Magna Scientia Advanced Research and Reviews

eISSN: 2582-9394

Cross Ref DOI: 10.30574/msarr

Journal homepage: https://magnascientiapub.com/journals/msarr/

(Review Article)

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The impact of anemia on prolonged ventilator use in critically ill patients: A literature review

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Magna Scientia Advanced Research and Reviews, 2024, 12(01), 133–141

Publication history: Received on 01 September 2024; revised on 10 October 2024; accepted on 12 October 2024

Article DOI: https://doi.org/10.30574/msarr.2024.12.1.0157

Abstract

Anemia is a common condition associated with critically ill patients admitted to intensive care unit (ICU), where 60% of ICU patients experience anemia and 61% of anemic and tranfused patients present in the ICU require mechanical ventilation. The presence of anemia in critically ill patients is associated with increased risk of mortality, cardiovascular morbidity, and decreased oxygen-carrying capacity, potentially prolonging the need for mechanical ventilation. Mechanical ventilation is the primary method of supporting organ function for patients receiving treatment in the ICU. According to epidemiological studies, up to 70% of patients hospitalized to the ICU require mechanical ventilation at some time during their stay. Studies regarding the correlation between anemia and the length of ventilator use are rarely known. Therefore, researchers are interested in conducting research on the correlation between anemia and length of ventilator use. This review is expected to be useful for enriching knowledge about the relationship between anemia and length of ventilator use in critically ill patients. However, further research is needed with more comprehensive variables to determine the impact of anemia on prolonged ventilator use, risk factors of weaning failure, pathogenesis of anemia, and treatment used in critically ill patients.

Keywords: Anemia; Mechanical ventilation; Ventilator; Critically ill patients; ICU.

1. Introduction

Anemia is a common condition associated with critically ill patients admitted to intensive care unit (ICU) (Rawal et al., 2016). Approximately 60% of ICU patients are anemic and 61% of anemic and tranfused patients present in the ICU require mechanical ventilation (Czempik & Krzych, 2022; Elsayed et al., 2022; Jati et al., 2023). The presence of anemia in critically ill patients is associated with increased risk of mortality, cardiovascular morbidity, and decreased oxygen-carrying capacity, potentially prolonging the need for mechanical ventilation (Smith et al., 2016). Mechanical ventilation is the primary method of supporting organ function for patients receiving treatment in the intensive care unit (ICU) (Alemayehu et al., 2022). According to epidemiological studies, up to 70% of patients hospitalized to the ICU require mechanical ventilation at some time during their stay (Abate et al., 2023).

Previous study has suggested that anemia may impair ventilator weaning and extubation ability (Jati et al., 2023). Lower hemoglobin levels during the ventilator weaning process increase the respiratory muscle load and reduce arterial oxygen content, which impairs oxygen delivery. A study in Taiwan in 2013 stated that patients with hemoglobin levels ≥8 g/dL had a higher chance of being successfully weaned off the ventilator than those with levels <8 g/dL (Lai et al., 2013). In addition, the presence of anemia in patients receiving long-term mechanical ventilation may impair their ability to stop using ventilatory support (Ghiani et al., 2019).

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Studies regarding the correlation between anemia and the length of ventilator use are rarely known. Therefore, researchers are interested in conducting research on the correlation between anemia and length of ventilator use in critically ill patients.

2. Review Content

2.1. Anemia

2.1.1. Definition of Anemia

The term "anemia" refers to a drop in erythrocyte content or blood's ability to carry oxygen due to a drop in packed cell volume, red blood cell (RBC) count, or hemoglobin concentration below the recommended level (Padalino et al., 2016). Anemia is not a diagnosis, but a description of an underlying condition. Depending on the origin, severity of onset, and existence of concomitant comorbidities, particularly cardiovascular illness, anemic individuals may or may not exhibit symptoms (Turner et al., 2023). Hemoglobin values <12.0 g/dl in women and <13.0 g/dl in males are considered anemia (World Health Organization, 2011). The ability of the blood to transfer oxygen to the body's tissues is dependent on hemoglobin; if there are insufficient red blood cells or hemoglobin, this ability will be diminished (World Health Organization, 2022).

Anemia is a common condition linked to critically ill patients admitted to an ICU, with a prevalence of 60–66% of patients at admission, 90% of patients on day three and 97% of patients on day eight in the ICU are anemic (Czempik & Krzych, 2022; Lasocki et al., 2020; Napolitano, 2018, Rawal et al., 2016). According to Jati et al. (2023), 61% of anemic ICU patients need mechanical breathing.

