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A New Approach of Several Minimally Invasive Procedures for Improvement of the Outcome in Preterm Infants

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Abstract

BACKGROUND: Based on the last update of European Consensus Guidelines on Management of Respiratory Distress Syndrome, the following study is new for our clinic approach for minimally invasive respiratory support in preterm infants.

AIM: The aim is to find out if the implementation of several minimally invasive procedures leads to a reduction of the frequency and severity of chronic complications and improved outcomes in extremely premature infants.

MATERIALS AND METHODS: Infants are below 30 gestational weeks, divided into two groups – therapeutic – 37 infants on standardized early respiratory management protocol which includes: High-flow continuous positive airway pressure (20l/min ≥ 15 PEEP) in the delivery room, support of spontaneous breathing and non-invasive mechanical ventilation, avoidance of hypothermia and LISA shortly after birth, and control group – 46 infants that received standard respiratory support (positive pressure ventilation – invasive and non-invasive in the delivery room, most infants ≤ 27 weeks gestational age were intubated and received early surfactant, extubation "when being ready" – usually after few days).

RESULTS: The duration of mechanical ventilation, oxygen therapy, and hospital stay is shorter in the therapeutic group ($p < 0.05$). Severe bronchopulmonary dysplasia is not found in the interventional group, 26% of the patients in the control group have severe form of the disease ($p = 0.001$). Severe intraventricular hemorrhages are found in 11% of the infants in the therapeutic group and 28% in the control group ($p = 0.06$).

CONCLUSION: Due to the changed protocol, we report increased survival of ELBW infants without severe chronic complications. The acute pulmonary injury, acquired in the perinatal period, is directly connected with the development of BPD. For this reason, all the changes that we introduced in our clinic (heat management, support of spontaneous breathing, "open up" lungs – high flow PEEP/CPAP, and LISA during spontaneous breathing) contribute to the lower frequency of severe chronic complications and high percentage of ELBW infants, who do not develop severe BPD.

Introduction

In the era of the current precise medicine with the survival of high percentage extremely low birth weight (ELBW) infants, the frequency of chronic complications – bronchopulmonary dysplasia (BPD), brain hemorrhages, and retinopathy of prematurity, is unacceptably high. Since 2006, a group of leading neonatology experts from different European countries has meetings every 3 years with the main aim to review the most recent literature data and to establish consensus guidelines for optimal treatment of newborns with risk or with developed respiratory distress syndrome (RDS) to reduce the frequency of the chronic complications of prematurity. The first "European Consensus Guidelines for the Management of RDS" was published in 2007 and the last update was in published 2019 [1]. The key points in the consensus are connected with trial-proven practices in the delivery room and the first hours of cardiopulmonary adaptation such as lung protection with non-invasive ventilation – nasal continuous positive airway pressure (nCPAP) and oxygen titration, avoiding hypothermia ($t < 36.5°C$), surfactant replacement therapy as early as possible, and less invasive surfactant administration (LISA). Undoubtedly, LISA is the method of surfactant administration with proven efficiency regarding reduced chronic morbidity and mortality [2], [3], [4].

The following study, based on the last update of the European consensus and the "Viennese concept" (support of spontaneous breathing in the delivery room with side position, tactile stimulation, high-flow CPAP, and early Surfactant, given without intubation with a thin catheter) [2], is new for our clinic complex approach to minimally invasive respiratory support in ELBW infants. The need for a new protocol was based on our disappointing results for the past 5 years before 2019, connected with the high percentage of ELBW infants on mechanical ventilation (nearly 75%), a high percentage (44%) with intraventricular hemorrhages (IVH), and frequency of BPD survivors at 36 weeks gestational age (GA) nearly 60%. We hypothesized that the implementation of several minimally invasive

procedures may lead to a reduction of the frequency and severity of chronic complications and improved outcomes in extremely premature infants.

Materials and Methods

The study was designed as a single-center, prospective trial. For a period of 2 years (between January 2019 and January 2021), 83 ELBW infants that needed respiratory support in the delivery room were followed. The protocol of the study was reviewed and approved by our institutional review committee and was conducted according to the Good Clinical Practice. Written informed consent was signed by the parents. Inclusion criteria were gestational age below 30 weeks and lack of major inborn malformations. Several team members were educated on how to apply the new procedures. The protocol consists of the following changes in our clinical practice:

1. In the delivery room, high-flow CPAP is applied (20l/min≥15 PEEP) with titration of the O_2 concentration (10% steps) according to the values of saturation, and heart rate from pulse oximetry readings every minute.
2. Reinforcement of spontaneous breathing (relaxed positioning, side position, and caffeine citrate 20 mg/kg in the first 20−30 min after admission in neonatal intensive care unit (NICU), no initial positive pressure ventilation, if possible).
3. Stress reduction – waiting for complete stabilization in the delivery room and transport to NICU on nCPAP.
4. Heat loss reduction (immediate wrapping in a polythene bag under a radiant warmer, humidified, and heated gas).
5. Early/prophylactic surfactant application while the baby is spontaneously breathing under nCPAP – LISA (during the first hour after birth).

