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IMPACT OF PERMISSIVE HYPERCAPNIA ON RESPIRATORY AND NON-RESPIRATORY OUTCOMES IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME

Paediatrics

Sabina Terzic Neonatal intensive care unit, Pediatric clinic, Clinical center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Suada Heljic Neonatal intensive care unit, Pediatric clinic, Clinical center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

INTRODUCTION: Respiratory distress syndrome (RDS) is significant cause of morbidity and mortality amongst preterm infants. Permissive hypercapnia (PH) is ventilation strategy that could be sparing for immature lungs, but its effects have not been studied enough.
AIM: The aim of this paper is to explore impact of PH on respiratory and non-respiratory outcomes in preemies with RDS.
METHODS: The study was conducted in University hospital in Sarajevo, Bosnia and Herzegovina. Inclusion criteria were fulfilled by 158 infants, classified into hypercapnia (69) and normocapnia (89) group. We analyzed respiratory and non-respiratory outcomes.
RESULTS: We have found shorter duration of respiratory support in PH group. There were no differences in BPD, ROP, NEC, IVH, pulmonary leaks and bleedings, sepsis, duration of hospitalization, nor lethal outcome.
CONCLUSIONS: PH could reduce respiratory support of preterm infants with RDS, but not sufficiently to reduce BPD. It has no influence on evaluated non-respiratory outcomes.

KEYWORDS

RDS, permissive hypercapnia, respiratory and non-respiratory outcomes

INTRODUCTION

According to WHO [1] it is estimated that every year there is 15 million preterm births, and this number is growing. Despite great improvements in treatment, these children keep having greater mortality and morbidity rates, as well as long term disabilities. Considering the fact that respiratory distress syndrome (RDS) is the most commonly treated disease in NICUs, many activities were done on its prevention and therapy. Prevention of preterm birth and antenatal steroid use have the major influence. Still, a lot of prematurely born babies need surfactant replacement and invasive ventilation. Although lifesaving, invasive ventilation carries a great risk for bronchopulmonary dysplasia[2] and ventilator induced lung injury. It also extends duration of hospital stay, and risk for infection. One of the proposed measures to minimize lung injury during mechanical ventilation is strategy of permissive hypercapnia that allows PaCO2 levels above normal (>50mmHg, or 6.6 kPa), and accelerates weaning form the ventilator. Studies have found less BPD and less lethal outcomes at the age of 36 weeks[3]. However its impacts are not yet well studied, and there are no clear recommendations for its use. The aim of this study is to enrich knowledge of permissive hypercapnia's impact in preterm babies.

PATIENTS AND METHODS

This study was conducted at University hospital in Sarajevo, Bosnia and Herzegovina. It included 158 prematurely born infants with RDS. Patients were divided in two groups: 1) permissive hypercapnia (PH) - patients whose PaCO2 values in > 60% of the blood gases were 6.6-8.0 kPa, 2) normocapnia (NC)- patients whose PaCO2 in > 60% of the blood gases were 4.6-6.6 kPa. PH had 69 (43.7%) patients, and NC 89 (56.3%). At admission we registered data regarding BW, GA, Apgar score, CRIB score, prenatally given steroids. RDS was treated according to European guidelines for management of RDS using nasal continuous positive airway pressure (CPAP), conventional mechanical ventilation, or high frequency oscillatory ventilation. When indicated, we have used bovine surfactant (Survanta®). Patients were graded as heavy respiratory distress syndrome when they needed surfactant and/or mechanical ventilation, or mild without it. We have collected and analyzed data of duration of respiratory support, oxygen dependency, respiratory (pneumothorax, pulmonary bleeding, BPD), and non-respiratory complications (ROP, NEC, IVH, EOS, LOS, duration of hospital stay, and survival).

