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ORIGINAL ARTICLE

Bundles to Prevent Neonatal Ventilator Associated Pneumonia in Neonatal Intensive Care Unit

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ABSTRACT:

Background: Ventilator-associated pneumonia (VAP) is a serious healthcare-associated infection in neonates receiving mechanical ventilation in NICUs, increasing morbidity, mortality, and hospital stay durations. This study aimed to determine the impact of ventilator bundles of care practices on the rates of VAP in mechanically ventilated neonates. **Methods:** This randomized controlled trial study on 98 neonates requiring mechanical ventilation for ≥48 hours were randomly allocated into two equal groups. The bundle group received a VAP preventive care bundle including reinforced hand hygiene, 45° head elevation, left lateral positioning, oral care with chlorhexidine, ventilator circuit care, early weaning, and prevention of accidental extubation. The conventional group received routine infection control measures. Clinical, radiological, and laboratory data including complete blood count, arterial blood gases, C-reactive protein, and endotracheal aspirate cultures were collected. **Results:** During follow-up, the conventional group exhibited significantly worse clinical and ventilator parameters, with higher rates of new chest findings. Peak inspiratory pressure, respiratory rate, and FiO_2 were significantly elevated compared to the bundle group. VAP incidence was markedly higher in the conventional group (30.6%) versus the bundle group (8.2%). Additionally, mechanical ventilation duration and hospital stay were significantly prolonged in the conventional group. Kaplan-Meier survival analysis revealed better outcomes in the bundle group, with 100% survival versus a 12.2% mortality rate in the conventional group. **Conclusion:** Implementing a VAP preventive bundle significantly reduced VAP incidence, improved respiratory and clinical outcomes, and enhanced survival in mechanically ventilated neonates.

Keywords: Ventilator-associated pneumonia; Neonates; Mechanical ventilation; Prevention bundle;Clinical outcomes

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a serious and common complication among neonates who require mechanical ventilation in neonatal intensive care units (NICUs). It is defined as a lung infection that develops 48 hours or more after the initiation of mechanical ventilation, affecting neonates who are particularly vulnerable due to their underdeveloped immune systems, immature respiratory function, and increased exposure to invasive procedures. VAP is not only associated with prolonged hospital stays but also increases the risk of long-term respiratory problems, neurodevelopmental delays, and other systemic infections [1].

The causes of VAP in neonates are multifactorial and typically involve aspiration of oropharyngeal or gastric secretions, bacterial colonization of the respiratory tract, and contamination through equipment such as endotracheal tubes or ventilators. The pathogens commonly associated with neonatal VAP include gram-negative

organismslike *Pseudomonas aeruginosa*, *Klebsiellapneumoniae*, and *Escherichia coli*, along with gram-positive organisms such as *Staphylococcus aureus* [2].

The diagnosis of VAP in neonates can be difficult, as their symptoms may be subtle or non-specific, making early detection a challenge. The clinical presentation may include fever, increased respiratory distress, and changes in blood gas measurements, but these signs can overlap with other conditions [3].

Moreover, the management of VAP in neonates requires not only antibiotic treatment but also a comprehensive approach to support lung function and minimize further respiratory complications. As a result, preventing VAP in neonates is far more effective than attempting to treat the infection after it has occurred [4].

To combat this serious complication, the concept of a "VAP bundle preventive strategy" has been developed as a systematic, evidence-based approach to prevention. A VAP prevention bundle is a set of coordinated interventions that aim to reduce the risk of infection in neonates receiving mechanical ventilation. These bundles focus on best practices that target various aspects of care, from patient positioning to oral hygiene, to minimize the risk of pathogen colonization and aspiration. The bundle approach is grounded in the understanding that there is no single intervention that can prevent VAP, but rather a combination of strategies that, when implemented together, can substantially reduce its incidence [5].

The importance of a VAP prevention bundle in neonates extends beyond reducing infection rates. By focusing on comprehensive care and preventive strategies, the bundle approach has the potential to improve the overall experience for families and caregivers. A systematic approach to VAP prevention reassures families that their newborns are receiving the highest standard of care, which can have a lasting positive impact on their trust in the healthcare system[6].

Despite the growing body of evidence supporting the use of VAP prevention bundles in neonatal intensive care units (NICUs), significant gaps remain in the research, particularly in relation to the optimal implementation and efficacy of these strategies. While several studies have demonstrated a reduction in VAP rates through the application of bundles, the variability in outcomes across different hospitals and healthcare systems suggests that there are still unanswered questions regarding the exact composition of the most effective bundles, the ideal timing and frequency of interventions, and the long-term impact of these practices on mechanically ventilated neonates.

Aim of the Work:

The aim of this study was to determine the impact of ventilator bundles of care practices on the rates of VAP in mechanically ventilated neonates.

METHODS

This randomized controlled trial was conducted in the Neonatal Intensive Care Unit (NICU), Pediatric Department, Children's Hospital, Zagazig University, and Clinical Pathology department, Zagazig University over a one-year period from October 2023 to October 2024. The study included 98 mechanically ventilated neonates who were randomly assigned, in a 1:1 allocation ratio, using a single-blinded, closed-envelope technique, into two equal groups. The Bundle Group comprised 49 patients who received care based on a structured ventilator-associated pneumonia (VAP) prevention bundle. The Conventional Group included 49 patients who received the standard routine infection control practices routinely implemented in the NICU at Zagazig University hospitals. After our Local Ethics Committee has approved the protocol (IRB#11211-15/10-2023), Parents' or guardians' written informed consent was acquired for research participants. The World Medical Association's code of ethics for human research, the Helsinki Declaration, was followed throughout the entire study procedure.

