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Does Prone Positioning Decrease Mortality Rate in ARDS? A Systematic Review

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DOES PRONE POSITIONING DECREASE MORTALITY RATE IN ARDS?

A SYSTEMATIC REVIEW

by

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is a clinical condition in which the lungs suffer severe irreversible, large-scale damage causing a grievous form of hypoxemic respiratory failure. Acute respiratory distress syndrome is one of the most evasive diagnosis confronted in the Intensive care unit (ICU) as the name, definition and diagnostic standards have adapted over the past four decades. An ARDS diagnosis is established by physiological criteria and continues to be a diagnosis of exclusion, which makes it crucial that medical professionals expand their knowledge base to effectively diagnose ARDS. Patients admitted with ARDS have high mortality rates ranging from 40 to 60 percent. High-level quality supportive care continues to be the sole option for ARDS treatment. Even with improved supportive care, however, ARDS prognosis is still poor. Extended prone positioning (PP) has been shown to increase alveolar recruitment end expiratory lung volume, thereby improving oxygenation and survival. Unfortunately, few studies have examined the association of mortality and prone positioning in ARDS. A systematic review was conducted to examine the following research question: Does prone positioning compared to supine positioning in patients with ARDS decrease mortality rates? This systematic review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Critical Appraisal Skills Programme (CASP). A literature review was performed and data were collected from each study. A cross study analysis was performed and PP was found to reduce mortality rate in patients who were severely hypoxic. The reviewed studies demonstrated that incorporating early and longer periods of PP may improve mortality in ARDS patients, but further research is needed.

Table of Contents

Does Prone Positioning Decrease Mortality Rate in ARDS? A Systematic Review

Background/Statement of the Problem

Acute Respiratory Distress Syndrome (ARDS) is a clinical condition in which the lungs suffer severe, large-scale injury interrupting their ability to take up oxygen. In the United States, 190,600 people develop Acute Lung Injury (ALI), resulting in a mortality rate of 37.9% or 74,500 deaths per year. Collectively, ALI and ARDS cause approximately twice as many deaths per year as breast cancer or prostate cancer and several times more than HIV/AIDS (Acute Respiratory Distress Syndrome, 2017). According to a study conducted by Schwartz, Malhotra, and Kacmarek, (2017) the rate of ALI is 18–79 incidents/100,000 persons per year, versus 13–59 ARDS incidents/100,000 persons per year.

Acute respiratory distress syndrome is associated with a high mortality rate and severe hypoxemia, which typically occurs in patients already in the Intensive Care Unit (ICU) (Taccone et al., 2009). Prone positioning is currently recommended for ARDS patients with moderate to severe hypoxemia as a rescue plan. The prevalence of ARDS with mortality rates greater than 50% was reported in most clinical studies performed between 1979 and 1994. Despite medical advances and research in the past 30 years, ARDS mortality rates continued to be greater than 50% until recently (Taylor, 2005). Newer studies that implement prone positioning show a decrease in mortality rates of 32%-45% (Udobi, Childs, & Toujier, 2017).

The occurrence of ARDS depends on several factors and includes infectious diseases, such as sepsis and pneumonia. Trauma patients and those who have aspirated stomach contents such as vomitus, blood, mucus or food into the lung are also at high risk

for ARDS. Other chronic diseases such as chronic obstructive pulmonary disease (COPD), asthma, and emphysema, which decrease lung compliance hindering lung tissue oxygenation, contribute to the occurrence of ARDS. Infections, like sepsis and pneumonia, cause inflammation which lead to lung tissue injury. The leakage of blood and plasma from the lung capillaries to the alveoli result in moderate to severe hypoxemia. Mechanical ventilation (MV) is required to deliver higher concentrations of oxygen and remove carbon dioxide from the body. ARDS patients account for 15 to 18 % of all ventilated patients (Wiener-Kronish, Gropper, & Matthay, 1990).

Alternating a patient's position from supine to prone can enhance the dispersion of perfusion to ventilated lung domains, diminishing intrapulmonary shunting and improving oxygenation; however, a variety of opinions exist among clinicians regarding the efficacy of prone versus supine positioning (Dickinson, Park, & Napolitano, 2011).

The purpose of this paper is to conduct a systematic review to determine if prone positioning compared to supine positioning in patients with ARDS decreases mortality rates.

Next, the review of the literature will be presented.

Literature Review

The healthcare system in the United States has developed into one that depends on clinical decision-making influenced by evidence-based research. The process of understanding a disease pathophysiology can help determine the most suitable medical management, which requires a thorough review, critique and understanding of the current research on the subject matter. Examining available research indicates that prone positioning (PP) may affect mortality in ARDS patients.

Pathophysiology of ARDS

Acute respiratory distress syndrome is one of the most common causes for admission to the intensive care unit (ICU) setting. The hallmark of ARDS is increased capillary permeability which causes injury to the capillary endothelium and alveolar epithelium. The result is a buildup of protein-rich fluid inside the alveoli and the release of proinflammatory cytokines. This cascade of events leads to reduced fluid removal from the alveolar space, resulting in hypoxemia (Pierrakos, Karanikolas, Scolletta, Karamouzos, & Velissaris, 2012). Improvement of hypoxemia can be confirmed by several methods including a constant distribution of transpulmonary pressure and the creation of more negative pleural pressure. This stimulates the enhancement of the ratio of ventilation to perfusion (Oliveira et al., 2016).

Phases of ARDS

Diffuse alveolar damage (DAD) and ARDS are associated with lung capillary endothelial injury. There are three phases of ARDS and they include the exudative, proliferative, and fibrotic phases (Udobi et al., 2017).

Phase one. During the exudative phase water, protein, inflammatory fluids, and red blood cells escape into the interstitium and an alveolar lumen occurs due to damage to the alveolar epithelium and vascular endothelium. Alveolar collapse results due to irreversible damage to the type I alveolar cells by depositing proteins, fibrin and cellular debris that damage the surfactant-producing type II cells (Udobi et al., 2017).

Phase two. During the proliferative phase, type II cells multiply with epithelial cell formations resulting in fibroblastic reaction and remodeling (Udobi et al., 2017).