Kolmogorov-Smirnov test has been used for estimation of possible sample deviation from normal distribution. Independent samples t-test was calculated to compare observed clinical parameters between PH and NC groups. When samples have deviated statistical significant values from normal distribution, Mann-Whitney (MW) test was additionally applied. Chi square test was used for comparing frequency data. Statistical tests were carried out at the 5% significance level. All statistical analyses were implemented within MedCalc® software ver. 17.2.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Two groups did not differ regarding gestational age (29.2 ± 3.08 in PH vs. 28.29 ± 3.01 in NC group). BW was statistically significantly higher in PH group comparing to NC (1,539 ± 584 vs. 1,348 ± 504). There was no statistically significant difference between groups regarding mode of delivery (P=0.62), proportion of inborn patients (P=0.95), condition at birth (CRIB score P=0.3, Apgar score P (1') = 0.26, P (5') = 0.29), antenatal steroid use (P=0.53), surfactant use (P=0.94) or the severity of RDS (P=0.49) (Tab.1).

Table 1. Population Characteristics

	Hypercapnia group	Normocapnia group	p		
Gestational age (weeks) mean±SD	29.2± 3.08	28.29±3.01	0.08		
Birth weight (grams) mean±SD	1538.55±584.0	1347.47±504.39	0.0290		
Cesarean section	38/69 (55.07%)	45/89 (50.56%)	0.62		
Inborn patients	54/69 (78.26%)	70/89 (78.65%)	0.95		
CRIB score mean (range)	2.66 (0-17)	3.29(0-23)	0.3		
Apgar 1	5.40 ± 2.39	4.96 ± 2.43	0.26		
Apgar 5	6.40 ± 2.26	6.02 ± 2.11	0.29		
Antenatal steroid use No (%)	25/69 (36.23%)	28/89 (31.46%)	0.53		
Surfactant use No (%)	36/69 (43.7%)	47/89 (56.3%)	0.94		
Respiratory distress sy	Mild	Severe	Mild	Severe	0.49
	41/69	28/69	53/89	36/89	

We have found statistically significant difference between groups regarding duration of mechanical ventilation 5.84 vs. 8.2 (P=0.0163), CPAP days 3.67 vs. 4.71 (P<0.0001), and overall oxygen dependency 11.38 vs. 15.41 (P=0.0097), all favouring hypercapnia group. There was no difference in respiratory complications: pneumothorax P=0.68, and pulmonary bleedings (P=0.25). Children with pulmonary bleeding needed more time on mechanical ventilation if belonged to

NC group, it was not the case in PH group (Kendall's Tau=0.104, P=0.2127). Groups did not differ regarding BPD (P=0.20), ROP (P=0.55), NEC Bell stage <IIIA (p=0.85), NEC Bell stage ≥IIIA (P=0.85), IVH≥III/cystic PVL (P=0.07), EOS (P=0.6), LOS (P=0.18), duration of hospital stay (P= 0.36), and survival (P<0.9).

TABLE 2. RESPIRATORY AND NON-RESPIRATORY OUTCOMES

	Hypercapnia group	Normocapnia group	p
Days on mechanical ventilation mean (range)	5.84 (1-47)	8.20 (0.5-56)	0.0163
CPAP days mean (range)	3.67 (1-14)	4.71 (0.5-34)	<0.0001
Overall oxygen dependency (days) mean (range)	11.38 (1-85)	15.41 (1-100)	0.0097
Pneumothorax No (%)	5/69 (7.24%)	8/89 (8.98%)	0.68
Pulmonary bleeding No (%)	3/69 (4.34%)	8/89 (8.98%)	0.25
BPD No (%)	8/69 (11.6%)	17/89 (19.1%)	0.20
ROP No (%)	1/53 (1.9%)	2/52 (3.8%)	0.55
NEC Bell stage <IIIA No (%)	6/69 (8.7%)	12/89 (13.5%)	0.34
NEC Bell stage ≥IIIA No (%)	2/69 (2.9%)	3/89 (3.4%)	0.85
IVH≥III/cystic PVL No (%)	6/69 (8.69%)	18/89 (20.22%)	0.07
EOS No (%)	2 (2.89%)	4 (4.49%)	0.60
LOS No (%)	18 (26.08%)	32 (35.95%)	0.18
Duration of hospitalization (days) mean (range)	28.36 (1-197)	32.33 (1-135)	0.36
Death No (%)	20/69 (28.99%)	25/89 (28.09%)	>0.9

DISCUSSION

This paper is an attempt to make contribution to medical knowledge regarding the optimization of ventilation of premature infants, with focus on permissive hypercapnia. Despite lack of clear recommendations, it seems that this strategy has already found its place in clinical practice, because hypocapnia is relatively uncommon during mechanical ventilation, while hypercapnia is more often found[4].

