Abstract. The present study presents the experience gained in the Newborn Intensive Care Unit (NICU) of ‘Maria S. Curie’ Emergency Clinical Hospital for Children, 077120 Bucharest; 2Discipline of Pediatrics, Faculty of Medicine, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest; 3Department of Surgery, ‘Sf. Pantelimon’ Emergency Clinical Hospital, 021659 Bucharest; 4Discipline of Surgery, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest; 5Department of Cardiology, ‘Maria S. Curie’ Emergency Clinical Hospital for Children, 077120 Bucharest; 6Department of Pneumology, ‘Marius Nasta’ National Institute of Pneumology, 050159 Bucharest; 7Discipline of Pneumology, Faculty of Medicine, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest; 8Department of Obstetrics and Gynecology, ‘Sf. Pantelimon’ Emergency Hospital, 021659 Bucharest; 9Discipline of Obstetrics and Gynecology, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest; 10Department of Histopathology, ‘Alexandru Trestioreanu’ National Institute of Oncology, 022328 Bucharest; 11Discipline of Histopathology, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest; 12Department of Pediatric Surgery, ‘Maria S. Curie’ Emergency Clinical Hospital for Children, 077120 Bucharest; 13Discipline of Pediatric Surgery, Faculty of Medicine, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest, Romania

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Correspondence to: Dr Bogdan Socea, Discipline of Surgery, ‘Carol Davila’ University of Medicine and Pharmacy, 37 Dionisie Lupu Street, 020021 Bucharest, Romania
E-mail: bogdan.soea@umfcd.ro

*Contributed equally

Abbreviations: NICU, neonatal intensive care unit; CDH, congenital diaphragmatic hernia; iNO, inhaled nitric oxide; HFOV, high-frequency oscillatory ventilation; VIS, Vasoactive-inotropic score; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy

Key words: congenital diaphragmatic hernia, severe pulmonary hypertension, bedside surgery, NICU infrastructure

analysis of a control group was used to provide a reference to the survival rate for non-operated patients. The present study is based on data from 10 cases of newborns, surgically operated on, on average, on the fifth day of life. The main reasons for operating on-site included hemodynamical instability and the need to administer inhaled nitric oxide (iNO) and high-frequency oscillatory ventilation (HFOV). There were no unforeseen events during surgery, no immediate complications, no surgery-related mortality. One noticed drawback was the unfamiliarity of the surgery team with the new operating environment. Our experience indicates that bedside surgery improves the likelihood of survival for critically ill neonates suffering from CDH. No immediate complications were associated with this practice.

Introduction

Diaphragmatic hernia is determined by a defect in the diaphragm that allows the abdominal viscera to protrude into the thoracic cavity. Most of the cases are congenital diaphragmatic hernia (CDH) interfering with the normal development of the lungs, while acquired diaphragmatic hernias are most commonly of traumatic origin (1,2). According to the European Surveillance of Congenital Anomalies, the reported incidence of CDH in 2019 for all pregnancies from 20 weeks onwards was 3.11 per 10,000 and 2.15 per 10,000 for live-born infants (3). This study focuses on neonatal CDH cases as this
is one of the most complicated conditions that could be surgically operated on-site.

The Newborn Intensive Care Unit at ‘Maria S. Curie’ Emergency Clinical Hospital for Children is one of the largest units of this type in Eastern Europe. Built in 2013, inspired by the Iowa Neonatal Intensive Care Unit, the NICU provides specialized intensive care treatment for surgical neonatal patients. There are 27 beds in individual rooms with areas of approximately 12 square meters (Fig. 1). Each room is equipped with central air flow system (6 air change cycles per hour), different types of light (natural light, 2 ceiling projectors for procedures, and 1 indirect light), pendants with outlets for O₂, medical air, vacuum, iNO, CO₂, helium and areas for hand washing and disinfection. In addition, every room is equipped with one open incubator, one ventilator, one or two docking stations with 10 syringe pumps each, one transcutaneous monitor, central monitoring, alarming equipment software, electronical data sheet for the patients/ICCA, individual medical cart for medication and consumables with extendable table for procedures.