2.1.2. Anemia in Critically Ill Patient

The determinants of anemia in critical illness are complex and often multifactorial (Napolitano, 2018). The etiologies of anemia are not only due to factors which generate admission to the ICU, such as trauma, surgery, and gastrointestinal bleeding, however, they can also be caused by blood losses during ICU hospitalization due to invasive procedures such as drainage, catheterizations, dialysis, and repeated blood samplings (Juárez-Vela et al., 2022; Rineau et al., 2015). In spite of those, anemia in critical patients can be caused by nutritional (iron, folic acid, vitamin B12) deficiency, and increased destruction of RBCs or RBC precursor in the bone marrow due to toxins and drugs (Rawal et al., 2016). Based on a study in France, another major mechanism involved in anemia in critical illness is inflammation. Inflammation is a major contributor to "anemia of inflammation" or "anemia of chronic disease". Inflammation impairs bone marrow erythropoiesis, suppresses erythropoietin synthesis, and reduces red blood cell lifespan (Rineau et al., 2015).

In recent studies, inflammation is associated with anemia in sepsis patients, so it is often called sepsis-related anemia. Hepcidin is a key regulator in this kind of anemia as it is able to reduce plasma iron levels through direct inhibition of intestinal iron absorption; increasing iron storage in macrophages by decreasing ferroportin expression in intestinal mucosa and macrophages. Elevated interleukin (IL)-6 in patients with sepsis can induce a sudden increase in hepcidin synthesis, causing a decrease in plasma iron. Plasma iron can be depressed by inflammation markedly (>50%) and rapidly (24 hours) (Jiang et al., 2019). In addition, sepsis was associated with increased circulating EPO levels compared to healthy control values, but ICU patients had a smaller increase in EPO compared to healthy subjects with the same level of anemia, implicating a blunted EPO response in the pathophysiology of anemia in critical illness (Loftus et al., 2019).

2.1.3. Treatment of Anemia

Anemia treatment is a key aspect in the treatment of critically ill patients (Tanner et al., 2022). Previous research suggests that the best treatment for anemia of critical illness would be resolution of the underlying disease that led to anemia of critical illness (Czempik & Krzych, 2022; Napolitano, 2018). In addition, another treatment that can be used is red blood cell transfusion. Red blood cell transfusion is the fastest way to increase hemoglobin levels in severe anemia (Du Pont-Thibodeau et al., 2014). About 27% of patients in postoperative ICUs and 16% in medical ICUs receive blood transfusions during their ICU stay (Elsayed et al., 2022).

Prior research has demonstrated that, in comparison to a liberal approach, red blood cell transfusion with a limited hemoglobin threshold is safe and may lower in-hospital mortality in critically ill individuals (Czempik & Krzych, 2022). It has been demonstrated that a restrictive blood transfusion protocol, with a hemoglobin threshold of less than 7 g/dL, is beneficial in lowering overall mortality, infections, and cardiac issues in critically ill patients (apart from those with cardiovascular disease, such as acute myocardial infarction or unstable angina). For patients with acute cardiovascular illness and early stages of severe sepsis, hemoglobin values of 9–10 g/dL are recommended. Also, according to this study, giving packed red blood cells (PRBCs) to critically ill patients improves oxygen delivery, which lowers tissue hypoxia (Rawal et al., 2016). It is important to emphasize, nonetheless, that red blood cell transfusion is not completely risk-free, as it raises the possibility of infection complications and patient's mortality (Du Pont-Thibodeau et al., 2014; Loftus et al., 2019). When treating anemia in critically ill patients, transfusion danger should be weighed against low oxygen content risk, taking into account the patient's physiological situation (Spinelli & Bartlett, 2016).

Erythropoietin (EPO) is a glycoprotein hormone produced by the peritubular cells of the renal cortex which stimulates red blood cell production in response to low partial pressure of oxygen (pO_2) (Schoener & Borger, 2024). Exogenous erythropoietin administration has been investigated as therapeutic strategy for the management of critically ill anemic subjects, with mixed results in large randomized trials (Loftus et al., 2019). A meta-analysis of studies on erythropoiesis-stimulating agents (ESA) stated that ESA therapy reduced in-hospital mortality, but adverse effects and thromboembolic events were found to be increased in the ESA-treated group, however the association of adverse effects and thromboembolic events was not statistically significant (Litton et al., 2019).

