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Mortality Rate in Mechanically Ventilated Neonates: A Developing Country Experience

Wesam A. Mokhtar[1], Laila M. Sherief[1], Naglaa M. Kamal[2*], Sherief EA Kamel[1]

1. Pediatric Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
2. Pediatric Department, Faculty of Medicine, Cairo University, Cairo, Egypt

ABSTRACT

Background: Although a great improvement has been achieved in the outcome of sick neonates with the effective widespread introduction of mechanical ventilation in neonatal intensive care units, a significant proportion of high fatality is still detected among such patients. This study was conducted to identify the complications, outcome, and causes of death among a sample of critically ill Egyptian neonates subjected to mechanical ventilation using pressure-controlled mode.

Methods: The statistical population of this study were prospectively enrolled in the current study and consisted of 240 eligible patients fulfilling the study inclusion criteria. Those with multiple congenital malformations or post-surgical cases were excluded from the study. The data regarding medical record, clinical examination, indication for mechanical ventilation, complications related to mechanical ventilation, and outcome were collected, recorded, and analyzed.

Results: The incidence of complications related to mechanical ventilation was obtained at 104 (43.3%), and VAP observed an increase (20%). Furthermore, the complications related to disease patterns were reported to be 56.7% and 22.5% for sepsis and septic shock. It has been revealed that 124 (51.7%) of the studied neonates had favorable outcomes; however, the remaining 116 (48.3%) of the subjects passed away with a significant increase in the incidence of VAP (P=0.013). It was reported that smaller gestational age and lower birth weight were the most significant risk factors.

Conclusion: In Egypt; as a developing country, the mortality rate among critically ill neonates undergoing mechanical ventilation with pressure-controlled mode was significantly high, approaching 48.3%, with VAP being the most common cause of death.

Keywords: Mechanical ventilation, Mortality, Neonates

Introduction

It is well emphasized that the neonatal period is an extremely sensitive period of life due to the presence of specific medical and health problems that occur mainly in those born prematurely or with low birth weight (1). It has been reported that among the 130 million neonates born annually worldwide, 4 million cases die in the early first 4 weeks of life (2). In developed countries, the main cause of mortality in the early neonatal period is congenital anomalies which are chiefly non-preventable. However, in developing countries, prematurity, infections, and birth asphyxia are still predominant (3) with the mortality rate ranging 40-60% (4).

Mechanical ventilation (MV) is a fundamental part of intensive care services (5). Its widespread use in neonatal intensive care units (NICU) has been associated with cardinal improvement of the survival of critically ill neonates (6). There has been a dramatic decline in neonatal mortality rate in developed countries due to the availability of MV and the introduction of surfactant and total parenteral nutrition (7). Nevertheless, the effective functioning of NICU not only depends on expensive high technology equipment and complex infrastructure but also on medical and nursing expertise and multidisciplinary support team of laboratory and radiological services (4).

The outcome of ventilated neonates is dependent on several factors, such as the primary

* *Corresponding author:* Naglaa M. Kamal, Pediatric Department, Faculty of Medicine, Cairo University, Cairo, Egypt. Tel: 00966565580081; Email: Nagla.kamal@kasralainy.edu.eg

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disease condition, gestational age, birth weight, and associated comorbid clinical conditions (8). There are inadequate data about the outcome of neonates undergoing MV in developing countries, including Egypt. Therefore, this study was conducted to investigate the outcome of MV using pressure-controlled mode in critically ill Egyptian neonates and causes of mortality and its risk factors. The current study primarily aimed to assess mortality risk factors related to MV in mechanically ventilated neonates in Egypt. Other comorbidities and complications related to underlying diseases encountered during the period of MV were considered as secondary objectives.

Methods

This prospective cohort study was conducted at the NICU of Zagazig University Children Hospital, Egypt, from January 2017-June 2018. The population of this study consisted of all critically ill neonates receiving mechanical ventilation with pressure-controlled mode. Both term and pre-term neonates were entered into the study, excluding those with multiple congenital malformations or post-surgical cases.