Inclusion criteria: Neonates of both sexes who were maintained on mechanical ventilation for at least 48 hours.Neonates were excluded from the study if they met one

or more of the following conditions: age older ne month;diagnosis ofthan o aspiration pneumonia, defined as infectious complications following the introduction of a large volume of oral material into the lower respiratory tract **[7]**or if their caregivers declined to provide consent for participation tudyin the s

Intervention and Study Procedures

In the current study, neonates in the bundle group received a structured ventilator-associated pneumonia (VAP) prevention bundle, while those in the conventional group received the standard infection control measures routinely applied at the NICU of Zagazig University.

In the Bundle Group, several preventive interventions were implemented simultaneously. Hand hygiene reinforcement was a cornerstone of care, where all healthcare providers received periodic training and reminders regarding hand hygiene protocols. Hand hygiene was strictly practiced before and after patient contact, ventilator handling, and the use of contaminated equipment, with compliance monitored through direct observation and the provision of alcohol-based sanitizers.

Another essential component was head-of-bed elevation, maintaining the neonate's bed at a 45° angle unless contraindicated by clinical conditions such as spinal deformities or unstable injuries. This position aimed to reduce the risk of aspiration and facilitate ventilator-associated secretion drainage, with documentation of positioning recorded every shift.

Additionally, left lateral positioning was employed to minimize aspiration risk and improve secretion clearance. Neonates were maintained in this position for at least 2 hours at a time, with repositioning thereafter, and respiratory status monitored accordingly.

For oral hygiene care, two complementary practices were introduced. First, the neonates' gums were gently brushed using a soft silicone brush with sterile saline once every shift or as clinically indicated. Second, a chlorhexidine mouth spray (0.12%) was applied to the oral mucosa at 12-hour intervals to reduce pathogenic colonization. Both procedures were carefully documented, and any adverse reactions were promptly evaluated.

In terms of equipment care, ventilator circuit management involved changing circuits only when visibly soiled or malfunctioning, while ensuring all connections were regularly checked for sterility and functionality. The timing of changes and circuit integrity were recorded daily.

Early weaning from mechanical ventilation was actively pursued whenever the neonate's clinical condition permitted. Criteria for initiating weaning included stable respiratory parameters, improved blood gases, and appropriate neurological status. The process was gradual and carefully monitored by both the attending physician and respiratory therapist. Any extubation attempts and their outcome were documented.

Lastly, to prevent accidental extubation, frequent checks of endotracheal tube position were performed using appropriate securement devices. Any accidental extubation events were recorded, with prompt evaluation of underlying causes and implementation of corrective measures.

In the Conventional Group, patients received the routine infection control program applied in the NICU, consisting of hand hygiene, use of personal protective equipment, proper environmental cleaning and disinfection, changing infant incubators every 5 days, and performing incubator disinfection as per hospital protocol.

Diagnosis of VAP was established based on a combination of clinical, radiological, and microbiological criteria. Clinically, patients exhibited worsening respiratory signs, deterioration in arterial blood gas values, and either leucopoenia or leucocytosis. Radiological diagnosis relied on detecting new or progressive infiltrates, consolidation, cavitation, or pneumatocele on chest imaging. Microbiological confirmation was achieved through positive sputum or endotracheal aspirate cultures [8].

All enrolled neonates underwent a comprehensive clinical assessment at the time of admission to the Neonatal Intensive Care Unit (NICU).

A thorough clinical examination was performed for all enrolled neonates upon admission and regularly during their NICU stay. This included assessment of vital signs, general appearance, and a detailed systemic examination.

Vital signs were carefully monitored and recorded. Temperature was measured rectally using either a mercury or digital thermometer, with a normal range defined between 36.5°C and 37.5°C **[9].** Heart rate was determined by palpating the brachial artery or auscultating the precordial region using a stethoscope, with normal values ranging from 120 to 160 beats per minute. Blood pressure was measured using an appropriately sized cuff applied to the right upper arm while the neonate was asleep or quietly awake. Systolic blood pressure (SBP) values were considered normal between 60–90 mmHg, while diastolic blood pressure (DBP) ranged from 30–60 mmHg. For accuracy, three successive measurements were taken. Respiratory rate was counted over a full 60 seconds by gently observing abdominal or chest movements, with normal rates ranging between 30 and 60 breaths per minute **[10].**

General appearance was evaluated with particular attention to neonatal posture. A normal posture was characterized by clenched fists, flexed elbows, hips and knees, and arms and legs held closely to the anterior body surface, resembling the intrauterine fetal position during the final months of gestation.

Chest examination included inspection for abnormal respiratory movements, chest wall retractions, nasal flaring, visible pulsations, and dilated chest veins. Palpation was performed to assess chest movements during respiration and to confirm symmetry between both sides. Auscultation was conducted to identify normal vesicular breath sounds or any adventitious sounds such as rhonchi or crepitations.

Cardiac examination began with inspection of the precordial area to detect the apex beat position and any abnormal visible pulsations. Palpation was carried out to evaluate the location and extent of the apex beat and to identify any palpable thrills. Auscultation was performed across the standard precordial areas to assess the quality of heart sounds, including the presence of abnormal sounds such as gallop rhythms, additional heart sounds (S3 or S4), pericardial rubs, or abnormal splitting of the second heart sound (S2), murmurs.

Abdominal examination included inspection for dilated veins, visible pulsations, abnormal pigmentation, masses, and the condition of the umbilicus. Superficial palpation was performed to detect areas of tenderness, subcutaneous nodules, or superficial masses, while deep palpation was used to identify organomegaly or deep-seated masses. Auscultation was also conducted to assess the frequency and character of intestinal sounds.