Based on a study in Australia, it was found that intravenous iron, however it may come with an elevated risk of infection, dramatically reduces anemia and the need for red blood cell transfusions in hospitalized patients when compared to either oral iron or no iron at all (Litton & Lim, 2019). In chronic illnesses with anemia of inflammation, such as chronic renal disease, inflammatory bowel disease, and heart failure, intravenous iron improves hemoglobin, functional performance, and quality of life (Shah et al., 2022). Nevertheless, there have been concerns about this kind of treatment because iron has been linked to the virulence and proliferation of bacteria that cause nosocomial infections, and lowering iron levels may be the body's protective reaction to sepsis. Before this therapy may be widely used, more study is required (Rawal et al., 2016).

2.2. Ventilator

2.2.1. Definition of Ventilator

A mechanical ventilator is a device that functions to move air in and out of the lungs with the aim of supporting the patient's breathing efforts, either partially or entirely (NHLBI, 2022; Prasad & Patil, 2022). The increasing use of mechanical ventilation is associated with greater hospitalization in intensive care units and is due to the advent of sophisticated surgical procedures, an aging population, more aggressive medical, neurological, and oncological treatments, and better care for critical illnesses (Zisk-Rony et al., 2019).

Mechanical ventilation can be divided into two: non-invasive ventilation and invasive ventilation. Non-invasive mechanical ventilation involves use of a machine that delivers oxygen and removes carbon dioxide through an external device (such as a face mask). Patients who have mild to moderate respiratory difficulties as a result of an acute or long-term medical problem are most frequently candidates for this kind of ventilation (Walter, 2021). In the other side, invasive mechanical ventilation uses an endotracheal tube (ETT) as the interface (as opposed to non-invasive ventilation in which the interface is a face mask). In addition to serving as the conduit for delivery of mechanical breaths, the ETT protects the airway, allows for suctioning of secretions, and facilitates select procedures, including bronchoscopy. Invasive mechanical ventilation reduces inspiratory work of breathing, redistributes blood flow from exercising respiratory muscles to other tissues in patients in shock, and enables lung-protective (low tidal volume) ventilation in patients suffering from acute respiratory distress syndrome (ARDS). All of these benefits help stabilize patients with hypoxemic and hypercapnic respiratory failure (Walter et al., 2018).

2.2.2. Indication of Ventilator

Mechanical ventilators are usually used in conditions that cause low oxygen levels (such as pneumonia) or high carbon dioxide levels (such as chronic obstructive pulmonary disease) (Walter, 2021). Prasad & Patil (2022) divide the main indications of mechanical ventilation into 3: decreased ventilatory drive, increased ventilatory workload, and inadequate respiratory muscle function.

Decreased ventilatory drive

The ventilatory drive, or more commonly called respiratory drive, is the intensity of the output of the respiratory centers, using the amplitude of a physiological signal as a measure for intensity (Jonkman et al., 2020). Simultaneously taking into account the ventilatory demands, as determined by the activity of respiratory centers in reaction to CO_2 (brain curve); the actual ventilatory response to CO_2 (ventilation curve); and metabolic hyperbola, can explain changes in respiratory drive. Numerous processes that impact the brain, ventilation curves, and metabolic hyperbola during severe illness significantly change respiratory drive. The inspiratory flow-generation pathway is always disrupted, sometimes severely, in critically ill individuals. A separation between the brain and ventilation curves results from mean inspiratory flow and tidal volume not matching respiratory drive, and actual ventilation being lower than ventilatory demands at a given $PaCO_2$. Since the metabolic hyperbola is one of the two variables that determine $PaCO_2$ (the other being the ventilation curve), its upward or downward movements increase or decrease respiratory drive, respectively (Georgopoulos et al., 2024).

Increased ventilatory workload

According to Bach et al. (2021), there are several conditions that cause increased inspiratory load, namely chest wall stiffness, airway obstruction, and diaphragm weakness. For example, in patients with asthma and chronic obstructive pulmonary disease (COPD) there is a significant increase in ventilatory workload (Muñoz-Cofré et al., 2024). In patients with asthma, there is inflammation and muscle tightening around the airways, which makes it harder to breathe (World Health Organization, 2024). Meanwhile in people with COPD, there are several processes such as destruction of parts of the lung, mucus blocking the airways, and inflammation and swelling of the airway lining which can cause the airways to become narrow (World Health Organization, 2023).