The ‘Maria S. Curie’ Hospital provides medical care to children of all ages, but it presents no delivery room. As such, all patients admitted to the NICU are transferred from referral hospital either by neonatal ambulance transport or helicopter. There are indications that the stress endured during the transport worsens the medical condition of the patients at the admission time. Transferring unstable neonates over long distances is frequently associated with notable deterioration of the general condition. Similar risks, albeit with lower incidence and severity, can occur during the patient’s transfer from the NICU to the operating room (OP) (4). Performing the intervention in the NICU can thus avoid the complications associated with the discontinuation of monitoring, dislocation of artificial airways, accidental removal of vascular access, hypothermia or variations in heart rate and blood pressure (5,6).

Bedside surgery is a well-established practice at ‘Maria S. Curie’ NICU as both the technical equipment and medical expertise allow for this type of intervention (Fig. 2). Since 2011, a series of onsite interventions have been performed, including surgery for retinopathy (laser therapy and avastin injections), ligation of the patent ductus arteriosus, emergency atrial septostomy, placement of extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT) hemodialysis catheter, external ventricular drainage for hydrocephalus, tracheostomy, pleural drainage, peritoneal dialysis catheter placement and procedure.

Patients and methods

The present study is based on the retrospective analysis of 22 patients with CDH that were admitted to ‘Maria S. Curie’ NICU between January 2011 and December 2020. The COVID-19 pandemic did not affect the provision and the quality of the medical care in our unit. Specifically, the study was not influenced as there were no positive patients in our data sample as well as in the NICU during this time. The dataset supporting this study consists of 10 patients that were surgically operated on-site in the NICU. In addition, a control group of 12 patients that could not be operated on even on-site due to severe respiratory and hemodynamically instability was used to provide a reference to the survival rate for non-operated patients. Two patients were excluded from the control group due to very severe status at the time of the admission in the NICU followed by death within 12 h.

For all analyzed cases, the decision to surgically operate on-site or not to operate at all, was made following a multidisciplinary discussion involving medical doctors from the neonatology, cardiology, anesthesiology, and surgical team, with the outcome documented in a medical report. The criteria to operate on-site, as well as the decision regarding proper surgery time, was a team decision based on clinical and hemodynamical stability of each patient, dependent on the inotropic medication, high-frequency oscillatory ventilation (HFOV), iNO and ECMO procedures. An additional consideration was the operatory infrastructure as it is not possible to administer NO and apply HVOF in the OR. The arguments supporting this type of intervention were presented to the parents and in all cases the decision to operate was supported by parental consent (except for one emergency operation for pneumoperitoneum). For the cases admitted during the COVID-19 pandemic, strict regulations to prevent in-hospital dissemination of Sars-cov-2 infection were observed consisting of RT-PCR testing at admission, mask wearing by hospital personnel, and frequent disinfection of the surfaces (7).

Upon admission into the NICU, a series of investigations were performed according to the internal evaluation protocol for CDH. These investigations included microbiological studies (microbial skin culture, blood culture), complete blood count, kidney function, coagulation screening and inflammatory tests, genetic tests, and serial blood gas tests. In addition, echocardiography was performed to exclude associated malformations, to measure the right-to-left shunt, to estimate the severity of pulmonary hypertension and to evaluate the anatomy and velocities at the pulmonary veins and pulmonary arterial branches. The protocol also included brain and kidney ultrasound and chest X-ray to evaluate the mediastinal shifting, pneumothorax, severity of atelectasis and the presence of fluid at the side of the herniation. In the past few years, since it has become possible to have patients on ECMO; the levels of B-type natriuretic peptide (BNP) are used as a prognostic marker for the development of pulmonary hypertension as well as the need for ECMO (8-11). In addition, a series of personal general data was collected and analyzed (e.g. antenatal diagnosis, sex, gestational age, type of birth, Apgar score) as well as details of the care procedure immediately after delivery (e.g. intubation, type of ventilation and peripheral capillary oxygen saturation (SpO₂) with minimal fraction of inspired oxygen (FiO₂) on the first day of life). Since all newborns were transferred to our clinic mainly on the first day of life, this general data was collected in the hospitals where the children were born.