Laboratory Investigations

A series of laboratory investigations were performed for all enrolled neonates as part of their routine evaluation and clinical monitoring. These investigations included a complete blood count (CBC), arterial blood gas (ABG) analysis, C-reactive protein (CRP) assay, and sputum or endotracheal aspirate cultures.

Complete blood count (CBC) was conducted using the Sysmex XN-1000 (Germany). The system operates on the principle of electrical impedance, where whole blood is passed between two electrodes through a narrow aperture that allows only one cell at a time to pass. The passage of each cell alters the electrical impedance, enabling cell counting and sizing. The CBC results included hemoglobin concentration, total and differential white blood cell counts, and platelet counts.

C-reactive protein (CRP) levels were measured using the BT-1500 system (Biotecnica Instruments, Roma, Italy). This assay is based on a turbidimetric immunoassay technique, wherein turbidity is generated by the formation of insoluble antigen-antibody complexes. The reaction is nonlinear and endpoint, with measurements taken at a wavelength of 340 nm within a temperature range of 18°C to 37°C. The measuring range extended from 0.0 to 22 mg/dL. A CRP level of 10 mg/dL or higher was considered positive, indicative of significant inflammation or infection**[11]**.

Arterial blood gas (ABG) analysis and sputum or endotracheal aspirate cultures were also performed as part of the diagnostic and monitoring protocol for ventilator-associated pneumonia (VAP). ABG results provided data on pH, partial pressures of oxygen and carbon dioxide, and bicarbonate levels to assess the neonates' respiratory and metabolic status. Microbiological cultures from endotracheal aspirates were processed to identify causative pathogens and guide appropriate antimicrobial therapy.

Sample Collection:

Respiratory specimens were obtained from mechanically ventilated neonates using a sterile suction technique. Each neonate was positioned in a semi-reclined or supine position, as clinically appropriate, to facilitate aspiration. Strict aseptic precautions were followed, including hand hygiene and the use of sterile gloves. A sterile suction catheter was introduced gently through the endotracheal tube (ETT) and advanced until resistance was felt, typically at the level of the carina. Suction was applied for no more than 10–15 seconds per attempt to minimize the risk of mucosal trauma. The procedure was repeated as necessary until an adequate sample of respiratory secretions, approximately 0.5–1mL, was collected in a sterile sputum trap or collection container. All samples were promptly transported to the microbiology laboratory for culture and sensitivity analysis**[12].**

Microbiological Processing:

The collected samples were incubated under appropriate conditions: at 37°C for 24–48 hours for bacterial pathogens, and up to 7 days for fungal growth, or as indicated based on clinical suspicion. Isolated pathogens were identified based on colony morphology, Gram staining, and a series of biochemical tests. In certain cases, molecular diagnostic techniques such as PCR were utilized for confirmation. Antimicrobial susceptibility testing was performed for positive cultures using either the disk diffusion method or E-test technique, according to the organism's characteristics and laboratory protocol, to guide appropriate antibiotic therapy **[13].**

Chest radiology:

Radiological evaluation was performed for all enrolled neonates. A plain chest X-ray was routinely done on the day of admission, following endotracheal intubation and initiation of mechanical ventilation, and subsequently during follow-up or whenever clinically indicated. In cases where chest X-ray findings were inconclusive, such as suspected pleural effusion, pneumothorax, pneumatocele, cavitary lesions, or other complications, a non-contrast chest computed tomography (CT) scan was performed to provide further diagnostic clarification.

Mechanical ventilation data and parameters:

Regarding mechanical ventilation, neonates were placed on assisted ventilation for various clinical indications including congenital pneumonia, respiratory distress syndrome (RDS), meconium aspiration syndrome, persistent apnea of prematurity, persistent pulmonary hypertension, and congenital heart diseases, or combinations of these conditions. Ventilatory parameters were recorded at the time of admission and throughout the follow-up period. These included peak inspiratory pressure (PIP), defined as the maximum airway pressure reached during the inspiratory phase and typically maintained below 30–35cm H_2O; positive end-expiratory pressure (PEEP), representing the pressure preserved in the lungs at the end of expiration above atmospheric pressure; respiratory rate (RR), reflecting the number of ventilator-delivered breaths per minute; and fraction of inspired oxygen (FiO_2), which denotes the percentage of oxygen concentration in the inhaled gas mixture. Adjustment of these parameters was based on the neonate's clinical status, blood gas analysis, and radiological findings.

Statistical analysis:

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 27 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages, while continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed continuous data were expressed as mean ± standard deviation (SD), whereas non-parametric data were expressed as median,

minimum, and maximum values. Appropriate statistical tests were applied according to the type of data. The Chi-square test was used to compare categorical variables between groups. The independent samples Student's t-test was employed to compare normally distributed continuous variables, while the Mann-Whitney U test was used for non-parametric continuous variables. Additionally, binary logistic regression analysis was performed to identify significant predictors associated with the occurrence of ventilator-associated pneumonia (VAP). A p-value of less than 0.05 was considered indicative of statistical significance.

RESULTS

The current study included 98 mechanically ventilated neonates with mean age 7.4 ± 2.7 days. Most of the included patients were males (51%). Mean gestational age of the included patients was 36.4 ± 1.8 weeks and mean birth weight was 2446 ± 372 mg and about 6.1% of the patients were low birth weight. About 27.6% of the mothers of the included patients had different antenatal medical disorders and the most reported medical disorders were UTI (7.1%), diabetes (5.1%), hypertension (4.1%) and hypothyroidism (3.1%). Premature rupture of membrane occurred in 9.2% of patients.