Inadequate respiratory muscle function

The respiratory system consists of several respiratory muscles that form a complex pulmonary pump system. Coordination of these muscles is necessary for breathing (Kanwade & Bairagi, 2022). Some diseases may show symptoms of weakness in the respiratory muscles, such as in COPD patients which may be caused by hyperinflation of the lungs or flattening and shortening of the diaphragm (Kim et al., 2017; Silva et al., 2024). In addition, respiratory muscle weakness is also often found in patients with neuromuscular dysfunction. Some examples of neuromuscular dysfunction diseases are Guillain-Barré syndrome (GBS), post-polio syndrome, and amyotrophic lateral sclerosis (ALS) (Bourke, 2014).

2.2.3. Contraindication of Ventilator

Previous research states that contraindications to the use of non-invasive ventilators are divided into absolute contraindications and relative contraindications. The absolute contraindications include facial trauma/burns, fixed upper airway obstruction, active vomiting, and respiratory or cardiac arrest. Meanwhile the relative contraindications are a recent facial, upper airway, or upper GI tract surgery, inability to protect the airway, life-threatening hypoxemia, medical or hemodynamic instability (hypotensive shock, myocardial infarction requiring intervention, uncontrolled ischemia or arrhythmias), altered mental status/agitation, bowel obstruction, copious respiratory secretions, focal consolidation, undrained pneumothorax, and severe comorbidity (Gong & Sankari, 2022).

As for invasive mechanical ventilation, there are some contraindications to the use of endotracheal intubation. The contraindications to endotracheal intubation include facial trauma, severe airway trauma or obstruction that does not permit the safe placement of an endotracheal tube, severe cervical spine injury which requires complete immobilization, patients with Mallampati III/IV classification suggesting potentially difficult airway management, head trauma concerning for basilar skull fracture, active epistaxis, expanding neck hematoma, oropharyngeal trauma, and apneic patients (Ahmed & Boyer, 2023; Avva et al., 2023).

2.2.4. Complications of Ventilator Use

There are several complications associated with mechanical ventilation. These complications include barotrauma, volutrauma, ventilator-associated lung injury (VALI), ventilator-induced lung injury (VILI), acute hypoventilation, hyperventilation, complications associated with the artificial airway, alveolar collapse, infection of the patient's airway, excessive heat to the airway from the humidification system, and inadequate or excessive humidification (Cairo, 2020).

Barotrauma and volutrauma

Ventilator-induced barotrauma is a complication of intubation associated with high driving pressures and the use of positive end-expiratory pressure (Sah et al., 2021). Volutrauma is a term that describes ultrastructural lung injury resulting from overdistension that occurs during mechanical ventilation. The terms barotrauma and volutrauma reflect two sides of the same phenomenon, namely lung injury due to an enlarged volume and/or high airway pressure (Ioannidis et al., 2015).

Ventilator-associated lung injury (VALI)

Mechanical ventilation can cause VALI through the following four main mechanisms: 1) increased stress and strain, caused by high tidal volumes; 2) increased shear stress, i.e. opening and closing, of previously atelectatic alveolar units; 3) perfusion distribution and 4) biotrauma. The use of high tidal volumes in previously uninjured lungs can also lead to VALI (Sutherasan et al., 2014).

Ventilator-induced lung injury (VILI)

VILI is lung damage caused by overdistension at high lung volumes, and collapse/reopening of airway units at low lung volumes (Curley et al., 2016). VILI can occur due to high airway force. Changes in vascular forces (especially vascular cuts) from adverse heart-lung interactions can also synergize with airway forces to compound lung injury (Katira, 2019).

Alveolar collapse

Mechanical ventilation is necessary to support the injured lung to improve gas exchange, but mechanical ventilation can also exacerbate atelectrauma and recruitment/derecruitment which ultimately leads to ARDS (Kollisch-Singule et al., 2020). Alveolar distension and injury lead to increased alveolar permeability, alveolar and interstitial edema, alveolar hemorrhage, and hyaline membrane formation, resulting in reduced functional surfactant and thus alveolar collapse (Kumar & Anjum, 2023).

Acute hypoventilation

Acute hypoventilation can occur in patients receiving assisted ventilation if adequate alveolar ventilation is not available. Hypoventilation will cause an increase in $PaCO_2$ and acidosis pH. Rapidly increasing $PaCO_2$ levels and decreasing pH values can cause serious problems (Cairo, 2020).

Hyperventilation

Ventilator-induced hyperventilation is generally caused by improper ventilator settings. Ventilator removal becomes more difficult when the patient has prolonged hyperventilation (Cairo, 2020).

Airway infection

Ventilator-associated pneumonia (VAP) is the most common infection experienced among patients receiving invasive mechanical ventilation in the ICU (Oliveira et al., 2014). The presence of an ETT is one of the main causes of VAP development as airflow transfers pathogens to the distal airways, while the ability of the trachea to perform clearance decreases due to reduced tracheal cilia movement and impaired coughing (Coppadoro et al., 2019).

