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Invasive Lung Ventilation in the Patients with Sepsis and Mild Acute Respiratory Distress Syndrome Aggravates Sepsis Course

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Abstract: ***Research on the comparative efficacy of artificial lung ventilation in the patients with sepsis and mild acute respiratory distress syndrome under various regimens is the issue of today. The actual view on the topic being diverse, in most scientists view further research is needed. The objective of the research has been to compare the treatment outcomes of the patients with severe neurotrauma, sepsis, and mild acute respiratory distress syndrome (ARDS), depending on whether forced ventilation with regulated volume or non-invasive ventilation (NIV) is used as the regimen of ventilation support. Materials and methods: Involved in the randomized multicenter research were 60 men (mean age 43.8+8.6 years) with craniocerebral trauma, sepsis, and mild ARDS. The patients were divided into 2 groups (30 men in each) using random distribution method. In group 1, synchronized intermittent mandatory ventilation (SIMV) with regulated volume was used, whereas in group 2 continuous positive airway pressure (CPAP) was applied. Excluded from the research were those with impairment of consciousness, unstable hemodynamics, and X-ray evidence of pneumonia. In SIMV forced ventilation, respiratory volume was based on 4-6 ml/kg, the plateau level not exceeding 30 mbar, 8 mbar positive end-expiratory pressure (PEEP) being applied. Non-invasive lung ventilation was performed at 8 mbar PEEP, up to 15 mbar support pressure, the maximum pressure not exceeding 30 mbar. Results: In comparison with invasive lung ventilation, application of non-invasive lung ventilation in the patients with severe craniocerebral trauma, sepsis, and mild ARDS has been shown to contribute to the improvement of disease course, revealing itself in 1.32 times leukocytosis decrease, 2 times reduction in the blood serum procalcitonin content, as well as in 5 and 3 times decrease in the incidence of ventilator-associated pneumonias and mortality rate, respectively. Conclusion: Our findings taken into consideration, it may be concluded that application of non-invasive lung ventilation in the patients with mild ARDS and sepsis is appropriate, this treatment technique decreasing both the risk of ventilator-associated pneumonias and mortality rate. It can be argued that the application of non-invasive lung ventilation reduces the activity of septic process.***

Keywords: acute respiratory distress syndrome, non-invasive lung ventilation, sepsis

1. Introduction

Treatment of patients with ARDS as sepsis manifestation or aggravation is a burning problem. According to Dellinger RP, Levy MM., 2012 [1], sepsis is found roughly in 30 million people every year, 6 million cases being lethal. On the average, sepsis is diagnosed in about 30 percent of intensive therapy unit patients, the lethality rate being about 46 percent with the developing dysfunction of 2 organs or body systems, and 76 percent – when 3 organs or systems fail [2]. Statistically, 30 percent of septic patients develop ARDS. Artificial lung ventilation is a basic method of ARDS treatment with A evidentiary level, a regimen and parameters used being a critical point. According to most scientists, forced ventilation with the respiratory volume, based on 4-6 ml/kg b.w., the plateau pressure not exceeding 30 mbar, is an advisable ventilation regimen for the patients with ARDS as sepsis manifestation or aggravation [3]. Ventilator-associated pneumonia is known to be one of the first complications and frequent cause of death among the patients under artificial lung ventilation, non-invasive lung ventilation (NIV) being an effective method of prevention [4]. Some authors, in particular, Hodgson C., 2018 [5], believe it is possible, with reservations, to use NIV in mild ARDS, concurrently restricting the application of the method by certain conditions, primarily disorder of consciousness and unstable hemodynamics. As we see it, research on the comparative efficacy of artificial lung ventilation, both forced and NIV, is an essential issue of today.

The objective of the research has been to compare the treatment outcomes of the patients with severe neurotrauma, sepsis, and mild acute respiratory distress syndrome (ARDS), depending on whether forced ventilation with regulated volume or non-invasive ventilation (NIV) is used as the regimen of ventilation support.

2. Materials and Methods

Randomized multicenter research included 60 men (mean age 43.8+8.6 years) with acute craniocerebral trauma, sepsis, and mild ARDS. Anaesthesiology and intensive therapy units of the Ternopil University Hospital and Khmelnytsky Regional Hospital provided the basis for the research. Sepsis was diagnosed in the presence of the corresponding criteria, according to the sepsis conciliatory definition 2016, [6]. Mild ARDS was diagnosed on the basis of corresponding X-ray evidence and respiratory index reduction below 300 and above 200 mm Hg.