Vital parameters were recorded at admission time for all patients. The data recorded prior and after the intervention constituted the basis for the analysis of the surgically operated patients. These parameters included the following metrics: heart rate (HR) (continuously measured by electrocardiography), blood pressure (BP) as systolic blood pressure, diastolic blood pressure and mean arterial pressure (MAP), either intermittently measured peripheral or via central preductal arterial line, preductal oxygen saturation (SpO₂),
blood gas (capillary or arterial sample), glycemia, urine output, ventilation parameters, iNO, and the doses of the continuous intravenous medication as individual and as the Vasoactive-inotropic score (VIS). The VIS was calculated as:

dopamine dose (µg/kg/min) + dobutamine dose (µg/kg/min) + 100 x adrenaline dose (µg/kg/min) +100 x noradrenaline dose (µg/kg/min) + 10 x milrinone dose (µg/kg/min) (12).

In addition, the patient age at the day of the surgery, ASA anesthesiology risk, intraoperative events and modifications, the length of the intervention and surgery particularities (herniated organs, need for patch suture), immediate complication, long term complication and mortality were also recorded.

To evaluate infection, samples of tracheal aspirate and blood cultures were collected regularly. The results were correlated with the inflammatory and hematological markers, clinical signs of pneumonia or sepsis, and radiographic findings. C-reactive protein (CRP) is not collected in our unit in the first days after surgery as it has been shown that an elevated value is most likely a reaction due to post-operatory inflammation given that the patients can have drainage tubes or be on ECMO.

In terms of organization for the surgery time, there were no major changes in patient care; medication was left in place, ventilation was mainly maintained in HFOV mode, the radiant warmer was switched to matress manual mode and the temperature was monitored via a transcutaneous sensor. Although the risk of hypothermia was reduced by not transporting the patient to the OR, it was considered necessary to evaluate the changes in temperature during the surgery time. As is known, general anesthesia inhibits thermoregulation, and this effect is compounded by the fact that newborns (especially premature) have less brown fat and the skin surface exposed during surgery is proportionally larger relative to older children (13).

Our surgeons are able to perform this type of surgery with minimally invasive methods (laparoscopy, thoracoscopy), but it was considered that these unstable patients could not tolerate CO₂ insufflation, so they were all operated on via an open abdominal or thoracic approach (14). The anesthesiology team used total intravenous anesthesia, mainly midazolam (0.05-0.1 mg/kg/h) and fentanyl (2-10 µg/kg/h), while muscle relaxation was provided during the surgery time using atracurium or vecuronium. Pre- and post-surgery sedation was maintained by intermittent or continuous doses of narcotics and benzodiazepines.

The literature regarding on-site neonatal surgery is limited. While our dataset is affected by the same shortcomings as other studies (e.g., small sample size), our sample is homogenous in terms of weight, gestational age and sex distribution, which further supports the relevance of the results. The control group shares the same characteristics as the operable group with the notable difference that the respective patients could not be operated on.

The data were summarized and analyzed using Excel as part of the Microsoft Office 365 Suite and the results are presented using the relevant descriptive statistics.

The study was approved by the Ethics Committees of the ‘M. S. Curie’ Emergency Clinical Hospital for Children and ‘Carol Davila’ University of Medicine and Pharmacy (Bucharest, Romania). Written informed consent was obtained from the patients in order to use their data for academic purposes.

Results

The study covers a period of 10 years and is based on data collected from 10 newborn patients with CDH surgically operated on-site in the NICU. This represents 12.8% of the total of 78 CDH patients operated on in our clinic during the observation period.

In our test group, both sexes were equally represented, chronologically term newborns, one small and nine appropriate for gestational age (median birth weight 2,691 g; range 2,300-3,300). The type of birth was Cesarean section in 8 cases and spontaneous vaginal birth for 2 cases. Apgar scores ranged between 3 and 8. Six newborns were diagnosed antenatal with CDH [at a main gestational age of 26.5 weeks of gestation (WG)] and 4 of them were uninvestigated pregnancies, and for
this reason the common protocol of intubation immediately after birth was not applied. Two patients were reanimated via positive pressure ventilation (PPV) and intubated in the delivery room for respiratory distress and two of them were intubated after a few hours when the general status had deteriorated.

Relative to the test group, the control sample shared the same characteristics in terms of antenatal diagnostic, gestational age and birth weight. The patients included in the control sample had a relatively lower Apgar score, a higher intubation rate at birth and a higher need for iNO and inotropic medication. This indicated a worse medical condition from the first day of life which, in all cases, rendered the surgical operation not feasible. Table I presents the summarized statistics of both groups of patients included in this study.