There were 158 patients in this study, 43.7% (69) in PH, and 56.3% (89) in NC group. We had 48.7% female babies. Groups were similar according to population characteristics as it is seen in table 1.

During this study 106 infants were mechanically ventilated, 46 of them in HC and 60 in NC group. Total days of mechanical ventilation were 941, (449 in PH, and 492 in NC group). Mean value was 5.8 days in PH and 8.2 in NC. Mann-Whitney U= 1004.00, P=0.0163. These data are similar to previous studies[5,6]. In recent literature we can found different duration of mechanical ventilation in preterm infants with RDS, which depends on lots of factors like prenatal care, level of intensive care, treatment protocols, etc. Trend of shortening of this time is obvious and according to Ceylan[7] it is 77.3 hours. We explain longer duration of ventilation by poor antenatal steroid coverage: 33.54% in total. High frequency oscillatory ventilation was conducted in 7 children (4 in PH, 3 in NC group). Statistically significant shorter time on CPAP in PH group is also proved (3.6 vs. 4.7), Mann-Whitney U=1154.00, P=0.0012.

Duration of oxygen therapy (via nasal cannula, hood, etc.) was analyzed, with mean time on oxygen 9 days in PH group, range 1-65, and 9.47 in NC group, range 1-52 days. The difference was significant-Mann-Whitney U=725.50, P=0.0066. One of the very rare studies on permissive hypercapnia and oxygen use is above mentioned Marriani[5] study that found mean duration of oxygen therapy 15 days in PH and 32 days in NC group. Comparison with this study is limited by the fact that at the time of Marriani[5] study CPAP application was not in use as it is recently. Overall oxygen use is significantly shorter in PH group P=0.0097. There was less BPD in PH than in NC group, 8/69 (11.6%) vs. 17/89 (19.1%), but with no statistical significance (P=0.20). In PH group there were 5 patients with pneumothorax (7.24%), in NC group 8 patients (8.98%). All of them were treated with chest drain. Overall incidence was 8.22% which is similar to other studies[8-10], and more then data from Vermont Oxford Network Database, 2014[11] (4.1%) and data from the recent study[12] from our institution: 5%. There were more air leaks in NC group, but the difference is without significancy (P=0.68), making higher PaCO2 levels not more risky for pneumothorax. There is no reduction of mechanical ventilation (P=0.92), nor overall oxygen support (P=0.69) in patients with pneumothorax. Pulmonary bleeding is found in 3% to 5% preterm, artificially ventilated infants with severe form of respiratory distress syndrome, who often have open duct, and who have been given surfactant[13]. In our study, overall incidence of pulmonary bleeding was 11/158 or 6.96% with 3 cases in PH and 8 in NC group. Although absolute number is higher in NC group, difference is not of significance (P=0.25). According to literature[14,15] mortality caused by pulmonary bleeding reaches 81.25%, OR = 7.24. In our study it was 72.72%; RR=2.89 (95% CI=1.83-4.56, z=4.55, P<0.0001), OR=7.9 (95%= 1.998-31.457, z=2.944, P=0.0032). When mechanically ventilated, patients with pulmonary bleeding in PH group had less ventilation days comparing to patients in NC group.

PH did not affect non-respiratory outcomes (IVH/PVL, NEC, ROP) (table 2). These findings are similar to previous studies[5,16]. Groups were similar in context of infection (early and late onset sepsis), P=0.6 and P=0.18 respectively. Although we proved that PH shortens overall oxygen dependency, it did not significantly affect duration of hospitalization 28.36 (1-197) vs. 32.33 (1-135) days, P=0.36. There were 20/69 (28.99%) lethal outcomes in PH and 25/89 (28.09%) in NC group, P>0.9.

CONCLUSIONS

PH could reduce respiratory support and overall oxygen dependency of preterm infants with RDS, but not sufficiently to reduce BPD. However, it is as safe as normocapnia in meanings of pneumothorax and pulmonary bleeding. It has no influence on analyzed non-respiratory outcomes.

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