Table 1 showed that the most reported causes for mechanical ventilation were congenital pneumonia (59.2%), RDS (13.3%), PPHN (13.3%) and congenital heart defects (7.1%). Persistent apnea of prematurity was present in 6.1% of patients. On admission, mean temperature was 38.1 ± 0.67 C, mean heart rate was 101 ± 10.5 b/ m, mean respiratory rate was 44.7 ± 2.42 cycle/minute. Crepitation and bronchial breathing were present in 77.6% of patients.

Table 2 showed that during follow up, mean temperature was 36.8 ± 0.8 C as 80.6% had normal temperature while fever was persistent in 13.3% of patients and 6.1% of patients had hypothermia. Mean heart rate was 99.9 ± 29.4 beat/ minute and mean RR was 43.7 ± 10.8 cycle/ minute. Chest auscultation findings were improved in 80.6% of patients while 7.1% of patients had increased crepitations, 4.1% had new bronchial breathing and new diminished breath sound was reported in 8.2% of patients. Chest x- ray improved in 80.6% of patients while, new consolidations appeared in 8.2% of patients, new infiltrates appeared in 9.2% of patients and atelectasis appeared in 2% of patients. About 15.3% of patients showed increased and more thicker secretions and secretion color changed to purulent or reddish in 16.3% of patients.

Table 3 showed that during follow up, mean PIP was 15.2 ± 4.6 mmHg, mean PEEP was 5.3 ± 1.1 mmHg, mean RR was 44.7 ± 6.1 cycle/ minute and mean FiO2 was 44.5 ± 19.2%. illustrated that Mean duration of mechanical ventilation was 9.4 ± 3.1 days, mean length of hospital stay was 17.9 ± 5.2 days. According to the previous clinical, radiological and microbiological results, VAP was diagnosed in 19.4% of patients. Mortality rate was 6.1% as 6 patients died, and 92 patients (93.9%) were discharged alive.

Table 4; showed that there were no statistically significant differences between bundle and conventional groups as regards mechanical ventilation parameters on admission .

Table 5 showed that, during follow up, clinical and radiological findings were significantly deteriorated in conventional group than bundle group as higher percent of patients in conventional group had persistent fever or hypothermia ***(p= 0.009)***. Heart rate and respiratory rate were significantly higher among conventional group than bundle group ***(p= 0.04; 0.04)***. Higher percent of bundle group patients showed significant improvement in chest auscultation and chest radiology findings while higher percent of conventional group patients showed new clinical and radiological findings with statistically significant differences. Higher percent of conventional group had increased secretions and change the color of the secretion to purulent or reddish than bundle group with statistically significant differences ***(p= 0.002; 0.029)***.

Table 6 showed that total leucocytic count was significantly higher among conventional group than bundle group ***(p= 0.004)***. Otherwise, no statistically significant differences were found between bundle and conventional groups as regards hemoglobin, platelets, CRP. Higher percent of patients in

conventional group had positive sputum cultures than bundle groups ***(p= 0.005)***. Also, the frequency of the isolated organisms was significantly higher among conventional group than bundle group ***(p= 0.03)***.

Table 7 showed that during follow up, PIP, RR and FiO2 were significantly higher among conventional group than bundle group (p= 0.008; < 0.001; 0.017). Also showed that mechanical ventilation duration and length of hospital stay were significantly prolonged in conventional group than bundle group (p= 0.015; 0.046). Ventilator associated pneumonia was significantly higher among conventional group than bundle group (p= 0.005). All bundle group patients were discharged alive while 12.2% of conventional group patients died with statistically significant differences (p= 0.011).

As shown in **table 8,** Binary logistic regression analysis was used to assess the predictors for incidence of VAP among mechanical ventilated patients excluding the diagnostic clinical, radiological and microbiological criteria and excluding the consequences of VAP as changes in clinical and mechanical ventilation parameters. Presence of maternal disease increased the odds for incidence of VAP by 8.8 ***(p= 0.04)***. PROM increased the odds for VAP incidence by 7.3 ***(p= 0.03)***. Conventional group (absence of VAP preventive bundle) increased the odds for VAP incidence by 3.4 ***(p= 0.008)***. Also, White blood cell count was considered significant predictor for VAP among mechanical ventilated neonates ***(p= 0.04)***. Meanwhile, age, gestational age, weight, sex were not considered significant predictors for VAP incidence.

Table (1): Neonatal, Maternal and Clinical Characteristics on Admission:

	Total cohort (n= 98 patients)
Neonatal and maternal characteristics	
Age (days) Mean ± SD	7.4 ± 2.7
Sex No. (%) Male Female	 50 (51%) 48 (49%)
Gestational age (weeks) Mean ± SD	36.4 ± 1.8
Birth weight (mg) Mean ± SD	2446 ± 372
Low birth weight No. (%)	6 (6.1%)
Maternal medical conditions No. (%)	27 (27.6%)
Type of maternal medical conditions No. (%) Hypertension Pre- eclampsia Diabetes Hypothyroidism. Asthma UTI Antepartum hemorrhage. Polyhydramnios Oligohydramnios Meconium stain.	 4 (4.1%) 1 (1%) 5 (5.1%) 3 (3.1%) 1 (1%) 7 (7.1%) 1 (1%) 1 (1%) 1 (1%) 3 (3.1%)
PROM No. (%)	9 (9.2%)
Causes of mechanical ventilation and clinical characteristics of the included patients on admission	
Causes of mechanical ventilation No. (%) - Congenital pneumonia - RDS - Meconium aspiration - PPHN - Congenital heart defect	58 (59.2%) 13 (13.3%) 3 (3.1%) 13 (13.3%) 7 (7.1%) 6 (6.1%)