Phase three. During the fibrotic phase, collagen deposits in alveolar, vascular, and interstitial beds (Udobi et al., 2017). The main location of injury may be concentrated in the vascular endothelium in the case of sepsis or the alveolar epithelium in the case of aspiration of gastric contents (Harman, 2017). The injury to the alveolar lining cells also induces the creation of pulmonary edema.

Definition of ARDS

Medical professionals currently use the newly adoped Berlin definition of ARDS. Prior to the Berlin definiton, an older definition by the The American-European Consensus Conference (AECC) was used (Figure 1), which consisted of diagnostic criteria and defined parameters (Fioretto & de Carvalho, 2013).
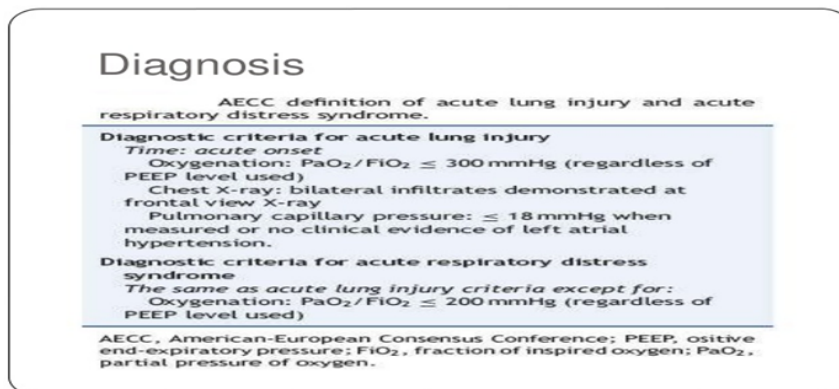

Figure 1. The American-European Consensus Conference (AECC) diagnostic criteria.

The newly adopted Berlin definition of ARDS consists of the following clearly defined parameters listed in Figure 2 (Fanelli et al., 2013). This revised definition aids clinical practitioners in the early identification of ARDS. The Berlin definition also eliminated the use of the term Acute Lung Injury (ALI) and changed the classification of ARDS to mild, moderate and severe corresponding to the PaO_2/FiO_2 ratio, reflected only with a CPAP or PEEP value of at minimum of $5cmH_2O$.

	ACUTE RESPIRATORY DISTRESS SYNDROME		
Timing	Within 1 week of a known clinical insult of new/worsening respiratory symptoms		
Chest Imaging [a]	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present		
	Mild	Moderate	Severe
Oxygenation [b]	$200 < PaO_2/FiO_2 \leq 300$ with PEEP or CPAP ≥ 5 cmH_2O [c]	$100 < PaO_2/FiO_2 \leq 200$ with PEEP ≥ 5 cmH_2O	$PaO_2/FiO_2 \leq 100$ with PEEP ≥ 5 cmH_2O
Patients/Mortality	22% / 27%	50% / 32%	28% / 45%

[b] If altitude higher than 1000 m, correction should be made: $PaO_2/FiO_2 \times$ (barometric pressure/760)
[c] This may be delivered non-invasively in the Mild ARDS group

The ARDS Definition Taskforce. JAMA 2012;307:2526-2533.

Figure 2. The Berlin definition of ARDS.

Causes of ARDS

The underlying causes of ARDS are divided into two categories: direct or indirect injuries to the lungs (Bandi, Munnur & Matthay, 2004). Contributing factors to direct lung injury include pneumonia, inhalation injury, fat, air, or pulmonary emboli, congestive heart failure, pulmonary contusion, aspiration of gastric contents, near drowning, and exacerbation of obstructive lung diseases (Bandi et al.). Indirect lung injury may be caused by sepsis, multiple transfusions, pancreatitis or massive trauma. (Bandi et al.). Other causes of ARDS are listed in Table 1.

Table 1

Causes of ARDS (Ware & Matthay, 2000)

Direct lung injury	Indirect lung injury
Common causes: - Pneumonia - Aspiration of gastric contents	Common causes: - Sepsis - Severe trauma with shock and multiple transfusions
Less common causes: - Pulmonary contusion - Fat emboli - Near-drowning - Inhalational injury - Reperfusion pulmonary oedema	Less common causes: - Cardiopulmonary by-pass - Drug overdoes - Acute pancreatitis - Transfusion of blood products

In their study of clinical differences between direct ARDS and indirect ARDS, Shaver and Bastarache (2014) found that 55% of ARDS cases were reported to be caused by direct lung injury, with pneumonia being the initiating component. The remainder were from extrapulmonary infections and were the result of sepsis in 80% of ARDS cases. Shaver and Bastarache concluded that ARDS patients with indirect lung injury had significant improvement in pulmonary oxygenation when recruitment maneuvers and higher positive end-expiratory pressure (PEEP) were employed.

Pneumonia

In the severely ill patient population, ARDS and pneumonia are closely associated. While nosocomial infections complicate ARDS treatment, pulmonary infections caused by respiratory viruses are frequently responsible for severe pneumonia, but most often are the single cause of ARDS.

Community acquired pneumonia (CAP). Community-acquired pneumonia (CAP) is the most common cause of ARDS outside of a hospital setting. The occurrence

of pneumonia during ARDS seems to be exceptionally high. Regardless of the cause, supportive care for ARDS patients is similar. Current studies identify sepsis as the main link between pneumonia and ARDS (Bauer, Ewig, Rodloff, & Muller, 2006).

Chan et al. (2007) conducted a prospective observational clinical study to evaluate the effects of prone positioning on inflammatory markers in patients with ARDS related to CAP. Twenty-two respiratory ICU adult patients with severe ARDS and CAP were included in this study. All patients were mechanically ventilated and divided into two subgroups, a supine group (*n*=11) and a prone group (*n*=11). The prone group was continuously mechanically ventilated for at least 72 hours. Lab values of plasma cytokines were gathered at the start of the study, at 24-hours and 72-hour intervals, and serial PaO2/FiO2 ratios were captured as well. Over time, a significant decrease in plasma IL-6 levels concentration in the PRONE group ($p = 0.011$), which predicted the fourteenth-day mortality of all ARDS patients. Prone position demonstrated a lower incidence or severity of lung injury and ventilator-associated pneumonia. This was due to defensive ventilator settings, which included high positive end-expiratory pressure (PEEP) levels of up to 15 cm H_2O and low tidal volume (TV). Prone position and PEEP showed some advantageous effects in improving oxygenation in patients with diffuse infiltrates but did not reduce mortality. Complications in the prone group included vomiting, tissue swelling, and pressure sores. The limitations of this study are related to its observational nature and low number of patients enrolled.

