрибкову терапію препаратами резерву, імунозамісну терапію; дитина отримувала парентеральне харчування, їй була призначена інфузійна програма з використанням препаратів крові за показаннями. Незважаючи на критично тяжкий стан дитини та морфофункціональну незрілість, у результаті лікування вона вижила, не має неврологічного дефіциту, маса її тіла збільшилася вчетверо від вихідної.

Висновки. Застосування мультимодальної комбінованої анестезії з використанням каудально-епідуральних блокад в інтра- та післяопераційному періодах, адекватна респіраторна та гемодинамічна підтримка, парентеральне на ранне ентеральне харчування у глибоконедоношеної дитини з НЕК, імовірно, позначилися на антиноцицептивному захисті та сприяли позитивному результату лікування після дев'яти ургентних операцій. Призначення антибіотиків резерву за принципом деескалації, враховуючи чутливість бактеріальної флори, здійснення бактеріологічного моніторингу й імунозамісної терапії мали позитивний ефект під час лікування сепсису, що ускладнив перебіг НЕК у новонародженого.

Necrotizing enterocolitis (NEC) is an acute necrotic intestinal syndrome of multifactorial and insufficiently studied etiology, which is characteristic mainly of the extremely preterm infants and is one of the main causes of morbidity and mortality in children born at a gestational age of less than 32 weeks [1–3]. In its pathogenesis, hypoxia and impaired mesenteric blood flow should be considered as the main link, leading to disruption of the barrier function of the intestinal mucosa, translocation of microbes into the bloodstream, and inflammation, triggering a cascade of cytokine reactions, ulceration of the mucosa, necrosis, and perforation [1,4,5]. Antibiotic usage and dysbiosis also play role in its pathogenesis [6–9].

Among risk factors of NEC are bottle-feeding and insufficient contact with mother's microbiome [1,6,9], low birth weight, low gestation term in birth, underweight to the gestation term, use of mechanical or assisted lung ventilation, premature rupture of membranes, black ethnicity, sepsis, outborn, hypotension, maybe also surfactant therapy and cesarean section [1,10].

Different authors consider a frequency of NEC development among premature babies to be from 5 % to 12 % [11,12], at the same time, several authors believe that the frequency of this pathology in recent years tends to increase [2,13]. However, the urgency of this problem is primarily due to the catastrophically high mortality rate [5,9,10], which the higher, the lower the baby's gestational age and birth weight are [7,10]. Among newborns with NEC requiring surgical intervention, mortality is 20–30 % [12], according to other authors – up to 60 % [3].

Despite the achievements of modern science, there is a problem of late diagnosis [14–16] and differential diagnosis of this pathology all over the world [3]. Some authors also pay attention to the lack of the precise indication for surgical intervention [17,18]. Among NEC complications are sepsis and septic shock, intestine perforation, multiple organ failure, short intestine syndrome, hepatic damage due to long parenteral feeding [4].

Common methods of NEC treatment are complete parenteral nutrition, antibiotics, probiotics, and surgical treatment in case of perforation [11,17]. Among today's promising researches is a development of a novel class of toll-like receptor 4 (TLR4) inhibitors [11]. In the prophylaxis of hard and lethal NEC complications struggle with vasa constriction leading to intestinal ischemia and perforation plays an important role [4]. One of the ways to combat vasoconstriction is an adequate anesthesia. There is a point of view that the advantage to caudal-epidural blockade should be given, which has such beneficial effects as reliable analgesia, intestinal desympathization, and, consequently, an increase in intestine blood flow, so – prevention of its ischemia, and activation of gastrointestinal motility [19].

Aim

To acquaint medical practitioners with the case of successful surgical treatment and intensive care of an extremely preterm infant with necrotic enterocolitis, complicated by intestinal perforation and sepsis of mixed bacterial and fungal etiology.

Materials and methods

The child was treated in the Neonatal Department of Anesthesiology and Intensive Care of the Communal Non-commercial Enterprise "City Children's Hospital No. 5" of Zaporizhzhia City Council. Blood analyses (clinical, biochemical), microbiological, X-ray and ultrasound examinations were performed by indications using the hospital equipment.

Patient's parents have signed informed consent.

Results

A child S. was born from the first pregnancy. On the 28th week his mother was hospitalized with a hard bilateral pneumonia, associated with COVID-19. A child was born via caesarian section because of placental abruption; birth weight was 1300 grams, length 42 cm, Apgar scale examination 5/6 degrees. Immediately after birth, tracheal intubation and transfer to mechanical lung ventilation (MLV) were performed.

On the third day after birth, the child was diagnosed with a hollow organ perforation. According to the abdominal organs radiography, free gas was found in the abdominal cavity projection, laparocentesis was performed, and the abdominal cavity was drained. The next day the child underwent a big operative intervention: laparotomy, revision of the abdominal organs, and suturing of the perforation of the stomach were provided.