	Total cohort (n= 98 patients)
- Persistent apnea of prematurity - Congenital pneumonia + PPHN - RDs + PPHN - Congenital heart defect + PPHN	1 (1%) 1 (1%) 1 (1%)
Temperature Mean ± SD	38.1 ± 0.67
Heart rate (beat/minute) Mean ± SD	101 ± 10.5
Respiratory rate (cycle/minute) Mean ± SD	44.7 ± 2.42
Chest auscultation No. (%) No significant findings Crepitations and bronchial breathing	 22 (22.4%) 76 (77.6%)

PROM: Premature rupture of membrane; UTI: Urinary tract infection.
RDS: Respiratory distress syndrome, PPHN: Persistent pulmonary hypertension of the newborn.

Table (2): Clinical and radiological findings during follow up:

	Total cohort (n= 98 patients)
Temperature Mean ± SD	36.8 ± 0.8
Fever pattern No. (%) Normal Persistent Hypothermia	 79 (80.6%) 13 (13.3%) 6 (6.1%)
Heart rate (beat/minute) Mean ± SD	99.9 ± 29.4
Respiratory rate (cycle/minute) Mean ± SD	43.7 ± 10.8
Chest auscultation No. (%) Improved New findings New crepitation New bronchial breathing New diminished breath sound	 79 (80.6%) 19 (19.4%) 7 (7.1%) 4 (4.1%) 8 (8.2%)
Chest radiology No. (%) Improved. New findings New consolidations New infiltrations Atelectasis	 79 (80.6%) 19 (19.4%) 8 (8.2%) 9 (9.2%) 2 (2%)
Increased secretions No. (%)	15 (15.3%)
Change color of secretion No. (%)	16 (16.3%)

Table (3): Mechanical Ventilation Parameters, VAP Frequency and Outcome

	Total cohort (n= 98 patients) Mean ± SD
Mechanical ventilation parameters during follow up	
PIP (mmHg)	15.2 ± 4.6
PEEP (mmHg)	5.3 ± 1.1
Respiratory rate (cycle/ minute)	44.7 ± 6.1
FiO2 (%)	44.5 ± 19.2
Frequency of VAP and outcome	
Duration of mechanical ventilation (days)	9.4 ± 3.1
Length of hospital stay (days)	17.9 ± 5.2
Ventilator associated pneumonia No. (%)	19 (19.4%)
Outcome No. (%) Survivors Non- Survivors	 92 (93.9%) 6 (6.1%)

PIP: Peak inspiratory pressure; PEEP: Positive end expiratory pressure.

Table (4): Comparison between bundle and conventional groups as regards mechanical ventilation parameters on admission:

	Bundle group (n= 49)	Conventional group (n= 49)	p value
PIP (mmHg)	17.04 ± 0.8	17 ± 0.9	0.8
PEEP (mmHg)	4.9 ± 0.7	4.8 ± 0.72	0.49
Respiratory rate (cycle/ minute)	44.6 ± 3.3	45.76 ± 3.2	0.088
FiO2 (%)	51.2 ± 6.08	50.3 ± 7.3	0.5

PIP: Peak inspiratory pressure; PEEP: Positive end expiratory pressure; Student t- test; Level of significance < 0.05.

Table (5): Comparison between bundle and conventional groups as regards clinical and radiological findings during follow up:

	Bundle group (n= 49)	Conventional group (n= 49)	p value
Temperature Mean ± SD	36.8 ± 0.6	36.8 ± 1.08	0.8
Fever pattern No. (%) Normal Persistent Hypothermia	 45 (91.8%) 4 (8.2%) 0 (0%)	 34 (69.4%) 9 (18.4%) 6 (12.2%)	*0.009*
Heart rate (beat/minute) Mean ± SD	110 ± 23.9	125.2 ± 33.4	*0.011*
Respiratory rate (cycle/minute) Mean ± SD	41.8 ± 8.6	45.7 ± 12.5	*0.04*
Chest auscultation No. (%) Improved New findings New crepitation New bronchial breathing New diminished breath sound	 45 (91.8%) 4 (8.2%) 2 (4.1%) 0 (0%) 2 (4.1%)	 34 (69.4%) 15 (30.6%) 5 (10.2%) 4 (8.2%) 6 (12.2%)	 *0.03* *0.02*
Chest radiology No. (%) Improved. New findings New consolidations New infiltrations Atelectasis	 45 (91.8%) 4 (8.2%) 1 (2%) 2 (4.1%) 1 (2%)	 34 (69.4%) 15 (30.6%) 7 (14.3%) 7 (14.3%) 1 (2%)	 *0.032* *0.01*
Increased sections No. (%)	2 (4.1%)	13 (26.5%)	*0.002*
Change color of secretion No. (%)	4 (8.2%)	12 (24.5%)	*0.029*

Chi square test; Student t- test; Level of significance < 0.05.