Ventilator associated pneumonia (VAP) and ARDS. Ventilator associated pneumonia (VAP) develops 48 hours or longer status post intubation with an endotracheal tube or tracheostomy tube. The cause is from the takeover of the lower

respiratory tract and lung parenchyma by microorganisms (Amanullah, & Posner, 2015).

Markowicz et al. (2000) conducted a multicenter prospective study at eight medical and

three medicals surgical intensive care units (ICUs) at 10 hospitals. The study set forth to

determine the risk factors of VAP in patients with ARDS. The study compared 134

patients (group A) with ARDS to 744 patients (group B) without ARDS and all patients

were mechanically ventilated for a minimum of 48 hours. Ventilator associated

pneumonia prevailed in 49 (36.5%) patients out of 134 with ARDS versus 173 (23%)

patients out of 744 without ARDS (p<0.002). The group with ARDS sustained a 58%

mortality rate (78 of 134) in the ICU compared with 39% of the patients without ARDS

(Markowicz et al., 2000). Although this study illustrates a clear increase risk of

ventilator associated pneumonia during ARDS, pneumonia does not appear to increase

the mortality rate in mechanically ventilated patients. Limitations included conducting

the study in the same hospitals without addressing possible specific risk factors of VAP.

Markowicz et al. determined that VAP prolonged mechanical ventilation in both ARDS

and VAP groups. The results corresponded to high mortality, prolonged hospital stay,

and increased health care costs.

Prone positioning in ARDS

ARDS is a syndrome with various hidden pathological activity. Prone positioning

was first detailed 40 years ago. Prone positioning can be used in mechanically ventilated

patients with severe, hypoxic, respiratory failure to enhance oxygenation. It is an

adjunctive rescue strategy available in managing patients with ARDS in the ICU (Guérin

et al., 2013). Koulouras, Papathanakos, Papathanasiou, and Nakos's (2016) review

effectively supports that prone positioning has an auspicious effect on gas exchange,

respiratory mechanics, lung protection and hemodynamics. In a prone position, the

dorsal area of the lung is converted to the nondependent area and the ventral the

dependent, leading to a considerable lung tissue mass in the dorsal section. Hence, when

the gravity of the lung is repositioned to the ventral region, the greater dorsal partition of

the lung becomes capable to re-inflate (Gattinoni, Taccone, Carlesso, & Marini, 2013).

Prone positioning in ARDS patients improves alveolar recruitment compared to that in

the supine position (Gattinoni et al., 2013). Prone positioning relocates transpulmonary

pressure, strain and pressure across the lung field, and offloads the right ventricle of the

heart (Koulouras et al., 2016).

A prospective observational study conducted by Mounier et al. (2009) focused on

prone positioning to reduce ventilator-associated pneumonia in hypoxemic patients with

ARDS and ALI. This study included 2,409 patients from 12 different ICUs over an

eight-year period. All patients required MV and were in the prone position with an

arterial oxygen tension and inspiratory oxygen fraction of less than 300 in the initial 48

hours. While prone positioning did not reduce 28-day mortality rate or decrease VAP

occurrence (HR 1.64 (95% CI 0.70–3.84); p= 0.25) it did delay hospital mortality (HR

0.56 (95% CI 0.39– 0.79); p<0.001) and was not linked with the VAP risk.

Mortality rate and prone positioning. A meta-analysis by Sud et al. (2010) was

conducted with the goal of evaluating the mortality rates in prone position ventilation for

acute, hypoxemic, respiratory failure with a PaO_2/FiO_2 ratio of less than 100 mmHg

contrasted with moderate hypoxemia PaO_2/FiO_2 ratio of more than 100 mmHg (risk ratio=

0.84, 95% CI [0.74, 0.96], P= 0.01). A total of 1,867 patients in ten studies were

examined. All patients had ARDS or an acute lung injury. The mortality rate was

determined at hospital discharge. The initial three days of prone therapy found

oxygenation better by 27–39% but the incidence of mortality was decreased by only 16%

among patients who were severely hypoxemic with a PaO2/FiO2<100 mmHg. Due to

slow enrollment, over half of the trials were terminated. Sud et al. (2010) demonstrated a

direct correlation between prone ventilation and the decreased incidence of mortality rate

in patients with severe acute hypoxemia (RR 0.84, 95% CI 0.74–0.96; p = 0.01) but

found no mortality reduction in patients with moderate hypoxemia (RR 1.07, 95% CI

0.93–1.22; p = 0.36; N = 1,169).

A meta-analysis of seven RCT's on PP and ARDS conducted by Abroug, Ouanes-

Besbes, Dachraoui, Ouanes, and Brochard (2011) concluded that mortality rate did not

remarkably decrease in the ICU when considering all seven RCT's (odds ratio= 0.91,

95% CI [0.75, 1.2], P= 0.39). Nevertheless, the more recent studies that applied PP > 17

hours per day had significantly reduced mortality rate on ARDS patients only (odds

ratio= 0.71, 95% CI [0.5, 0.99], P= 0.048) revealing the probable outcome on mortality

rate with prolonged PP duration.