Problems with humidification systems

Medical gas humidification processes play an important role in invasive and non-invasive ventilation, aiming to reduce complications arising from bronchial dryness. Passive humidification systems and active humidification systems are commonly used systems in routine clinical practice, where active humidification systems are associated with adjustable electric humidifiers, while passive humidification systems use filters capable of capturing heat and water vapor during the expiratory phase and redistributing it during the inspiratory phase. The limitations of humidification strategies are manifested by variability in patient physiology, device performance, and environmental conditions, which emphasizes the need for an individualized approach to gas conditioning (Re et al., 2024).

2.3. The Impact of Anemia on Length of Ventilator Use

Several studies have suggested that anemia may impair ventilator weaning and extubation, as well as being a risk factor for extubation failure (Artime & Hagberg, 2014, Jati et al., 2023). According to a study in Taiwan which the subjects were difficult-to-wean patients, hemoglobin levels of 8–10 g/dL and >10 g/dL were positively related with effective weaning in univariate analysis, compared to hemoglobin levels <8 g/dL. It was also discovered that the severity of the disease had a significant impact on the weaning process. Furthermore, the patient's hemoglobin level was impacted by the severity of the illness (Lai et al., 2013).

According to a research conducted in the United States, patients with hemoglobin concentrations less than 10 g/dl were more than five times more likely to need reintubation following a successful initial spontaneous breathing and extubation test, among 91 patients recovering from acute respiratory failure. Among 222 patients with COPD requiring invasive mechanical ventilation, the adjusted risk of death within 90 days of admission for anemic patients (hemoglobin, 12 g/dl) was 2.6 times that of those with normal values (12-15 g/dl) (Hayden et al., 2012).

An observational study conducted by Ghiani et al. (2019) on 378 prolonged mechanically ventilated and tracheotomized patients admitted to a national weaning center, showed that transfused and non-transfused patients differed significantly in terms of disease severity and comorbidities. In multivariate analysis, RBC transfusion was independently correlated with weaning duration and length of hospital stay; there was also a trend toward increased mortality in hospital, but no independent correlation with weaning outcomes or nosocomial infections. In contrast, hemoglobin level on the day of admission to the weaning center was independently associated with in-hospital mortality where mortality rate was significantly increased in patients with hemoglobin below 8.5 g/dl.

In clinical practice, weaning and extubation occur one after the other and are two isolated processes that pose distinct problems. Extubation failure is the need for reinstitution of ventilatory support within 24 to 72 hours of planned removal of endotracheal tube. A prospective observational study in Egypt involving 100 mechanically ventilated patients admitted to the respiratory intensive care unit (RICU) with various respiratory diseases found that reintubation is required for over 20% of patients. In comparison to the initial intubation process, reintubation is a more dangerous procedure that may have more negative effects. Reintubation patients had significatly longer duration of mechanical ventilation, as well as longer ICU stays, hospital stays, and increased fatality rates. Besides that, the reintubated group had considerably lower hemoglobin and albumin levels. 50% of reintubated cases expressed difficult weaning. On the other hand, 64% in non reintubated patients expressed simple weaning (El-Shenawy et al., 2022).

The severity of anemia on admission in critically ill patients is also associated with poor outcome, increased morbidity and mortality, and longer ICU length of stay (Czempik & Krzych, 2022; Lasocki et al., 2020; Warner et al., 2020). The presence of anemia in critical illness is associated with an increased risk of mortality, cardiovascular morbidity, and decreased oxygen-carrying capacity, potentially prolonging the need for mechanical ventilation. This will be particularly concerning in critically ill patients who already have a history of cardiopulmonary disease (Smith et al., 2016).

3. Conclusion

In conclusion, this review explores the relationship between anemia and length of ventilator use in critically ill patients in the ICU. Anemic patients have a longer duration of ventilator use and higher mortality compared to patients without anemia, but this condition is also influenced by the primary disease and treatment used in patients. This review highlights the relationship between anemia and length of ventilator use and emphasizes the need for a comprehensive strategy for the treatment of anemic patients with the aim of reducing mortality in the ICU. Therefore, further research is needed regarding anemia and duration of mechanical ventilation in critically ill patients with special consideration for the primary disease, risk factors for weaning failure, pathogenesis of anemia, and treatment used in critically ill patients.

Compliance with ethical standards

Acknowledgments

The author would like to thank all supervisors and various parties who have helped carry out this research well.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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