Table (6): Comparison between bundle and conventional groups as regards laboratory findings throughout hospital stay:

	Bundle group (n= 49)	Conventional group (n= 49)	p value
Hemoglobin (g/dL)	10.9 ± 0.9	11.04 ± 1.1	0.77
White blood cells (*10^3/mm^3)	6.5 (3.2, 19)	6.9 (3.1, 43)	*0.004*
Platelets (*10^3/mm^3)	223.9 ± 59	219.4 ± 85.4	0.76
C- reactive protein (mg/dL)	32.3 ± 11.6	38.05 ± 16.8	0.17
Positive sputum culture No. (%)	4 (8.2%)	15 (30.6%)	*0.005*
Type of organism No. (%) - Klebsiella - Staphylococcus aureus - Pseudomonas aeruginosa - Acinetobacter - Streptococcus species + E. coli - Staphylococcus + E. coli - Staphylococcus + Klebsiella	 1 (25%) 0 (0%) 1 (25%) 0 (0%) 1 (25%) 1 (25%) 0 (0%)	 3 (20%) 3 (20%) 3 (20%) 4 (26.7%) 0 (0%) 1 (6.7%) 1 (6.7%)	*0.03*

Chi square test; Student t- test; Level of significance < 0.05.

Table (7): Comparison between Bundle and Conventional Groups Regarding Mechanical Ventilation Parameters and Patients' Outcomes:

	Bundle group (n= 49)	Conventional group (n= 49)	p value
Comparison between bundle and conventional groups as regards mechanical ventilation parameters during follow up			
PIP (mmHg)	13.9 ± 3.4	16.4 ± 5.2	*0.008*
PEEP (mmHg)	5.1 ± 0.9	5.45 ± 1.2	0.13
Respiratory rate (cycle/ minute)	42.7 ± 4.8	46.7 ± 6.6	*<0.001*
FiO2 (%)	39.9 ± 13.2	49.08 ± 23.04	*0.017*
Comparison between bundle and conventional groups regarding patients' outcome			
Duration of mechanical ventilation (days)	9.18 ± 2.8	10.7 ± 3.3	*0.015*
Length of hospital stay (days)	18.4 ± 5.4	20.5 ± 4.9	*0.046*
Ventilator associated pneumonia No. (%)	4 (8.2%)	15 (30.6%)	*0.005*
Outcome No. (%) Survivors Non- Survivors	 49 (100%) 0 (0%)	 43 (87.8%) 6 (12.2%)	*0.011*

Student t- test; Level of significance < 0.05.

Chi square test; Student t- test; Level of significance < 0.05.

DISCUSSION

A VAP preventive bundle is a set of evidence-based practices designed to reduce the incidence of VAP in neonates requiring mechanical ventilation. The bundle includes a combination of interventions that target key risk factors for VAP, such as minimizing ventilator-associated risks, promoting optimal airway care, and preventing aspiration. By implementing these preventive measures in a

coordinated and systematic manner, NICU teams can significantly decrease the likelihood of VAP, improving both short-term and long-term health outcomes for neonates [14].

The importance our research extends beyond reducing ventilator associated pneumonia infection rates to trial for improving the overall experience for families and caregivers. Our approach to VAP prevention reassures families that their newborns are receiving the highest standard of care, which can have a lasting positive impact on their trust in the healthcare system

The novelty in our research compared to previous researches is our trial to establish near optimal composition of the most effective bundles of practices with near ideal timing and frequency of interventions, and studying the long-term impact of these practices on mechanically ventilated neonates.

Mean age of the included patients was 7.4 ± 2.7 days with semi- equal sex distribution of the included patients (males vs. females: 51% vs. 49%). There were no statistically age or sex differences between bundle and conventional groups. In the same line, *Pinilla-González et al*. compared 106 patients received VAP preventive bundle to 174 controls and did not find significant age or sex differences between both groups and reported high male prevalence among both groups (60.4% vs. 64.9%) [5]. *Jahan et al.* in another study included 19 neonates received VAP preventive bundle and 22 controls did not find significant age or sex differences between both groups [15].

Many studies proposed that male neonates were more prone to RDS and apnea of prematurity due to lower levels of surfactants than females, higher incidence of prematurity and slower lung maturity process and this could explain the higher male prevalence among the included patients in our study [16].

In the present study, mean gestational age was 36.4 ± 1.8 weeks, mean birth weight was 2446±372gm and 6.1% of the included patients were low birth weight with statistically insignificant differences between bundle and conventional groups. Low birth weight is a significant risk factor for congenital pneumonia, apnea of prematurity and RDS as reported in previous study [17]. *Wen et al.*, conducted a large study on 13490 neonates and demonstrated that gestational age and gestational weight are significant predictors for incidence of RDS *(p< 0.001)* [18].

Similar to the current study, previous studies did not find significant differences in gestational age between patients received either VAP preventive bundle or controls [19]. In contrast with the present study, previous study included 143 mechanically ventilated neonates reported higher percent of patients with low percent weight in both groups (77.4% and 77.7%) [20]. The controversial results could be explained by the differences in sample size as the later study included 143 patients.

In the present study, about 27.6% of mothers of the included patients had medical disorders during pregnancy and the most reported medical disorders were UTI (7.1%), diabetes (5.1%) and hypertension (4.1%). It was reported that maternal medical conditions had significant negative effect on lung maturity of neonates. *Hung et al.* conducted a study on 71 mothers and demonstrated that hypertension and pre- eclampsia were significant predictors for neonatal admission to ICU and respiratory failure [21].

More recent study included 102 neonates showed that gestational diabetes and hypertension were significant risk factors for RDS *(p= 0.035; 0.032)* [22]. Meanwhile, *Agashe et al.* [23]. reported that maternal hypertension and pre- eclampsia accelerated lung maturity in pre- terms, possibly because intrauterine stress increases endogenous corticosteroids, which are known to enhance surfactant synthesis. This aligns with the concept of a phenomenon called “stress-induced accelerated maturation .

One of the risk factors for neonatal ICU admission and neonatal respiratory failure is PROM. The current study demonstrated that PROM occurred in 9.2% of patients with significantly higher frequency among conventional group (bundle vs. conventional: 2% vs. 16.3%; *p= 0.014)*. Early loss of amniotic fluid negatively affects the production of the surfactants by the lungs, and

it leads to pre- term birth and preterm babies have underdeveloped lungs [25] .