Improving oxygenation with prone positioning. In a systematic review by

Tiruvoipati, Bangash, Manktelow, and Peek (2008), five randomized controlled

trials (RCTs) were included (n= 1,287) which aimed to evaluate the efficacy of prone

positioning in adult patients with ARDS. All studies examined PP ventilation and supine

ventilation in adults (>18 years) with ALI or ARDS who required intubation and were

appropriate for inclusion. The main outcome was mortality rate. The average age of

participants ranged from 40 to 66 years of age and the mean duration of PP ranged from

6-17 hours. Although the review found that prone positioning corresponds with higher

oxygen levels when compared to supine position (95% CI: 12.4, 10.0, p<0.001; five studies), prone positioning did not reduce ICU mortality, and had no meaningful statistical difference between ventilation in the prone and supine position, OR 0.98 (95% CI: 0.7, 1.3, p=0.91; four studies) (Tiruvoipati et al., 2008). There were many limitations that affected the overall strength of the findings. One of the main variations was a lack of consensus as to how long and how early prone therapy should be introduced and maintained with a varied mean duration of 6-23 hours per day (Tiruvoipati et al.). One study initiated prone position early and maintained it for a longer time, with an average of 17 hours per day for a 10-day period. This study proposed a 15% absolute and 25% overall reduction in mortality rates. These statistics suggest that early treatment and longer periods of pronation therapy could be advantageous in the treatment of ARDS patients (Tiruvoipati, et al.).

Another study by Ragaller and Richter (2010) focused on early assessment of oxygenation on specific ventilator settings in ALI and ARDS patients. A total of 99 patients out of 170 satisfied ARDS criteria with PEEP $\geq$ 10 cm H_2O and FiO_2 $\geq$ 0.5 for more than 24 hours experienced a mortality of 45.5%, in contrast to 55 patients who had only ALI and experienced a mortality of 20%. This study examined mortality rates of patients with ALI/ARDS and found that tidal volumes (6 ml/kg predicted body weight(PBW), low FiO_2 and a pressure limit < 30 cm H_2O can reduce mortality rates.

Obesity and survival of critically ill ARDS patients

Approximately 20% of intensive care unit patients are obese. Although obesity and being overweight are associated with higher mortality among the general population, it is not the case with patients who have septic shock and ARDS. This phenomenon is

referred to as the obesity paradox (Ni et al., 2017). Ni et al. (2017) proposed an

explanation for why obese patients have a lower incidence of ARDS and state that

obesity induces a low-grade inflammation that function as a "pre-conditioning cloud" that

defends the lung against a succeeding insult. Pre-conditioning indicates that a continual

pro-inflammatory status develops a protective environment restricting the damaging

incident of an aggressive strike, like sepsis or a ventilator-induced lung injury (Ball,

Serpa, Neto, & Pelosi, 2017). New evidence supports the existence of a defense reaction

called pre-conditioning cloud where obesity generates a low-grade inflammation,

consequently guarding the lung against additional insults (Figure 3) (Fernandez-

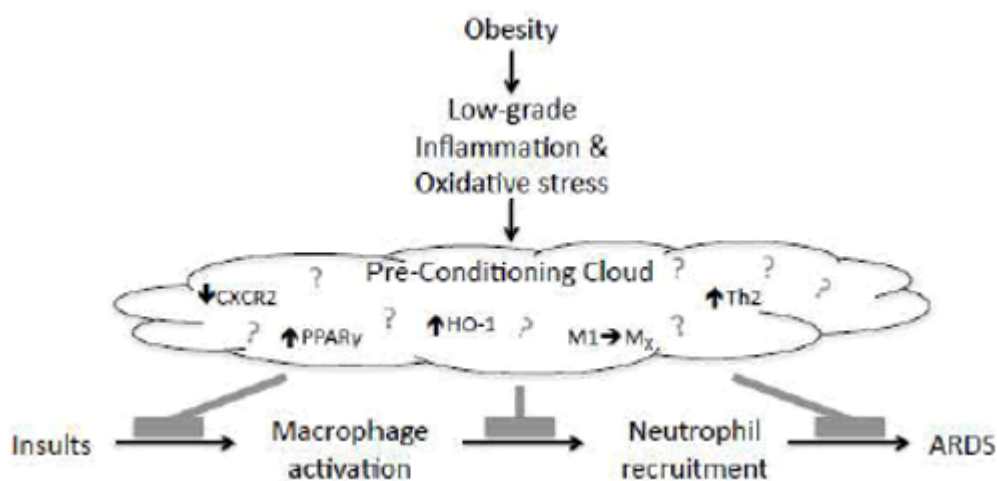Bustamante & Repine, 2012).

Figure 3. Obesity Pre-Conditioning Cloud (Fernandez-Bustamante & Repine, 2012).

Morbid obesity is associated with many co-morbidities and contributes to the

cause of higher mortality rates in both men and women. Critically ill obese patients with

ARDS, however, continue to have higher survival rates compared to normal weight

patients (Stapleton & Suratt, 2014).

Morbidly obese patients and ARDS. Measuring the esophageal pressure is a method used specifically in the obese surgical ARDS patient population. This method will aide in determining the effect of the chest wall on the transpulmonary pressure (P_L). Depending on the obtained transpulmonary pressure reading, PEEP can be titrated based on the physiological need of the patient in respiratory failure. Obtaining a positive transpulmonary pressure at end-exhalation allows for improved gas exchange, therefore accomplishing the overall treatment goal of a lower mortality rate (Hibbert, Rice, & Malhotra, 2012).

The effect of abdominal obesity on mortality in ARDS patients. Weig et al. (2014) conducted a retrospective study in which prone positioning was used from admission to day seven. Patients with ARDS (n=82) were separated into two subgroups: abdominal obesity (XL; n=41) or without obesity (ML; n=41), where abdominal obesity is described by a measurement of sagittal abdominal diameter of ≥26 cm (Weig et al.). The XL group had much higher renal failure rates and utilized increased invasive ventilator settings to support adequate oxygenation and ventilation. Abdominally obese patients developed renal failure (83% vs 35%; $P < .001$) and hypoxic hepatitis (22% vs 2%; $P = .015$) more often. Abdominally obese (XL) ARDS patients who underwent prolonged cumulative prone therapy exhibited a notable increase in mortality risk versus ML patients (likelihood ratio, $P = .0004$). In conclusion, the study advised a careful approach with the abdominally obese patients under treatment with prolonged prone therapy (Weig et al.).

In summary, a review of the literature revealed that prone positioning resulted in increased oxygenation levels in all patients and decreased mortality rates in severe ARDS patients in all the studies reviewed.

Next, the theoretical framework utilized for this systematic review will be discussed.