Despite receiving adequate treatment for their condition, all patients were respiratory and hemodynamically unstable and received inotropic and vasoactive agents in association of one, two or three drugs. As such, by the time of the surgery, half of the operated patients received adrenaline (main dose 0.08 µg/kg/min), 60% received noradrenaline (main dose 0.8 µg/kg/min), 60% received milrinone (main dose 0.5 µg/kg/min), 70% received dopamine (mean dose 15 µg/kg/min) and 60% were administered dobutamine (mean dose 12 µg/kg/min). Table II presents the simultaneously administered inotropic medication by the time of the surgery for patients that were operated on.

In order to have a more accurate assessment, the Vasoactive‑inotropic score (VIS) was calculated for each group. The VIS is usually used in ICUs to scale the amount of vasoactive and inotropic support and to evaluate the outcome after infant cardiac surgery (15,16) or in pediatric sepsis (17).

We centered the 2 samples for day ‘0’ representing the day of operation for the test group (main day 5) and the last day of survival for the control group (main day 4) to highlight the fact that the patients in the control group were not in the condition to be operated on (the patient with a 28‑day survival due to prolonged ECMO was not considered representative of the group).

The dynamics of the VIS values for the previous 3 days and for the post‑surgery 3 days for the operations are presented in Fig. 3.
consideration the severity of the cases. In 7 cases, the diaphragmatic defect was on the left side, and on the right side for the remaining 3 patients. The survivors were 3 left side CDH and 1 right side CDH newborns, confirming the previous findings in literature that the mortality is higher when CDH is on the right side (18). Regarding the type of surgery, primary repair was possible for 8 patients while the other 2 needed synthetical patch repair due to agenesis of the diaphragm. Both were associated with severe lung hypoplasia and did not survive.

In terms of the CDH anatomy, all our operated cases presented with the small intestine in the thorax. All left side CDH cases presented with herniated stomach and 85% had herniated large intestine and spleen. The liver was herniated in the thorax for 8 out of 10 cases. The other 2 cases (one left and one right side hernias) were also the specific cases exhibiting good outcomes, as the literature also suggests a positive prognosis for non-herniated liver (19,20).

Regarding the associated pathology of the operated patients, 8 cases presented congenital cardiac anomalies, 3 had hypoxic-ischemic encephalopathy and 1 patient was an infant exposed to an HIV-positive mother. All operated patients had persistent pulmonary hypertension and 9 of them associated cardiac failure.

In terms of the non-surgery-related complications, 1 patient had severe pulmonary hemorrhage, 2 patients had sepsis and 1 patient with chylothorax did not survive, while another patient with chylothorax and 1 patient with right jugular thrombosis and hydropericardium correlated with ECMO had good outcomes (Table III).

During surgery, the ventilator settings were maintained with constant maximal parameters for each patient in order to maintain preductal SpO₂ values above 85%. FiO₂ ranged from 65 to 100% (mean 95.5%) and mean airway pressure ranged from 6 to 20 cm H₂O (mean value 12.5 cm H₂O).

Regarding blood gas analyses, the pH values ranged from 7.17 to 7.5 (mean value 7.33). As shown in Fig. 4, 7 patients had a higher post-operative level of lactate, one presented a constant value and 2 had minimally decreased levels. Correlated with the pH level, 6 patients had a mild to severe increase in pCO₂ levels and 4 had a mild pCO₂ improvement. When SpO₂ was analyzed, before and immediately after surgery, 5 patients had an improved level, 2 had a constant level and another 2 had a slight decreasing trend. Since the precision of the capillary samples is insufficient when compared to arterial samples, the gas analyses were conducted in terms of relative improvement or deterioration and not necessarily in absolute value, in line with similar practices reported in the literature (21). A direct correlation between the gas analyses and the outcome was not established except for the 2 patients with the highest lactate levels who died days after the surgery. Several studies have shown that the NLRP3 inflammasome is critically involved in the pathogenesis of inflammation and sepsis in newborns, as well as in bronchopulmonary hypoplasia (22-24). Targeting this pathological pathway may be a future therapeutical target.

The body temperature was maintained within the standard range for all of the patients. The mean HR increased from 169.1 beats/min to 180.3 beats/min (Fig. 4).