Although the volume-targeted mode is one of the most important lung-protective strategies in neonates, in this study, it was necessary to exclude patients ventilated using this mode since its highly scarce application makes the interpretation of their data extremely difficult. This was one of the limitations of our study imposed by financial constraints, with the incomplete renovation of our NICU with only a scarce number of ventilators equipped with this mode in our unit.

The medical records of all patients were obtained and they were subjected to full clinical examination, which included gathering information about gender, gestational age, age on admission, weight on admission, mode of delivery, history of maternal illness and drug intake during pregnancy, history of antenatal maternal steroids intake, the need of resuscitation at birth, primary diagnosis on admission, and an indication of MV. The occurrence of any complications during MV was recorded, among which can be mentioned as pneumothorax, hospital-acquired infection, ventilator-associated pneumonia (VAP), chronic lung disease, failure of extubation, and pulmonary hemorrhage.

Ventilator-associated pneumonia is defined by the Center for Disease Control and Prevention as new and persistent radiographic infiltrates and worsening gas exchange in those who are ventilated for at least 48 h and who exhibit at least 3 of the following criteria: temperature instability with no recognized cause, leukopenia/leukocytosis, new onset of purulent secretions or change in the characteristic of respiratory secretions or increased respiratory secretions or increased suctioning requirements, apnea/tachypnea/respiratory distress, and bradycardia/tachycardia.

Failure of extubation after the improvement of the underlying disease and in the absence of sepsis was considered as a complication of MV and was mainly attributed to prolonged ventilation and localized laryngeal edema. The other cases that were also recorded included other comorbidities, such as shock, acute kidney injury, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, any other complications related to the underlying disease pathophysiology, natural history, and those not attributed to MV. Investigations were performed according to the international guidelines and protocols specific to the underlying diseases.

Neonates with respiratory failure or persistent apnea require assisted mechanical ventilation. Indicators of respiratory failure include (1) arterial blood pH of < 7.20, (2) arterial blood partial carbon dioxide pressure of 60 mmHg or higher, or (3) oxygen saturation of < 85% at oxygen concentrations of 40-70% and continuous positive airway pressure of 5-10 cm H_2O (9).

Time-cycled pressure-limited ventilation with synchronized intermittent mandatory ventilation mode (SIMV), synchronized intermittent positive pressure ventilation mode as primary modes, and pressure support ventilation mode as a weaning mode were the main ventilator modes used in this study. Ventilation parameters and variables were individualized according to the underlying cause of MV, lung compliance, and mechanics.

High-frequency oscillatory ventilation was utilized for 20 patients, among which 6 cases had severe respiratory distress syndrome (RDS) and/or congenital pneumonia, 6 subjects had air-leak syndromes, and 8 patients had a failure of conventional ventilation. Lung protective strategies were strictly followed during the period of MV; however, it was impossible to use volume-targeted mode as the main ventilatory mode due to the lack of enough ventilator machines providing this mode in our unit. Data were collected and recorded by physicians every 8 h (at every NICU shift) and more frequently in case of any new events to identify outcomes and causes of death. Patients were classified into the two groups of survived and passed away based on the outcome.

This study was carried out in accordance with the ethical standards of the Helsinki Declaration of 1964 as revised in 2008 and was approved by the local Ethics Committee of Faculty of Medicine, Zagazig University, Egypt. Informed consent was obtained from all patients' guardians for agreement to enroll their neonates in the study and for publishing study results.

Statistical Analysis

The collected data were computerized and analyzed in SPSS software (version 18.0) using frequencies and relative percentages to represent qualitative data and median (interquartile range) for quantitative data, which was not normally distributed. Moreover, the Chi-square test and fisher's exact tests were used to calculate differences between qualitative variables in different groups. Mann-Whitney U test was also applied to calculate differences between non-parametric qualitative variables in the two groups. A p-value of 0.05 was considered significant.