Theoretical Framework

The impact of evidence-based, quality practice has influenced the progress and growth of healthcare development. In addition, the creation of new clinical recommendations has made systematic reviews and meta-analyses the foundation of today's healthcare. According to Liberati et al. (2009), Preferred Reporting Items for Systematics Reviews and Meta-Analysis (PRISMA) was created in 2009 after the formerly used Quality of Reporting of Meta-Analysis or QUOROM statement (1999) was revised. It focused on the reporting of meta-analyses of randomized controlled trials, with the intent of improving quality assessment of studies and reporting. In 2005, the framework was changed from QUOROM to PRISMA to include systematic reviews as well as meta-analyses. The defined process for analyzing and scrutinizing the success or failure rates on prone positioning and the relationship to mortality will be guided by the PRISMA framework (Liberati et al., 2009). The PRISMA framework allows for standardization, illustration of the strengths and weaknesses and improvement of the quality of the systematic review (Liberati et al.).

The PRISMA checklist (Appendix A) contains 27 evidence-based items that can be used in developing and reporting this systematic review (Moher, Liberati, Tetzlaff, & Altman, 2009). The checklist items include components such as a title, abstract, Introduction, methods, data collection processes, synthesis of results, bias reporting and limitations. The author referred to the checklist when conducting the systematic review to ensure all items were addressed. It is essential to report all methods utilized when analyzing the data collected. In addition, PRISMA was utilized as a guide in developing data collection tables for this systematic review. The PRISMA tool also includes a flow

diagram, illustrated in Appendix B, which assisted in the process and organization of the literature review.

In addition to the PRISMA checklist and flow diagram, the author also utilized the Critical Appraisal Skills Programme (CASP UK, 2013) checklist for randomized control trials. Critical Appraisal Skills Programme consists of 11 questions to help the user interpret research evidence and further evaluate and ensure the quality of the randomized control trials. Critical Appraisal Skills Programme is an appraisal tool that focuses on three main areas when appraising a randomized controlled trial: Are the results of the study valid? What are the results? Will the results help locally? The 11 questions are designed to help think about these issues systematically. Question one and two are screening questions and can be answered quickly. If the answer to both is "yes" then it is worth proceeding with the rest of questions. There is some degree of overlap between the questions and the author will record a "yes", "no" or "can't tell" answer to most of the questions.

In addition, a cross study analysis was conducted using a process called descriptive data synthesis, which can be accomplished by both a narrative and a tabulation approach (Evans, 2003). Data synthesis will be accomplished by examining the main outcomes of the studies by examining the studies to find the similarities, differences, draw conclusions, and determine if the studies support each other.

Next, the methods section will be presented and discussed.

Method

Purpose/clinical question

The purpose of this paper was to conduct a systematic review to determine if prone positioning compared to supine positioning in patients with ARDS decreases mortality rates.

Inclusion/Exclusion Criteria

The PRISMA flow chart assisted in organizing the search results based on both inclusion and exclusion criteria determined by the author of the review. The result provided a final number of studies that were included in the systematic review. Inclusion criteria consisted of randomized clinical trials, meta-analyses or systematic reviews conducted in the last 18 years that included the following: met the newly adopted and currently used Berlin definition of ARDS and/or the old American-European Consensus Conference (AECC) diagnostic criteria for ARDS; intensive care unit patients with mild to severe ARDS, mechanically ventilated, prone position as compared to supine. Studies excluded were non-peer reviewed articles, not written in English, and those that included patients with chronic oxygen-dependent respiratory failure, a history of COPD, pulmonary fibrosis, interstitial lung disease, lung resection and lung cancer.

Search Strategy

The literature search was performed using Allied Health Literature (CINHAL), MEDLINE, Ovid, Medline and PubMed. The search terms accessed were: Acute Respiratory Distress Syndrome (ARDS); Acute Lung Injury (ALI); prone position; mortality and ARDS; and diagnosis and management of ARDS. An initial result of the medical literature search yielded over 2000 original articles, of which only 10 studies

were RCTs. The search was narrowed to peer-reviewed articles published after the year 2000. The records were screened and assessed for eligibility based on the inclusion and exclusion criteria.

Data Collection

Data were collected through utilization of a data collection table created by the researcher. Two tables were utilized to include basic general information and outcome measures. The first table was designed to include information about the randomized control trial's purpose, study design/setting, sample, method, and data analysis (Table 2). Table 2

Data Collection Tool 1

Purpose	Study Design/Setting	Sample	Method	Data Analysis

A second table was designed to collect information on other elements including days of ARDS before randomization, PaO2/FiO2 ratio/PEEP, prone position hours/day, mortality, results and limitations (Table 3).

Table 3

Data Collection Tool 2

Days of ARDS before randomization	PaO2/FiO2 Ratio mean/PEEP	Prone Position hrs./days Mean or Median	Mortality	Results	Limitations

Critical Appraisal Tool

The Critical Appraisal Skills Programme for RCT's (Table 4) was utilized to assess the trustworthiness of the studies and determine the validity, randomization, equality, precision of measurement tool, outcomes measured, generalizability of results, clinically relevant outcomes, and benefits of the trials (CASP UK, 2013)

Table 4.

CASP Randomized Controlled Trial Checklist

	11 Questions	Yes	Can't tell	no
1	Did the trial address a clearly focused issue?			
2	Was the assignment of patients to treatments randomized?			
3	Were all the patients who entered the trial properly accounted for at its conclusion?			
4	Were patients, health workers and study personnel 'blind' to treatment?			
5	Were the groups similar at the start of the trial?			
6	Aside from the experimental intervention, were the groups treated equally?			
7	How large was the treatment effect?			
8	How precise was the estimate of the treatment effect?			
9	Can the results be applied in your context? (or to the local population?)			
10	Were all clinically important outcomes considered?			
11	Are the benefits worth the harms and costs?			

(CASP UK, 2013)

Data Synthesis & Cross Study Analysis

All randomized controlled trials included within this systematic review were evaluated across the studies to compare the similarities and differences. A cross study analysis and comparison was performed between five trials that appraised PEEP at inclusion, duration of PP (hrs/day), days of pronation, and hospital mortality. This information was recorded within a data collection table created by the author of this review to compare the effects of prone positioning on mortality (Table 5).