In hand with the present study, *Agashe et al.* evaluated the risk factors for RDS among 142 neonates and demonstrated that PROM was significant predictor for respiratory failure[23].

In this study, there were multiple causes for mechanical ventilation and the most reported indications were congenital pneumonia (59.2%), RDS (13.3%) and PPHN (13.3%). There were insignificant differences between bundle and conventional groups as regards causes of mechanical ventilation. In the same hand, *Zhou et al.* [24] reported that congenital pneumonia, RDS, prematurity and congenital heart diseases were the most common indications for mechanical ventilation.

On the other hand, *Abu-Elenen et al.* showed that the most common indication for mechanical ventilation in their study was apnea of prematurity (32.6%) and RDS (28.1%) [19]. The controversial results could be related to the differences in the percent of LBW patients in the later study as in *Abu-Elenen et al,* 88.8% of patients with LBW as compared to 6.1% in our study [19].

There were multiple organisms which were isolated from sputum culture of the included patients, especially among non-bundle group. The most isolated organisms were Klebsiella, Staph, Pseudomonas and Acinetobacter. The present study showed that isolation of organisms from sputum culture was less frequent among patients received VAP preventive bundle than conventional *(p= 0.005).* In hand with the present results, *Azab et al.* reported lower frequency of positive sputum cultures among patients received VAP preventive bundle and the most isolated organisms were Klebsiella and pseudomonas [20].

In contrast with the present study, *Abu-Elenen et al.* did not find significant differences in number of positive sputum cultures between patients received VAP preventive bundle and who did not. However, he reported that the frequency of antibiotic use was significantly decreased during application of VAP preventive bundle *(p= 0.002)* [19].

Another study did not find significant differences in occurrence of MDR bacteria between patients who received and who did not receive VAP preventive bundle [24]. The contradictory results could be explained by presence of multiple factors which could affect the results of the sputum cultures. There might be differences between the studies in the type of empirical antibiotics, sensitivity of the bacteria, duration of the antibiotics and timing of sampling in relation to antibiotic initiation of MV induction.

The current study demonstrated that clinical, radiological findings and mechanical ventilator parameters showed significant deterioration after 48 hours among patients who did not receive VAP preventive bundle while VAP preventive bundle induced significant improvement in clinical, radiological findings and mechanical ventilator parameters. Based on the previous clinical, laboratory and radiological findings, VAP was diagnosed in 19 patients (19.4%) which was distributed as 4 patients out of 49 patients received VAP preventive bundle representing 8.2% and 15 patients out of 49 patients received basic routine infection control representing 30.6% and exhibiting statistically significant difference *(p= 0.005)* and reflecting that VAP preventive bundle is considered significant protector against incidence of VAP. These results were confirmed in the multivariate analysis for the predictors for VAP as non- implementation of VAP preventive bundle increased the risk for VAP by 3.4 (OR: 3.4) with p value *0.008*.

In concordance with the present study, *Pinilla-González et al.* reported a significant reduction in the pooled incidence density of VAP after implementation of VAP preventive bundle (1.93 episodes/1000 ventilator days) as compared to pre- implementation of this bundle (11.79 episodes/1000 ventilator days) with OR = 5.0766[5].

Also, more recent study demonstrated that VAP rate was significantly decreased from 60.7% to 31.5% *(p= 0.019)* after application of VAP preventive bundle [19].

Extensive hand hygiene training sessions were conducted throughout the study period, 6-steps hand washing posters were displayed on all sinks, alcohol-based hand rub

solution was placed at each bedside, and in the corridor and continuous monitoring and feedback were provided to the NICU care providers to improve compliance with hand hygiene. Contamination of ventilator circuit can also facilitate pathogenesis of VAP, thus collection in the tubing should be drained away regularly to prevent aspiration. We also adopted use of sterile reusable respiratory care equipment, sterile water in humidifier chamber, regular drainage of condensate from the breathing circuit and hand hygiene before and after contact with respiratory equipment. The attendant resident and the senior nurse of each shift assessed and monitored the implementation of all items used as VAP bundle preventive strategy and the nurses were asked to record these steps.

In contrast with the present study, *Gokce et al.* [26] did not find significant reduction of VAP incidence after implementation of VAP preventive bundle (p= 0.07) in spite of lower rates of VAP among patients received the bundle. However, he reported that head of the bed elevation and oral care significantly reduced VAP incidence *(p= 0.04; < 0.001)* while hand hygiene, Absence of visibly solid contamination in breathing circuits, periodically drain and discard of ventilator circuit condensate did not induce significant reduction of VAP incidence. The contradictory could be explained by the differences in the study design and analysis as in our study, we adopted all scales of VAP preventive bundle and assessed the overall effect of the combined scales. Meanwhile, *Gokce et al.* assessed the efficacy of each scale of VAP preventive bundle alone [26].

Mean duration of mechanical ventilation was 9.4 ± 3.1 days, mean duration of hospital stay was 17.9 ± 5.2 days and both were significantly lower among patients received VAP preventive bundle than conventional *(p= 0.015; 0.046)*. In agreement with the present study, recent study by *Abu-Elenen et al.* demonstrated that implementation of VAP preventive bundle significantly decreased duration of mechanical ventilation and length of hospital stay *(p= 0.001)* [19]. *Azab et al.* VAP preventive bundle implementation *resulted* in significant reduction of mechanical ventilation duration [20].