Microbiological wound discharge and blood testing for all patients was done prior to grouping. Gram-negative flora was found in 24 patients of group 1 and in 25 patients of group 2. Prevailing were Enterobacteriaceae or Acinetobacterbaumannii, which are sensitive to III, IV generation cephalosporins, as well as to aminoglycosides and carbapenems. Combination of cephalosporin and aminoglycoside was mostly applied as chemotherapy.

The patients were divided into 2 groups (30 men in each) using random distribution method. In group 1, forced invasive ventilation with regulated volume (SIMV) was applied. In group 2, NIV was applied as CPAP. Ventilation was performed with the use of Drager-Carina ventilator. Excluded from the research were the patients with disordered consciousness (below 13 on the Glasgow scale), as well as those with unstable hemodynamics or having X-ray evidence of pneumonia. In SIMV forced ventilation, respiratory volume was based on 4-6 ml/kg, the plateau level not exceeding 30 mbar, 8 mbar positive end-expiratory pressure (PEEP) being applied [7]. Non-invasive lung ventilation was performed at 8 mbar PEEP, up to 15 mbar support pressure, the maximum pressure not exceeding 30 mbar [8].

The amount of leukocytes in the peripheral blood and blood serum procalcitonin content was tested prior to the lung ventilation. First, mean values for all patients were calculated before grouping, regardless of the group they got into. In a week of ventilation, the patients of both groups were assessed with a view to the number of ventilator-associated pneumonias and peripheral blood leukocytes, as well as for peripheral blood procalcitonin content and the value of respiratory index.

Statistical processing included calculation of mean arithmetic values (M) and standard deviation (SD). The data array was tested for normal distribution using the Shapiro-Wilk test. Source data having normal distribution, Student t-distribution was used to determine statistical significance of different mean values. The levels of statistical significance were calculated, the changes regarded as significant at $p<0.001$. Microsoft Excel 2010 and Statsoft STATISTICA 10 programs were used for calculations. Clearance from the bioethics commission of Ternopil State National Medical University has been got.

3. Results and Discussion

Since all the patients had ARDS-aggravated sepsis, they revealed leukocytosis (on average $14.6 \cdot 10^9$/l), blood calcitonin content increase to 1.62 ng/ml, and decrease of respiratory index to 219.4 mm Hg.

Application of various lung ventilation regimens was accompanied by the changes in the values:

Table 1: Description of patients with severe craniocerebral trauma, sepsis, and mild ARDS in relation to the type of lung ventilation applied

	Before treatment	A week after ventilation in the regimen	
		SIMV	CPAP
Respiratory index	219.4±11.6	259.2±26.4	316.5±16.2*
mm Hg			
Blood	1.62±0.18	1.59±0.24	0.80±0.19*
ng/ml procalcitonin,			
Amount of leukocytes in peripheral blood $\cdot 10^9$/l	14.6±1.3	14.6±2.0	11.0±1.0*
Number of the patients with ventilator-associated pneumonia	0	5	1
Number of the patients who died	0	3	1

Footnote: *- reliable difference as compared with a previous group

Respiratory index is one of the main indicators which characterize the state of respiratory function [3]. Its reduction below 300 mmHg is regarded as a basic ARDS diagnostic criterion. The more evident hypoxia is, the more significant is respiratory index reduction. Respiratory index growing at the background of the treatment is an evidence of decreasing hypoxic processes. Though observed in both groups, respiratory index increase (1.44 times) was reliable at the background of NIV only. Respiratory index in the patients, who had been treated for a week with NIV, was 1.22 times the value in those who had undergone forced SIMV ventilation.

Blood procalcitonin content increase above 0.2 nmol/l is considered to be an evidence of sepsis. Prior to the treatment, we have noted blood serum procalcitonin content increasing to 1.62 nmol/l. Application of invasive lung ventilation has not been found to reduce procalcitonin content. The use of NIV resulted in reliable 2.03 times decrease in procalcitonin content. Blood serum procalcitonin content in the patients after NIV treatment was half the amount ($p<0.001$) at the background of SIMV ventilation.

Increasing blood procalcitonin content is indicative either of activated systemic infection or of the poor efficiency of antimicrobial therapy [9]. Thus, as compared with invasive ventilation, the application of NIV has been found to provide more effective treatment alongside with reliable decrease in the septic activity.

The similar conclusions can be drawn based on the analysis of changing amount of peripheral blood leukocytes. No changes in this indicator have been noted at the background of one week treatment using invasive lung ventilation, whereas NIV has been found to provide

reliable 1.32 times decrease (P<0.001) in the amount of blood leukocytes.