Pre-operative preparation included powerful antibacterial therapy applied by the de-escalation principle (from wider to narrower spectrum), infusion therapy according to physiological needs appropriate for newborns, which included crystalloid solutions (isotonic sterofundin), and native single-group plasma. The child was constantly on a ventilator with physiologic parameters ($V = 6-7$ ml/kg, RR 36–40 per minute, PEEP 5 cm, FiO_2 30 %), hemodynamic support was provided with dobutamine at doses of 5–10 μ g/kg/min.

After the preoperative preparation, the main indicators of homeostasis were stabilized and compensated (hourly diuresis 1.5 ml/kg/h; mean blood pressure (MBP) – 40–45 mm Hg), pH 7.33, peripheral blood saturation 92–96 %. During surgery the child underwent multimodal general anesthesia using a caudal-epidural block. We have previously studied this method of combined anes-

thetia with central spinal and caudal-epidural blockades in intra and postoperative period usage, and it showed the best results of anti-stress protection compared to other methods of combined general anesthesia for extensive and traumatic operations in newborns (Kurochkin M. Yu. *Central Neuroaxial Anesthesias in Newborn and Infants. Extended abstract of PhD dissertation.* KhMNU, Kharkiv, 2013).

We used the following technic of multimodal anesthesia: after premedication with atropine 0.01 mg/kg the induction with Sodium Oxybutyrate 150 mg/kg, myoplegia with atracurium besylate 0.5 mg/kg, analgesia by fentanyl 5 mcg/kg were provided. Then the caudal-epidural anesthesia with 2 mg/kg of bupivacaine 0.2 % was performed with bringing the volume of epidural bolus up to 1 ml/kg. The efficacy and term of caudal-epidural block onset were evaluated using impedance of the lower extremity (femur region) measurement before blockade and 15–20 minutes after it (Kurochkin, M., Davydova, A., Dmytriakov, V., Chemerys, Y., Krupinov, Y., Krupinova, O. and Svekatun, V. 2016. *Method for determining the onset of caudal-epidural anesthesia in children.* 112820).

In the case of necessity, ketamine 3–4 mg/kg and/or fentanyl 5 µg/kg were additionally added for analgesia during surgery. As for infusion during the intraoperative period, solution of sodium chloride 0.9 % and native plasma were infused in a ratio of 1:1 and at a rate of 15–20 ml/kg/h. Hemodynamics was maintained with dopamine at a dose of 7 µg/kg/min as it provides blood pressure consistency not only by increasing cardiac output, but also by peripheral vasoconstriction, and the experience of our hospital shows the advantage of using this drug versus dobutamine during extensive surgery in newborns.

In the postoperative period, the child underwent mechanical ventilation in the normoventilation mode ($V = 6\text{--}7$ ml/kg, RR 40–42 per minute, PEEP 5 cm, FiO_2 21–30 %). Infusion therapy according to the physiological need for fluid was conducted taking into account pathological losses (intestinal paresis) with general volume up to 150 ml per kilogram of weight, with electrolyte disorders correction such as additional KCl administration for hypokalemia episodes. Parenteral nutrition was used: the child received glucose 15 % 14–15 g/kg per day (in accordance with the rate of utilization of glucose 0.4–0.6 g/kg/hour); fat emulsions starting from 0.5 g/kg/day with a gradual increase to 2.5–3.0 g/kg; and solutions of amino acids from 1 g/kg/day to 3–4 g/kg/day. When the child began to assimilate the enteral feeding gradually, the doses of parenteral nutrition were reduced.

Postoperative analgesia was performed by a combination of intravenous continuous infusion of fentanyl at a rapid dosage of 5 µg/kg/hour and caudal-epidural blockades performed 1–2 times a day with 0.2 % bupivacaine solution (injected volume of local anesthetic with 0.9 % chloride sodium was 1.0–1.2 ml/kg) for 3–4 days. Then the dose of fentanyl was reduced to 3–2 mcg/kg/hour, intravenous paracetamol was added at a dose of 7.5 mg/kg 3–4 times daily. The same tactics of patient management was used in other cases of the perioperative period of all the following surgical interventions.

The infant's condition deteriorated critically after the 9th operation. The worsening was associated with the development of mixed fungal-bacterial etiology sepsis. Bacteriological examination data showed the presence of bacterial flora hospital strains in the pharynx, feces and blood: *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus haemolyticus*, *Escherichia coli*, *Enterobacter cloacae*, *Stenotrophomonas maltophilia*, *Candida non albicans*. The child had metabolic acidosis with the increased lactate level (pH 7.10–7.25, lactate up to 8 mmol/l), significant inflammatory changes in the blood (leucocytosis up to 38×10^9 with immature forms of neutrophils to 60 %), and the level of procalcitonin was 28.4 µg/ml.