Results

A total of 240 critically ill mechanically ventilated neonates (140 males and 100 females) were eligible for the study. The general neonatal and maternal demographic data and disease characterization of the study group are presented in Table 1. Accordingly, 55% of patients were born

Table 1. Demographic data and disease characteristics of the study subjects

Data	n=240	%
Neonatal general characterizations		
Gender		
Male	140	58.3
Female	100	41.7
Gestational age categories		
Severe (very) preterm (28-32 weeks)	92	38.3
Moderate (late) preterm (33-36 weeks)	40	16.7
Full-term (37-41 weeks)	108	45.0
Birth weight categories		
Extremely low birth weight (less than 1,000 g)	8	3.3
Very low birth weight (1,000 g to less than 1,500 g)	73	30
Low birth weight (1,500 g to less than 2,500 g)	60	25
Normal birth weight (2,500 g to less than 4,000 g)	100	41.7
5-minute Apgar score		
Good vitality (7-10 Apgar score)	144	60
Poor vitality (less than 7 Apgar score)	96	40
Maternal general characterization		
Maternal age (years old)		
Appropriate maternal age (20-34)	132	55
Non-appropriate- Low maternal age (less than 20)	64	26.7
Non-appropriate- High maternal age (more than 34)	44	18.3
Maternal risk factors		
Hypertension	56	23.3
Diabetes	43	20
PROM	44	18.3
No reported risk factor	92	38.3
Mode of delivery		
NVD	92	38.3
CS	148	61.7
Disease necessitating mechanical ventilation		
Respiratory distress syndrome of prematurity	68	28.3
Congenital pneumonia	40	16.7
Sepsis	40	16.7
Apnea	24	10
Perinatal asphyxia	20	8.3
Congenital Heart diseases	16	6.7
Persistent pulmonary hypertension	12	5
Air-leak syndrome	12	5
Meconium aspiration syndrome	8	3.3
Ventilation modes		
SIMV	84	35
SIMV+PSV	64	26.7
A/C	72	30
HFV	20	8.3

CS: Caesarian section, NVD: Normal vaginal delivery, PROM: Premature rupture of membrane, SIMV: Synchronized intermittent mandatory ventilation, A/C: Assist/Control, PSV: Pressure support ventilation, HFV: High-frequency oscillatory ventilation

Table 2. Complication of mechanical ventilation and disease-related complications among the studied group

Reported Complications	n=240	%
Complications related to mechanical ventilation	104	43.3
Ventilator-associated pneumonia	48	20
Sepsis	32	13.3
Bronchopulmonary dysplasia	10	4.2
Air leak syndromes	8	3.3
Extubation failure	6	2.5
Complications related to disease pattern	136	56.7
Septic shock and multi-organ failure	54	22.5
Acute respiratory acidosis and hypoxemia	40	16.7
Recurrent or intractable apnea	24	10
Acute kidney injury	12	5
Pulmonary hemorrhage	6	2.5

preterm, 58% had low birth weight, and 60% had a 5-minute Apgar score of > 7, with RDS and SIMV being the most common cause of MV and the most common mode used for ventilation, respectively.

Regarding reported complications of studied groups, the incidence of complications related to MV was estimated at 104 (43.3%), and VAP observed an increase (20%). Furthermore, the complications related to disease patterns were reported to be 56.7% and 22.5% for sepsis and septic shock (Table 2).

The outcome was favorable in 51.7% of the study subjects and they were discharged in good condition. However, the remaining 48.3% passed away. The most significant risk factors for mortality were found to be smaller gestational age and lower birth weight, and VAP was reported as the most significant complication (Table 3).