The patients were divided into two groups, based on whether in the delivery room the baby was supported by an educated team member or not, which was the only criterion for group inclusion. No statistically significant differences were found concerning gender and gestational age, the patients were spontaneously breathing with similar Apgar scores (Table 1).

First group (therapeutic, interventional) – 37 infants on standardized early respiratory management protocol. All parts of the protocol were applied. In the delivery room, we used 20 l/min flow through an appropriate small size mask to achieve 15 cmH_2O positive end expiratory pressure (PEEP), while the baby was spontaneously breathing (side position and caffeine citrate). Stress reduction means that all the patients were transported to the NICU only after full stabilization was achieved (heart rate >100/min and oxygen saturation >85% on pulse oximetry). When admitted to the NICU, temperature was measured and it should be above 36.5°C in order to be normothermic. All patients received surfactant less invasively with a thin catheter (LISA).

Second group (control) – 46 infants, followed retrospectively and prospectively, that received standard respiratory support (positive pressure ventilation – invasive and non-invasive in the delivery room, most infants ≤ 27 weeks gestational age were intubated and received early surfactant, extubation “when being ready” – usually after few days).

The short-term outcome (duration of mechanical ventilation, oxygen therapy, frequency of pneumothorax, and hospital stay) and the long-term outcome (frequency of IVH, BPD all degrees, Retinopathy of prematurity, and death) were analyzed and compared.

Statistical analysis

The statistical analyses were performed using MedCalc for Microsoft Windows (version 20.015, MedCalc). Statistical methods used include descriptive statistical analysis. Mann–Whitney U-test was used for continuous variables. The counting data were represented by n (%). The groups were compared using the Student’s t-test. A two-tailed $p < 0.05$ was considered to point out a statistically significant difference.

Table 1: Perinatal characteristics of the patients

Characteristic*	Therapeutic group (n = 37)	Control group (n = 46)	p
Weight (g)	865 (490–1090)	798 (410–1150)	0.082
GA	27.5 (25–30)	26.8 (24–30)	0.052
Percentage <26+0 weeks GA	10 (27)	16 (34)	0.193
Males, n (%)	18 (49)	28 (61)	0.278
SGA, n (%)	15 (41)	19 (41)	1.000
Apgar score, 1 min	2 (1-4)	2 (1-5)	0.760
Apgar score, 5 min	6 (3-7)	6 (2-7)	0.744
C-section, n (%)	35 (95)	33 (72)	0.009
Antenatal steroids	30 (81)	30 (65)	0.141

*Data are presented as an average value within range in brackets or as number and % (in brackets); student’s t-test, a two-tailed $p < 0.05$ is considered significant. GA: Gestational age, SGA: Small for gestational age.

Results

The patients in the groups have similar perinatal characteristics – gestational age (GA): the average GA in the first group is 27.5 ± 2.5 weeks, while the control group is 26.8 ± 2.5 weeks (Table 1).

Birth weight (BW) is not different in the two groups: The average BW in the therapeutic group is 865 ± 129 g, in the control group is 798 ± 216 g. In both groups, almost 41% of patients are small for gestational age (SGA), half of them with weight below the third percentile for gestational age.

No difference between the groups regarding gender (p = 0.278) and Apgar scores.

Almost all patients (95%) in the therapeutic group are delivered by cesarean section with a difference between the groups (p = 0.009). Antenatal steroids are equally applied in both groups.

Table 2 summarizes the short-term outcome of the patients in the groups. The average mechanical ventilation (both invasive and non-invasive) in the therapeutic group is 7.89 days, in the control group – 36.5 days (p = 0.001), and during the first week of life, only ten infants from the interventional group need invasive mechanical ventilation, while, in the control group, 27 babies are on invasive ventilation (p = 0.041). The patients in the first group receive O_2 for a shorter period than the patients in the control group (p = 0.003).

Table 2: Short-term outcome of the therapy

Characteristic*	Therapeutic group (n = 37)	Control group (n = 46)	p
Mechanical ventilation 1st week (invasive)	10 (27)	27 (59)	0.041
Mechanical ventilation during stay (days)	7.89 ± 8.7	36.5 ± 32.4	0.001
O2 therapy (days)	30.6 ± 18	46.3 ± 26	0.003
PDA	8 (22)	12 (26)	0.797
Pneumothorax	0	3 (6)	0.250
Hospital stay (days)	60.8 ± 21	93.8 ± 41.7	0.001

*Data are presented as number and % (in brackets); Student's t-test, a two-tailed p < 0.05 is considered significant. PDA: Persistent ductus arteriosus.