Table 5

Cross Analysis

Author, Year	PEEP at inclusion	Duration of PP hr/day	Mortality

Next, the results will be discussed.

Results

Data Collection and Critical Appraisal

The PRISMA flow diagram (Figure 4), illustrated below, along with the inclusion and exclusion criteria, were utilized to further remove and select randomized controlled trials and articles for this systematic review. A total of 301 non-duplicate articles were screened, and the abstracts reviewed for evidence of exclusion criteria that would consider them unsuitable for this systematic review. This process removed a total of 251 articles. The remaining 50 articles were reviewed for suitability for this systematic review based on both exclusion and inclusion criteria. The final elimination process omitted 45 articles, leaving a total of five RCT's for inclusion within this systematic review.
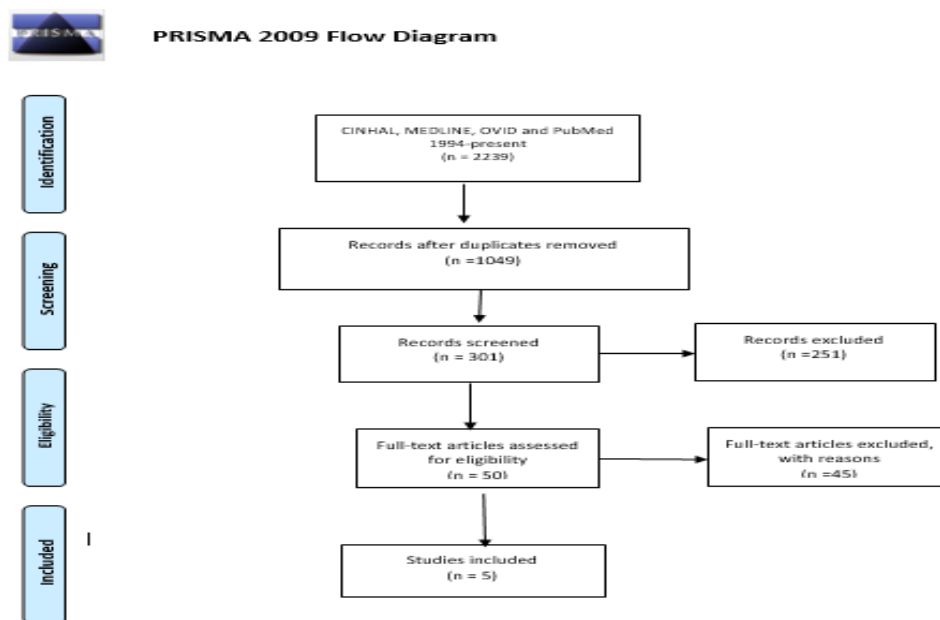
Figure 4. PRISMA Flow Diagram.

In a multicenter, randomized controlled trial by Gattinoni et al. (2001) (Appendix C-1) the authors compared traditional treatment in the supine position versus treatment in the prone position of patients with ARDS/ALI.   A pre-determined action plan was devised to include the placement of ARDS patients in prone positioning for ≥ 6hrs for 10 days; 304 patients were enrolled with 152 patients in the prone position and 152 in supine position.

Patients in the prone positioned group were arbitrarily assigned and stayed in a prone position for an average of 7.0±1.8 hours per day in the ten-day study period. Gattinoni et al. (2001) determined that the 10-day mortality rate did not notably vary between the prone group and the supine group (21.1% versus 25%; 32 vs. 38 deaths) but found that prone positioning patients had improved oxygenation and an increase PaO_2/FiO_2 ratio compared to supine patients 63% versus 44.6%, respectively (Appendix C-2). This study examined mortality at 10 days, discharge and 6 months. The conclusion of the study was that the mortality rate was 23% through the first 10-day study duration, 49.3% at the time of discharge from the intensive treatment unit, and 60.5% at six months with relative risk of death equal to 0.84 in the prone group; 95% CI, 0.56 to 1.27 and 1.05 concurrently at discharge from the intensive care unit with a 95% CI, 0.84 to 1.27 and 1.05 at six months with a 95% CI, 0.88 to 1.28. Gattinoni et al. established that PaO_2/FiO_2 ratio, calculated every morning, was significantly higher in the prone versus supine position (63.0±66.8 vs. 44.6±68.2, P=0.02). Although prone positioning is conceivably beneficial for patients with severe ARDS and hypoxemia, it does not promote survival; however, Gattinoni et al. did indicate the need for another study that is designed to elucidate the role of prone positioning in severe ARDS. The main limitation

of this trial included logistic issues with staffing that caused various levels of noncooperation, thereby causing 91 missed pronations over the 10-day period; also the authors s did not create a halt criteria.

The critical analysis of the Gattonni.et al. (2001) study is illustrated in Appendix H-1 using the CASP checklist tool. This study is a randomized control trial and provides a high level of evidence. Blinding of patients and investigators pertaining to results assessments was not reached in any of the trials as PP and the outcomes could not be blinded. A 95% confidence interval was reported by the authors and this study suggests that prone positioning might be useful when applied to severely hypoxemic patients.

Guérin et al. (2013) (Appendix D-1) conducted a prospective, randomized, controlled trial that aimed to evaluate the effect of prone positioning on mortality in the early stages of ARDS. Patients who were admitted to this study met the American–European Consensus Conference criteria of ARDS as defined as a PaO_2/FiO_2 ratio of <150 mm Hg, with an FiO_2 of ≥0.6, a PEEP of ≥5 cm of H_2O, and a tidal volume (TV) of about 6 ml/kg of predicted body weight; the criteria were established after 12 to 24 hours of mechanical ventilation (MV) in the participating ICU. Prone positioning sessions were first applied to the prone group within two hours after randomization. This RCT randomly selected 466 patients who were recruited from 26 ICUs with severe ARDS who were prone positioned for at least 16 hours or have been left in the supine position. A total of 229 patients were assigned to the supine group and 237 to the prone group. A 16% reduction in mortality rate at 28-days (primary outcome) was observed in the prone group compared with the supine group (16% vs. 32.8%; $P < 0.001$). The 90-

day reduction in mortality (secondary outcome) was 17.4% in the prone group compared with supine group (23.6% vs. 41.0%; P < 0.001) (Guérin et al.).