The incidence of ventilator-associated pneumonias at the background of forced ventilation was 5 (16.6%) against 1(3.3%) at the background of NIV, that is 5 times as many. According to Spalding M., et al., 2017 [10], ventilator-associated pneumonia occurs in 3% of patients every of the first 5 ventilation days, then in 2% of patients every day after. This statistics accepted, in 7 days of ventilation the morbidity rate for ventilator-associated pneumonia would have been 19%. However, in this research the morbidity rate was 16.6% for the patients with invasive lung ventilation that is a little lower than estimated theoretical value. NIV application resulted in the significant decrease in the probability of ventilator-associated pneumonia development.

More aggressive course of sepsis and increased mortality rate in the group with invasive lung ventilation can be attributed to the development of ventilator-associated pneumonia. NIV resulted in the death of one patient (3.3 percent of the total number in the group), whereas three patients died at the background of forced ventilation (10 percent). The procalcitonin level at the background of forced ventilation being reliably higher than that in NIV, it can be argued that the course of sepsis under forced ventilation was more aggressive. With septic patients having compromised immune system and invasive ventilation contributing to the development of ventilator-associated pneumonia, the role of invasive ventilation as a sepsis-aggravating factor becomes clear enough. It contributes to the development of pneumonia which aggravates the course of sepsis, the latter revealing itself in the increased procalcitonin level and amount of leukocytes in the blood, eventually increasing mortality rate.

Our findings make it reasonable to revert to the issue of NIV expediency for the patients with sepsis and light ARDS. To begin with, it is appropriate to cite the current views on the topic. It is worth noting that most of previous studies dealt with the issue of NIV application for the ARDS of various severity as the possibility in principle, the views of the scientists being different enough.

Sevransky J.E. et al., 2004 [11], failed to give a definite answer to the question whether the NIV application for the patients with sepsis and ARDS is possible and advisable. They recommended compulsory application of PEEP and respiratory volumes (4-5 ml/kg b.w.) for the ventilation of a corresponding cohort of patients. Meta-analysis by Agarwal R. et al., 2006 [12], argued that addition of NIV to the standard ARDS treatment would not eliminate necessity in the endotracheal intubation together with having no effect on the patients survival rate. Due to considerable heterogeneity of results, research findings were diverse. To clear up the issue, the authors concluded the need for extensive randomized controlled studies.

Nava S. et al., 2011 [13], studied NIV efficacy for the patients with ARDS of various severity. To the authors' mind, application of NIV as an alternative for invasive ventilation in the patients with severe or moderate ARDS is discouraged. The authors advocate NIV application for the treatment of hemodinamically stable patients with light ARDS. The researchers consider that NIV application may be very beneficial for the patients with reduced immunity in view of the fact that intubation greatly increases the risk of infection, pneumonia, and death in this group. In the authors' opinion, NIV application for the patients with severe or moderate ARDS is a problem, mostly for safety considerations owing to the need for urgent intubation in case of abrupt decline in the patients' health state. On the whole, the authors recommend cautious approach to the NIV application for the treatment of patients with ARDS.

Bello G. et al., 2012 [14], stand for NIV application as a first-line method for the treatment of mild ARDS, combined with the immunosuppression of various origin.

In a prospective randomized controlled research Wang X. et al., 2014 [8], compared the period of ARDS patients stay on the artificial lung ventilation at the background of SIMV forced ventilation and NIV, decrease in the period of stay on ventilation for NIV-exposed patients having been noted.

Tucci M.R., Costa E.L., 2016 [15], think that application of NIV in ARDS is not preferable as compared with invasive ventilation. However, in view of diverse findings they recommend that the issue should be further studied.

Meta-analysis of the treatment outcomes of 227 patients with ARDS by Luo J. et al., 2016 [16], argued that NIV application had no effect on the mortality rate in the corresponding cohort of patients.

Grassi A. et al., 2017 [17] stick to the opinion that, though possible in ARDS, NIV application involves thorough selection of patients, since in some cases it may result in deterioration of the health state that would require urgent intubation. The latter may be accompanied by the complications capable of both deteriorating treatment outcomes and increasing mortality rate. In the authors' opinion, death rates at the background of forced ventilation and NIV are similar.

The above-mentioned views and our findings taken into consideration, the reasonability for the application of NIV in septic patients with mild ARDS should be concluded as it contributes to the decrease both in the risk of ventilator-associated pneumonias and in the mortality rate. It can be argued that owing to this septic activity declines, whereas treatment results improve.

4. Conclusions

In comparison with forced invasive lung ventilation, the application of non-invasive lung ventilation in the patients with severe craniocerebral trauma, sepsis, and mild ARDS has been shown to contribute to the improvement of disease course, revealing itself in 1.32 times leukocytosis decrease, 2 times reduction in the blood serum procalcitonin content, as well as in 5 and 3 times decrease in the incidence of ventilator-associated pneumonias and mortality rate, respectively.

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