We report no difference between the groups regarding acute complications such as PDA and pneumothorax (p = 0.797; 0.250).

The hospital stay is shorter in the therapeutic group (60.8 days) than in the control group (93.8 days) with p = 0.001.

Table 3 systematizes the long-term outcome of the therapy and compares the frequency of the most severe chronic diseases–intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), and different degrees of bronchopulmonary dysplasia (BPD) in the groups. In the therapeutic group, we report a 100% survival rate, in the control group 89% of the infants survive with p = 0.062.

Table 3: Long-term outcome of the therapy

Characteristic*	Therapeutic group (n = 37)	Control group (n = 46)	p
IVH (all)	25 (67)	33 (72)	0.810
IVH (severe)	4 (11)	13 (28)	0.060
PVL (cystic)	1 (3)	4 (9)	0.375
ROP (all)	9 (24)	13 (28)	0.804
BPD at 36 weeks – not found	15 (41)	7 (15)	0.013
BPD 36 weeks - mild	15 (41)	8 (17)	0.027
BPD 36 weeks - moderate	7 (18)	16 (35)	0.141
BPD 36 weeks - severe	0	12 (26)	0.001
Death	0	5 (11)	0.062

*Data are presented as number and % (in brackets); Student's t-test, a two-tailed p < 0.05 is considered significant. IVH: Intraventricular haemorrhage, PVL: Periventricular leukomalacia, ROP: Retinopathy of prematurity, BPD: Bronchopulmonary dysplasia.

Severe IVH (3 and 4 grade) have 11% of the patients in the first group, while, in the control group, 28% are with a severe form of the disease (p = 0.060). Regarding PVL, we report no difference between the groups (p = 0.375).

Mild BPD have 41% of the patients in the first group and 41% of the babies in this group lack BPD. Compared with the control group, we report a statistically significant difference regarding the milder and absent BPD (p = 0.027; 0.013). Only moderate BPD is similar in the groups (p = 0.141). The patients in the therapeutic group do not have severe BPD, while this form of the disease is found in 26% of the patients in the control group (p = 0.001).

Discussion

The short-term outcome is determined by the duration of O_2 therapy, mechanical ventilation, acute adverse effects, and survival (Table 2). In the therapeutic group, the duration of the mechanical ventilation and O_2 therapy is shorter compared to the control group. Similar results report Teig *et al*., giving the impression of shorter mechanical ventilation. This contrast could probably be explained with the different therapeutic approach that includes not only the minimally invasive respiratory support but also feeding, antibiotic use, nurse care, etc. [5].

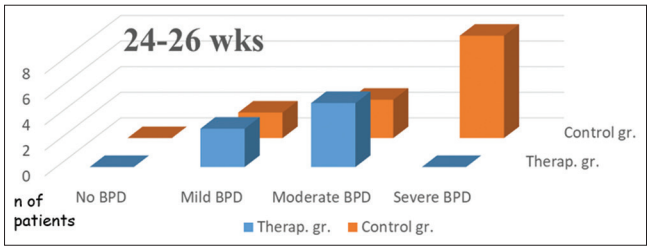

Figure 1: BPD in neonates 24–26 weeks. BPD: Bronchopulmonary dysplasia; wks: Weeks of gestation

Pneumothorax and persistent ductus arteriosus (PDA) are frequent complications in ELBW infants on mechanical ventilation during the early neonatal period. Katrin Klebermass-Schrehof *et al*. report more frequently PDA in their therapeutic group, and no difference in the manifestation of pneumothorax, which is more common for neonates that received CPAP in the delivery room [2]. We find no difference between the groups regarding these acute complications probably because of the relatively small number of patients.

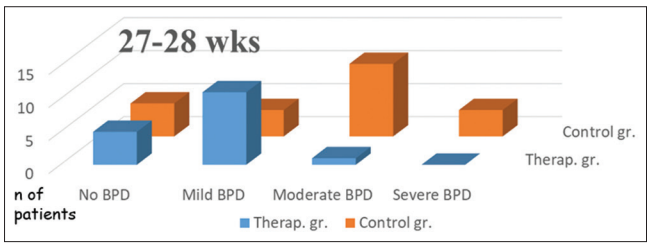

Figure 2: BPD in neonates 27–28 weeks. BPD: Bronchopulmonary dysplasia; wks: Weeks of gestation

Numerous factors determine the duration of the hospital stay, most important of which are the gestational age and the weight of the patients. As the infants from both groups have similar perinatal

characteristics, we assume that the minimally invasive support and the shorter mechanical ventilation and O_2 therapy are probable reasons for the shorter hospital stay of the patients in the first group and their favourable outcome.