The child received combined antibiotic therapy, which was de-escalated at the highest age-appropriate dosages: vancomycin 40 mg/kg in combination with meropenem 60 mg/kg, followed by colistin 70 ME/kg/day. Antifungal therapy was a combination of fluconazole and mycalfungin with a later switch to caspofungin. Immunocompensatory therapy was carried out with preparations of normal human immunoglobulin in a total dose of 1 g/kg. After intensive therapy, the clinical and laboratory signs of sepsis regressed.

The course of the disease in the child was considered to be very severe, with the development of relapses and complications.

Upon the whole during few months, the infant underwent 9 surgeries:

1. The 3rd day of life: laparocentesis, abdominal drainage due to bowel perforation, III stage peritonitis;
2. The 4th day of life: laparotomy: abdominal revision, closure of gastric perforation;
3. Day 12: relaparotomy; abdominal revision; end-to-end jejunostomosis due to intestinal perforation, excision of the perforated part of the intestine; application of an end ileostomy (*Fig. 1*);
4. Day 66: end-to-end ileoanastomosis, cutting adhesions;
5. Day 79: laparotomy, cutting adhesions, intestine intubation;
6. Day 93: relaparotomy, cutting adhesions, resection of ileum (after perforation and adhesion to another part of the intestine), ileo-ileoanastomosis;
7. Day 107: relaparotomy, abdominal revision, releasing of adhesions, end-to-end ileo-ileoanastomosis, intestine intubation; postoperative period also had signs of intestinal obstruction;
8. Day 116: relaparotomy; revision of the abdominal organs; releasing of adhesions; application of end-to-end ileo-ascendo-anastomosis; postoperative period with free gas in the abdomen (as a result of failure of the previous anastomosis);
9. Day 120: relaparotomy, abdominal revision, end-ileostomy, abdominal sanitation.

Six months later, at the age of 13 months ileostomy was closed and intestinal integrity was restored.

The infant received full and then partial parenteral nutrition. After the last 9th operation, at the age of 4 months, the baby's body weight was 3800 g. On discharge from the intensive care unit to the neonatal pathology department on the 6th month of life, his body weight was 4930 g



Fig. 1. Intestine perforation. Free gas in the abdomen.

(+3630 g since birth) and before discharge from the hospital at the age of almost 7 months it was 5300 g (more than 4 times weight gain). It is important that the child has no neurological deficit and develops according to age.

Discussion

The uniqueness of this case is that the patient had the highest risk of an adverse outcome (grade 4–5 on the ASA anaesthetic scale), but underwent nine extensive surgical interventions, survived and almost fourfold body weight gain. The initial severity of the condition was determined by extreme prematurity with very low birth weight, intrapartum hypoxia due to premature abruption of the placenta. Morpho-functional immaturity of all organs and systems eventually contributed to the development of ulcerous-necrotic enterocolitis with subsequent gastric and intestinal perforations, diffuse peritonitis, and later sepsis of mixed bacterial-fungal etiology.

In other Ukrainian clinics, usage of neuroaxial blockades in infants with NEC is not common. However, we have had positive experience with them for several years. From our point of view, in this clinical case caudal-epidural anesthesia made it possible to reduce the dosage of narcotic analgesics significantly, and at the same time eliminated ischemic disorders of splanchnic blood flow due to the sympathetic component of the blockade. This contributed to a more rapid recovery of intestinal peristalsis.

In our opinion, the leading role in favorable outcome was played by multimodal combined anti-stressor anesthesia, including caudal-epidural blocks in the perioperative period; effectively conducted respiratory and hemodynamic support, parenteral nutrition and infusion therapy, powerful antibacterial, antifungal and immune replacement therapy, as well as high reserve capacity of the patient's organism.

Conclusions

1. The use of multimodal combined anaesthesia using caudal-epidural blocks in the intra- and postoperative periods, adequate respiratory and haemodynamic support, parenteral and therapeutic enteral feeding in an extremely preterm baby with NEC, probably contributed to reliable antinociceptive protection and positive treatment outcome after 9 urgent operations, contributing to 4-fold body weight gain, survival, and recovery.

2. The administration of reserve antibiotics and antifungal drugs according to the de-escalation principle, considering the sensitivity of the bacterial flora to them, bacteriological monitoring and immune replacement therapy, had positive results in the treatment of NEC complicated by sepsis in extremely preterm infant.

Prospects for further research. In the future, it is planned to study the effect of caudal-epidural blocks on the course of NEC in preterm neonates when applied in the early stages (intestinal paresis before the stage of intestinal pneumatosis and perforation). Also perspective in our opinion will be the study of the effect of central neuroaxial anesthesia on the processes of tissue repair and regeneration after extensive abdominal operations in newborns.

Funding

This work was conducted as a part of scientific research of Zaporizhzhia State Medical University "Scientific substantiation of diagnostic strategies, optimization of treatment and improvement of rehabilitation and prophylactic algorithms in the monitoring of children of different ages", state registration No. 0120U101143.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 28.01.2022
Після доопрацювання / Revised: 18.03.2022
Прийнято до друку / Accepted: 28.03.2022

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