Table 3. Factors affecting mechanical ventilation outcome

	Outcome		P-value
	Survived neonates n=124	Passed away neonates n=116	
Neonatal factors			
Gender, n (%) †			
Male	68 (54.8)	72 (62.1)	0.570
Female	56 (45.2)	44 (37.9)	
Gestational age, weeks‡			
Median (IQR)	37 (30.2-39.8)	31 (28-38)	0.000*
Min-Max	29-41	28-39	
Gestational age categories, n (%) §			
Sever (very) preterm (28-32 weeks)	24 (19.4)	68 (58.6)	0.006*
Moderate (late) preterm (33-36 weeks)	24 (19.4)	16 (13.8)	
Full term (37-41 weeks)	76 (61.2)	32 (27.6)	
Birth weight, kg ‡			
Median (IQR)	2.5 (1.42-3.79)	1.45 (1.05-3.5)	0.005*
Min-Max	1,350-3,950	950-3,900	
Birth weight categories, n (%) §			
Extremely low birth weight (less than 1,000g)	4 (3.2)	4 (3.5)	0.023*
Very low birth weight (1,000g to less than 1,500g)	20 (16.1)	52 (44.8)	
Low birth weight (1,500 g to less than 2,500g)	28 (22.6)	32 (27.6)	
Normal birth weight (2,500 g to less than 4,000 g)	72 (58.1)	28 (24.1)	
5-minutes Apgar score, n (%) †			
Good vitality (7-10 Apgar score)	80 (64.5)	64 (55.2)	0.460
Poor vitality (less than 7 Apgar score)	44 (35.5)	52 (44.8)	
Maternal factors			
Maternal Age, years old‡			
Median (IQR)	26 (19-32)	28 (16-38)	0.965
Min-Max	18-34	16-40	
Maternal risk factors§			
Hypertension	28 (22.6)	28 (24.1)	0.370
Diabetes	20 (16.1)	28 (24.1)	
PROM	16 (12.9)	28 (24.1)	
No reported risk factor	60 (48.4)	32 (27.6)	
Mode of delivery, n (%) †			
NVD	40 (32.3)	52 (44.8)	0.319
CS	84 (67.7)	64 (55.2)	
Mechanical ventilation related complications (104 patients)			
VAP	14 (11.3)	34 (29.3)	0.013*
Nosocomial sepsis	12 (9.7)	20 (17.2)	0.223
BPD	4 (3.2)	6 (5.2)	0.593
Air leak syndromes	4 (3.2)	4 (3.5)	0.954
Extubation Failure	4 (3.2)	2 (1.7)	0.598
Disease related complications (136 patients)			

Table 3. Continued			
Septic shock & and multi-organ failureMOF	26 (21)	28 (24.1)	0.677
Respiratory acidosis & and hypoxemia	32 (25.8)	8 (6.8)	0.005*
Recurrent or intractable apnea	20 (16.1)	4 (3.5)	0.020*
Acute kidney injury	8 (6.5)	4 (3.5)	0.069
Pulmonary hemorrhage	0 (0)	6 (5.2)	0.450

Statistical analysis: †Chi-square test, ‡Mann-Whitney U test, §Fisher's exact test

* Significant at $P < 0.05$

NVD: Normal vaginal delivery, CS: Caesarian section, IQR: Interquartile ration, PROM: Premature rupture of membrane, BPD: Bronchopulmonary dysplasia, VAP: Ventilator-associated pneumonia

No significant difference was revealed regarding the different types of mode used for ventilation (P=0.255). It should be noted that, in the survived group, a significant increase was observed in those with respiratory acidosis and hypoxemia and those with recurrent apneic spells, compared to cases in the neonates who passed away (P=0.005 and P=0.020, respectively) (Table 3).

Discussion

Neonatal MV has been probably the single most important factor contributing to the rapid decrease in neonatal mortality within the last two decades. Assisted ventilation facilities can save neonates with perinatal hypoxia, birth asphyxia, severe apnea, cardiovascular collapse, severe progressive respiratory distress with impending respiratory failure, and respiratory muscles fatigue (10).

In this study, out of the total 240 critically ill neonates, 140 (58.3%) and 100 (41.7%) of the cases were respectively male and female. Similarly, in a study conducted by Bhatt et al., males were the most predominant gender accounting for 57.65% of their population (11). Based on the results of the current study, 55% of the cases were born prematurely and 58.3% of the subjects weighed less than 2,500 g, which can partly explain the high mortality rate reported in our study and the research performed by Bhatt et al. (11).

The NICU of Zagazig Children Hospital is a tertiary center. Concerning disease pattern among ventilated neonates recruited from those centers, RDS was revealed to be the most prevailing disease (28.3%), followed in equal percentages by congenital pneumonia and sepsis (each 16.7%). Regarding, apnea of prematurity was reported to be 10% prevalent, while perinatal asphyxia and congenital heart diseases each accounted for 6.7%. It was also found that persistent pulmonary hypertension and air leak syndromes each contributed by 5%. Meconium aspiration syndrome was the indication of ventilation in 3.3%. A more or less similar pattern was observed in the studies released from other developing countries, where RDS was the most reported indication of MV among ventilated neonates (4, 5, 10-12). This similarity can be explained by common social and financial constraints shared by different developing countries.