In conclusion, Guérin et al. (2013) (Appendix D-2) were able to establish a significant reduction in 28 and 90-day mortality rates when prolonged prone positioning is applied early to patients with severe ARDS. Limitations of this trial included only a handful of ICUs that complied with recording the data of patients who were not included in this study but were qualified making it unfeasible to fully understand the physiological condition of the precluded patients.

As seen in Appendix H-2 (Guérin et al., 2013), the critical analysis of this study was strong based on "yes" answers to all questions, except one: patients were not blinded by treatment but stratified according to ICU. A confidence interval of 95% was reported, therefore prone positioning may be employed to ARDS patients to improve mortality.

Fernandez et al. (2008) (Appendix E-1) conducted an open randomized trial in 17 medical-surgical intensive care units to determine the effect on survival of ARDS patients when prone positioning is used as an early and continuous therapy. Despite their early and ongoing protective ventilation, a total of 40 mechanically ventilated patients with refractory ARDS were included in this study. Patients were randomized to continue in the supine position or to proceed to early prone position (18 hours/day) until recuperation or death (within 48 hours). Clinical characteristics, oxygenation, lung pressures, and hemodynamics were monitored. Patient outcomes, complications, sedation, duration of mechanical ventilation, ICU visits, and hospital stays were recorded. This study continuously assessed and recorded oxygenation, lung pressure, clinical data, and hemodynamics. Status-post randomization, MV was assigned to tidal volume (TV) of 6–

8 ml/kg with patient's ideal body weight and positive end-expiratory pressure (PEEP)

based on FIO2 demands. The static pressure of the respiratory system was limited to 30

cmH2O and respiratory rate up to 35 breaths per minute. The latter setting would be

applied after one hour to the chosen position, prone or supine, and sustained for an

average of eighteen hours per day. PaO2/FIO2 ratio was inclined to be higher in prone

than in supine patients after 6 hours (202 ±78 vs. 165 ±70 mmHg) reaching statistical

significance on day 3 (234 ±85 vs. 159 ± 78). As seen in (Appendix E-2) the sixty-day

mortality rate in prone position reached the targeted 15% absolute increase (62% vs.

47%) but fell short to reach significance due to the small sample and for that reason the

study was discontinued prematurely. This randomized study, however, did suggest the

advantageous effect of early continuous prone therapy on the survival of ARDS patients.

   The Fernandez et al. (2008) study was critically analyzed (Appendix H-3). The

low enrollment of patients forced the study to end prematurely and not all the patients

who entered the trial were properly accounted for at the end of the study. A confidence

interval was not reported by the authors, and the study population was much smaller than

some of the other studies that were reviewed, therefore possibly impacting the validity of

the study .

   Taccone (2009) (Appendix F-1) conducted a randomized multi-center-controlled

trial that involved 342 patients of which 168 patients were in the prone group and 174 in

supine group. Then the patients were stratified into subordinate groups based on their

hypoxemia level; with a moderate hypoxemia group M: n = 192 (94 prone, 98 supine);

and severe hypoxemia group n = 150 (74 prone, 76 supine). All the patients with ARDS

received mechanical ventilation and fulfilled the diagnostic criteria of ARDS (PaO_2:

FIO$_2$ ratio $\leq$ 200 mm Hg). Patients were randomized to undergo supine position (n = 174) or prone position (20 hours per day; n = 168) during mechanical ventilation. Both groups of prone and supine position were extended to 20 hours until the acute respiratory symptoms subsided, or until the end of the primary outcome at 28-days and a secondary outcome at six months mortality. Sequential Organ Failure (SOFA) scores were accumulated daily to assess the severity of organ dysfunction or failure and other physiological factors were recorded at 12-hour intervals.

As seen in (Appendix F-2) this study demonstrated that prolonged prone positioning did not correlate to a better survival advantage, as prone and supine patients had similar 28-day mortality rates (31.0% vs 32.8%; RR, 0.97; 95% CI, 0.84-1.13; $P=.72$) and 6-month mortality rates (47.0% vs 52.3%; RR, 0.90; 95% CI, 0.73-1.11; $P=.33$).

The critical appraisal of the Taccone et al. trial (2009) (Appendix H-4) suggested that determination about additional therapeutic interventions were not identified in the study protocol. Antibiotic treatment, sedation and nutrition were not included in the trial protocol. The Taccone et al. trial had a fair sample size of 342 patients and reported many significant findings. The sample enrollement was very specific: it included mechanically ventilated patients with PaO$_2$: FIO$_2$ ratio $\leq$ 200 mm Hg with moderate hypoxemia and PaO$_2$: FIO$_2$ ratio $\leq$ 100 mm Hg with sever hypoxemia. This study measured the primary outcome of mortality from any cause. Most of the critical analysis questions of this RCT were scored as "yes" except one that asked if patients, health workers and study personnel blinded to treatment. A confidence interval of 95% was identified by the authors.

Mancebo et al. (2006) (Appendix-G1) conducted a randomized controlled trial in 13 intensive care units with a primary outcome measuring intensive care unit mortality and a secondary outcome of hospital mortality. This study included 136 patients who were intubated for 48 hours and were diagnosed with severe ARDS status post 48 hrs. Sixty patients were randomized to supine and 76 to prone positioning. Prone position was employed for a mean of 17 hours per day, for a mean of 10 days, utilizing 718 turning procedures. The mortality rate was appraised to be 58% (35/60) in the supine position and 43% (33/76) in the prone position, representing a 15% absolute and 25% relative decrease.

Mancebo et al. (Appendix G-2) inferred patients who were prone positioned within the first 48 hours of meeting ARDS criteria and continued PP for most of the day had a 15% absolute relative decrease in mortality rate in contrast with patients who were in the supine position $(p = 0.12)$. This study was discontinued due to the small sample size related to a significant decrease in the number of patients enrolled. In conclusion, Mancebo et al. suggested that prone positioning is safe and may reduce mortality in patients with severe ARDS.