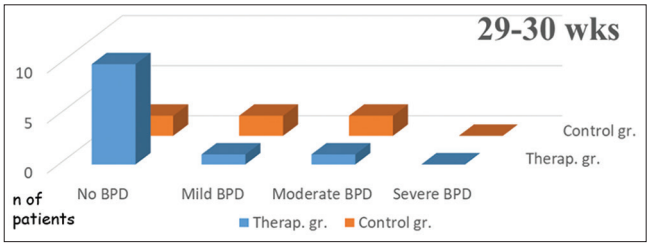

Figure 3: BPD in neonates 29−30 we eks. BPD: Bronchopulmonary dysplasia; wks: Weeks of gestation

The current new approach aimed to improve the survival of ELBW infants with a reduction of severe chronic complications (Table 3). According to a lot of clinical trials [2], [6], LISA could increase the survival of ELBW infants. The founder of the less invasive surfactant administration Angela Kribs *et al*. proves that LISA does not increase survival without BPD, but rather contribute to greater survival without severe degrees of complications [7].

The frequency of IVH (all grades) is high in all patients without difference between the groups. Published data from Pérez-Iranzo *et al*. state that LISA reduces the frequency of severe IVH in premature infants with RDS [6]. Similar results report Katrin Klebermass-Schrehof *et al*. [2]. Our results are borderline concerning the severe IVH ($p = 0.060$). We assume that the difference is due to the relatively smaller number of patients in the groups.

We do not report any difference between the groups concerning the frequency of ROP in contrast to the data from Katrin Klebermass-Schrehof *et al*., who report ROP more frequently in the therapeutic group, which is probably as a result of the increased survival of ELBW infants (≤ 24 weeks) in their trial [2].

The efficiency of the new approach is determined mainly by the changes in the frequency of BPD. The severity of the disease is assessed according to O_2 requirements in 36 weeks of gestation. The final results of our trial determine the high efficiency of the new approach concerning the reduction of severe forms of BPD. The frequency and severity of BPD depend on a lot of prenatal and postnatal factors, mainly the low gestational age. The more premature the baby the most likely it is to develop chronic lung disease [8]. For that reason, we decided to analyze the frequency and severity of BPD in the groups according to the gestational age of the infants (Figures 1-3).

All premature babies 24−26 weeks have different degrees of BPD. While in the control group 61.5% of the patients have severe BPD, in the therapeutic group, most of the patients (62.5%) are with a moderate degree of the disease. We assume that, due to the implementation of the new approach, there are no patients with severe BPD in the smallest extremely premature babies.

Premature babies without BPD are found in both groups at 27−28 weeks of gestation. The main difference is again the severity of the disease. In the control group predominate patients with moderate BPD–46%, while in the therapeutic group, most of the patients are with mild chronic lung disease–65%.

There are no patients with severe BPD at 29−30 weeks of gestation, which constellation is not surprising for these gestational weeks. However, in the therapeutic group, most of the patients do not have BPD–83%, while, in the control group, 33% have moderate and 33% have a mild degree of the disease.

The acute pulmonary injury, acquired in the perinatal period, is directly connected with the development of BPD. For this reason, all the changes that we introduced in our clinic, provide haemodynamic stability, reduce the possibility of acute pulmonary injury and contribute to the lower frequency of severe chronic complications and the high percentage of ELBW infants, who do not develop BPD. Similar results are reported from other authors, who emphasize on completely minimally invasive approach toward ELBW infants during the first “golden” hours after birth [9], [10], [11].

Conclusion

The algorithm changes in our clinic completely correspond to the main idea in the last update of “European Consensus Guidelines for the Management of RDS”. As a result, we report:

1. Significant reduction in days of invasive mechanical ventilation during the hospital stay, many ELBW infants were never mechanically ventilated.
2. Reduction of the duration of O_2 therapy.
3. Shorter hospital stays.
4. Decreased severe morbidity in extremely premature infants–severe BPD and IVH.
5. Significant reduction in mortality in ELBW infants.

We consider that the above-reported data come as a result of:

1. Changed “concept”–heat management, support of spontaneous breathing, “open up” lungs with high flow PEEP/CPAP, LISA during spontaneous breathing.
2. Introduction of a standardized protocol.
3. Educated and experienced team.
4. Improved cooperation between obstetricians, midwives, and neonatologists.

Statement of Ethics

Written informed consent for publication was obtained from the parents. The protocol of the study was reviewed and approved by our Institutional Ethical Committee and was conducted according to the Good Clinical Practice.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

P.R. conceived the work performed the literature search, substantially participated in data acquisition, interpretation, and analysis; she finally reviewed the manuscript critically for important intellectual content. V.D. managed the clinical cases, provided data for the paper, and critically reviewed the manuscript for important intellectual content. All authors approved the final version of the report.

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