The cases of this study were prospectively followed during their hospital stay for the development of complications. Regarding, 43.3% and 56.7% of the complications were related to MV and progression of the underlying diseases, respectively. Ventilator-associated pneumonia was the most common complication related to MV (20%), followed by sepsis (13.3%), while septic shock and multi-organ failure were the most common complications reported as a result of the progression of the underlying diseases (22.5%). Tayel et al. carried out a study in Egypt to investigate the incidence of VAP during the application of preventive bundles among ventilated neonates (13). The findings of the mentioned research showed a cumulative incidence of 37.6% for VAP, which was in line with our results. The reason for the agreement of these results can be attributed to the similar demographic characteristics, health care system, and financial resources in these two Egyptian studies.

On the contrary, Sharma and Baheti (8) reported the occurrence of VAP in only 2 (2.77%) out of their 71 mechanically ventilated cases, while 4 (4.16%) subjects developed BPD. In a study carried out by Thatrimontrichai et al. in Thailand, VAP incidence was estimated at 13.3%, with low birth weight being the most significant independent risk factor (14). In a recent French study published in 2018, the VAP incidence rate was 8.8 per 1,000 invasive MV days, with those with low birth weight less than 1,000 g being significantly at risk (15).

The results of some studies showed that sepsis and multi-organ failure were the most commonly encountered complications in general and related to disease progression (16, 17). The outcome was favorable in 51.7% of our samples

who had been successfully weaned from MV and discharged from the hospital; nevertheless, the remaining 48.3% passed away. The most determinant mortality risk factors were revealed to be small gestational age and low birth weight. Fidanovski et al. similarly identified low birth weight as independently associated with a significantly higher risk of mortality (18). Similar survival rates were reported from other studies performed in developing countries, which ranged from 25% to 64% with better outcomes among those with higher gestational age and birth weight (12, 16, 19-21).

In this research, VAP was found to be the top causative factor regarding the most significant complication related to MV increasing mortality risk in our samples (P=0.013). This might be partly explained by the used artificial airways which bypass the neonatal defense mechanism against inhaled pathogen and partly by improper implementation of infection control guidelines which call for urgent action.

Significantly lower mortality risk was observed among those with acute respiratory acidosis and hypoxemia and intractable apnea (P=0.005 and P= 0.020, respectively), which might be attributed to the disease-associated hypercapnia acting as a lung-protective strategy.

One of the limitations of the current study was related to the inadequacy of published data regarding the neonatal mortality caused by VAP in Egypt since it made it impossible to compare the results of our study with those of other research performed locally. Therefore, it is needed to conduct a multicenter study to confirm our findings. Furthermore, in the current study, the underlying factors attributing to this high VAP incidence in our population and the results of a prospective study with root-cause analysis highlight the necessity to address this problem and plan a strict improvement project to decrease the mortality rate of VAP among ventilated neonates.

Limitations

Volume-targeted mode of ventilation is an important lung protective strategy in neonatal ventilation. Nonetheless, it was not used in the current study due to a lack of enough ventilator machines programmed with this mode in our unit, which was considered an important limitation of our study. It is recommended to conduct a multicenter study and root cause analysis for the high mortality rate and high prevalence of VAP.

Conclusion

It was revealed that the mortality rate among critically ill ventilated neonates using pressure-controlled mode was still high in Egypt, as a developing country, approaching 48.3%. Ventilator-associated pneumonia was found as the most common cause of mortality among critically ill ventilated neonates. Consequently, it is required to adopt measures and develop projects to resolve this problem.

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Authors' contributions

WM, LR: set the idea of the study, designed the study, and collected data; WM, NK: reviewed literature and drafted the manuscript; SK: performed data analysis and critically analyzed data. All authors reviewed and approved the manuscript for final publication.

Conflicts of interest

The authors declare no conflict of interest.

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