Historically, the ECMO procedure could be provided in our clinic since 2016 and for this reason, most patients with severe CDH underwent surgical repair despite the ECMO criteria being met. For 2 patients (both included in the control group) who were on veno-venous ECMO, the surgery was not possible due to severe, unstable respiratory and hemodynamic...
status. However, the only patient under ECMO included in the test group was also the first patient in our clinic who was put on ECMO (veno-venous initially, then veno-arterial due to cardiac failure) and operated on with a good outcome.

The overall mortality rate for the test group (i.e., where on-site surgery could be performed) was 60% due to the severity of the cases. However, the negative outcomes were not determined by perioperative events. In contrast, none of the patients in the control group (i.e., not operated patients) survived more than a mean age of 4 days (range from 1 to 9 days of life, with an extreme of 28 days of life for one patient on ECMO). Other characteristics such as associated comorbidities or complications were not relevant when comparing the groups.

**Discussion**

The present study demonstrated that bedside surgery increases the chances of survival for the most severe congenital diaphragmatic hernia (CDH) cases that cannot be transferred to the operating room (OR). Nevertheless, the OR still provides the most appropriate facilities for surgical procedures. An increasing number of clinics around the world are applying this method and it can therefore be considered a lifesaving practice for unstable patients that cannot be transported to the OR (25-28).

We found that eliminating the stress of transporting newborns to the OR reduces the risk of hypothermia and
maintains the hemodynamic balance. Keeping the same ventilation mode together with continuous NO are important factors in keeping our patients stable, as nitric oxide (NO) and high-frequency oscillatory ventilation (HFOV), cannot be administered during transport or in the OR.

Performing procedures on-site with continuity of care by neonatal medical staff is an additional advantage not only to the patients but also to the anesthetist who may be unfamiliar with the patient's ventilation type mode and medication.

One of the concerns when performing surgery outside the OR is the risk of infection. None of the patients analyzed in our sample suffered from post-operative infection. This can be partially explained by the fact that our NICU is equipped with all the necessary equipment to provide the sterile setup necessary for surgery, as demonstrated also by other authors (29).

The medical literature indicates that there is no ideal time for repairing CDH (30,31). In our case the decision to operate on-site, rather than not to operate at all, was primarily based on expert opinion. The operations were conducted in the neonatal transition period, as soon as the infants were considered physiologically stable for surgery. This approach has a subjective component as no objective method of determining the proper timing has been published to date.

We consider the Vasoactive-inotropic score (VIS) as a reliable marker that can be used to quantify cardiovascular and hemodynamic support, allowing comparison of patient populations across studies.

There are several limitations to this study. The limited case number may have contributed to the nonsignificant difference and heterogeneous characteristics between the operated and unoperated patients. The data were collected retrospectively from patient records and electronic health records and was not designed as a study from the beginning. It was also a single-center study and may not be generalizable to all institutions that care for CDH patients. Further studies should be designed to compare the performing of surgery in the NICU or in the main OR.

In conclusion, our experience indicates that bedside surgery increases the chances of survival for the very severe cases, non-transferable to OR. This conclusion is also confirmed by the comparative analysis with a representative sample of patients for which surgery was not possible to be performed. The possibility to operate on-site is one of the most relevant characteristics that differentiates the test from the control sample, further supporting the conclusion that the intervention seriously influences the survival rate.

Neonatal surgery in the NICU is a safe procedure that can be utilized in cases of neonates with severe respiratory failure, severe pulmonary hypertension and hemodynamically unstable. As such, it is recommended for ICU planners to consider creating the infrastructure needed to conduct on-site surgery in the NICU.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

AEG, CGC, BS, AMB, CMH, MD, FJA, MC and CF were responsible for conceptualization of the research concept. CGC, FDM and RIS performed validation of the data and formal analysis. AEG, CGC, BS, MD, FJA and MC searched the literature for similar work and articles and had major contributions in writing the manuscript. CGC, BS, MD, FJA and MC critically reviewed the manuscript for important intellectual content, edited the manuscript and supervised the research. AEG, CGC and RIS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committees of the ‘Maria S. Curie’ Emergency Clinical Hospital for Children and ‘Carol Davila’ University of Medicine and Pharmacy (Bucharest, Romania) (nr 6/2021).

Patient consent for publication

Written informed consent was obtained from the patients in order to use their data for academic purposes.

Competing interests

The authors declare that they have no competing interests.

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