In contrast with the present study, *Azab et al.* did not find significant effect of VAP preventive bundle implementation on duration of hospital stay [20]. Also, *Pinilla-González et al.* did not find significant differences in mechanical ventilation duration or length of hospital stay between patients received VAP preventive bundle and who did not [5]. The contradictory results could be explained by the differences in the main causes of mechanical ventilation between the different studies.

Out of 98 patients included in this study, 6 patients died and all of them belonged to the patients who received the basic routine infection control *(p= 0.011)*. Survival analysis showed better survival benefits of VAP preventive bundle over conventional group *(p= 0.011)*. a gentle slope from 21 to 90 days after initiation of MV. The curves of MV withdrawal and ICU/HCU
discharge were almost identical, having an initial steep slope and transition to a gentle slope in the last third of the curve

Out of 98 patients included in this study, 6 patients died and all of them belonged to the patients who received the basic routine infection control *(p= 0.011)*. Kaplan-Meier Survival analysis showed better survival benefits of VAP preventive bundle over conventional group as all bundle group patients were discharged alive while 12.2% of conventional group patients died with statistically significant differences (*p= 0.011)*. The analysis in the conventional group had a gentle slope of cases of death after day 12 of initiation of mechanical ventilation then a steep slope after day 20 of mechanical ventilation.

The results came in agreement with the results of previous study which demonstrated that mortality rate decreased from 14% to 2.7% after implementation of VAP preventive bundle *(p< 0.001)* [24].

On contrary to the present study, VAP preventive bundle did not have significant effect on mortality rates (VAP preventive bundle vs. conventional: 25.8% vs. 17.3%; p= 0.22) in previous study [20]. Another study by *Gokce et al.* did not report significant

effect of VAP preventive bundle on mortality rate [26]. He reported an explanation for this finding as he claimed that causes of death were other than VAP.

Multivariate analysis was done to assess the predictors of neonatal VAP. The analysis confirmed the protective effect of VAP preventive bundle against incidence of VAP as compared to conventional even after being adjusted for the confounders and this was discussed before.

The current study demonstrated that age and sex were not significant predictors for VAP. These results came in agreement with a previous study which compared 13 VAP patients to 13 controls and did not report age or sex as significant predictors for VAP [27]. Similarly, *El- Sayed et al.* [28] did not find significant sex differences between VAP and no- VAP patients. Also, *Pahwa et al.* [29] did not find significant differences between VAP and non- VAP patients as regards age and sex.

The present study showed that gestational age, weight and being low birth weight were not significant predictors for neonatal VAP. Similarly, *Dang et al.* [30] could not find significant differences between VAP and non- VAP groups as regards gestational age or weight.

On contrary to the present study, *El-Sayed et al.* compared 45 VAP patients to 70 non- VAP patients and demonstrated that gestational age and weight were significant predictors for VAP *(p= 0.001; 0.005)* in the univariate analysis [28]. Presence of other confounders or risk factors for VAP could affect the analysis, and the contradictory results were obtained in the univariate analysis which was not adjusted for presence of confounders.

The present study reported that presence of maternal diseases and PROM were significant predictors for VAP *(OR: 8.8; 7.3: p= 0.04; 0.03).* In hand with the present study, *Pahwa et al.*[29] showed that presence of maternal medical disorders increased the risk for VAP. In contrast with the present study, *Dang et al.* [30] did not find significant differences between VAP and no- VAP patients as regards PROM or associated medical disorders.

The current study reported that white blood cell count was a significant predictor for incidence of VAP as increase in WBC by 1000 increased the odds for VAP incidence by 1.7 time *(p= 0.04)*. Similarly, recent study demonstrated that increasing white blood count after mechanical ventilation is a significant predictor for incidence of VAP [28].

There were some Challenges and limitations for our preventive bundle of VAP. First of all, maintaining45-degree angle may be difficult if severe respiratory distress or cardiovascular instability are present. Also, despite early weaning from ventilator is one of our bundle practices, premature neonates or neonates with severe respiratory distress may not be ready for this so prolonged mechanical ventilation may be unavoidable. The third limitation was the need for Ongoing training which require dedicated time, and administrative support and with presence of staff turnover in NICUs and the transient nature of many healthcare providers due to rotations, that may result in rare occasions of inconsistent implementation of some preventive practices which were corrected rapidly.

Conclusion:

The study demonstrated that applying a VAP preventive bundle in neonates on mechanical ventilation markedly reduced VAP incidence, improved respiratory and clinical outcomes, and enhanced survival rates. The bundle approach should be recommended as a standard preventive strategy in neonatal intensive care units.

Conflict of interest: None.

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Availability of the data: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: A.H, and E.A, contributed to data collection and analysis. H.K was responsible for manuscript writing and preparing the article for publication. All authors reviewed and approved the final version.

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Table (S1): Multivariate analysis for predictors for VAP among mechanically ventilated neonates:

Predictors	95% confidence interval		Estimates	Odds ratio	p value
	Lower	Upper			
Age	0.85	3.8	0.58	1.8	0.12
Sex (male)	0.006	3.8	-1.8	0.16	0.25
Gestational age	0.34	3.57	0.09	1.1	0.86
Birth weight	0.99	1.02	0.006	1.007	0.18
Low birth weight	2.9	3.4	8.06	3.1	0.81
Maternal diseases	1.46	5.3	11.4	8.8	*0.04*
PROM	2.08	2.55	8.9	7.3	*0.03*
Groups (conventional)	0.18	6.3	1.2	3.4	*0.008*
White blood cells	1.009	3.15	0.6	1.7	*0.04*

PROM: Premature rupture of membrane; Binary logistic regression; Level of significance < 0.05.

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