The critical appraisal (Appendix H-5) of the Mancebo et al. trial revealed that with only 142 patients in the sample, the study was limited as it was permanently halted due to low enrollment among patients within the randomization window. The appraisal also noted that the study design did not see the need to record complications during routine supine treatment. Complications related to PP were not recorded and therefore caution should be taken when interpreting the data. This makes comparison of the effectiveness of this study more difficult. Answers to the critical analysis questions were

all "yes" except one pertaining to patients, health workers and study personnel not being blinded to treatment.

Cross Study Comparison and Analysis

The randomized control trials used for this systematic review were analyzed across studies using a table created by the author. This table was used to record and analyze the PEEP at inclusion, duration of PP hr/day, and mortality (Appendix I).

All the randomized control trials included within this systematic review reported that PP tended to decrease mortality in ARDS patients, particularly when used simultaneously with lung protective measures and longer PP duration. Each of the studies evaluated mortality in relation to the implementation of prone vs. supine positioning as a treatment of ARDS in mild to severe hypoxic mechanically ventilated patients. There were variations in the techniques and results and only one study by Gattinoni et al. (2001) included mild to severe ARDS patients as a criterion for enrollment. The four remaining studies examined patients from moderate to severe ARDS.

The most profound decreases in mortality were found within the studies involving longer duration of PP in conjunction with lung protective plan of action. The study conducted by Guérin et al. (2013) reported 28-day mortality rates between the prone and supine groups (16% vs. 32.8%) ($p<0.001$). Mancebo et al., (2006) reported mortality rates between the prone and supine groups (58% vs 43%) (p =0.12). The institution of PP in relation to the phase of respiratory failure and duration of PP was different; 7 hours/day in the Gattinoni et al. study; 17 hours/day for a duration of 10 days in the Mancebo et al. study; 17 hours/day for four days in the Guerin et al. study; 17 hours per

day for 8 days in Taccone et al study.; and 18 hours per day with unknown number of days in the Fernandez et al. study.

In all the studies, neither the patients nor the researchers were blinded, as some of the patients were consented and awake prior to intubation, sedation, and pronation. In each of the five studies, the effect of the time spent in the prone positioning was assessed comparing studies of longer versus shorter time spent in prone therapy. Excluding the Gattinoni et al. (2001) study, which had the lowest duration of PP (7 hours/day), the remaining four trials used PEEP and FiO2 ratio as a criterion for stopping prone positioning. Gattinoni et al. found that, while placing ARDS patients in prone positioning improved oxygenation, it did not improve mortality rate. Taccone et al. (2009), Fernandez et al. (2008), Mancebo et al. (2006), and Guérin et al. (2013) all reported improved oxygenation and mortality rates were lower when patients were placed in prone positioning compared to supine positioning. Mancebo et al. further expanded on Gattinoni et al.'s study on the effectiveness of prone positioning vs. supine positioning by focusing on lengthening the duration of prone positioning in a 24-hour period. Mancebo et al. revealed a mortality trend reduction with prone positioning use as reflected in 15% absolute and 25% relative reduction versus supine ventilation positioning (p=0.12).

The studies by Guerin et al. and Taccone et al. implemented prone therapy for 17 hrs./day over a 10-day period and concluded that mortality is improved when compared to conventional treatment of supine positioning. In contrast, studies performed by Gattinoni et al. used the same amount of PEEP of >5cm as Guérin et al., but the prone positioning duration was only 7 hours/day, with insignificant mortality rate between prone versus supine positioning (21.1% versus 25%, CI=95%) at the end of 10-days

(50.7% versus of 48%, CI=95%), at the time of discharge from the ICU (62.5% versus

58.6%, CI=95%), and at six months. Guerin et al. elaborated on refining the treatment of

severely hypoxic ARDS patients indicating that patients who were PP for $\geq$ 12 hours

daily had a lower mortality rate. In conclusion, four out of five RCTs identified the

major contributing factor for the efficiency of prone positioning to include a minimum of

12 hours daily, but all five studies demonstrated an apparent increase in PaO2/FiO2 ratio

within hours of prone positioning.

Next, the summary and conclusions section will be presented.

Summary and Conclusions

Acute Respiratory Distress Syndrome is a clinical condition in which the lungs suffer severe, large-scale injury interrupting their ability to take up oxygen. Acute Respiratory Distress Syndrome is associated with high mortality and severe hypoxemia (Taccone et al., 2009). Prone positioning is currently recommended for patients with ARDS as a rescue plan secondary to severely hypoxemic patients positive response to increased oxygenation (Koulouras et al., 2016). However, the initiation and application of prone positioning in ARDS patients continues to be a topic of much debate, despite its increased use in the treatment of hypoxemic patients. The tightly established link between prone positioning and improved oxygenation in ARDS implies that it may decrease mortality rates, but further research is needed.

The purpose of this paper was to conduct a systematic review to determine if prone positioning compared to supine positioning in patients with ARDS decreases mortality rates. A literature review was conducted utilizing inclusion and exclusion criteria determined by the author. The PRISMA flow diagram was used to assist in the organization and collection of data regarding the literature search. The research question was: Does prone positioning compared to supine positioning in patients with ARDS decrease mortality rates? The CINAHL, MEDLINE, OVID, and PUBMED databases were searched during this systematic review process. The search strategy followed the procedures as identified within the PRISMA flow diagram and the 27-item PRISMA checklist (Moher et al., 2009). Five randomized control trials were included in the review. Data collection was performed utilizing a data extraction form constructed by the author. The randomized control trials were subject to critique using the Critical

Appraisal Skills Programme (CASP) to determine the quality of the studies. Data were collected from the studies and recorded within tables. .Information obtained from each study included the author, year, purpose, study design, setting, treatment, protocols, method, data analysis, days of ARDS before randomization, Pa02/Fi02 Ratio /PEEP, number of hours in the prone position, mean or median, outcome/mortality, results, and limitations.

In all studies that implemented prone positioning, the groups with the longest duration of PP had the lowest mortality rate. Gatttinoni et al.'s (2001) study lacked reliable data on mortality due to the slower rate of enrollment and the disinclination of staff to refuse the use PP in the control group. The study by Mancebo et al. (2006) revealed a decrease in mortality (15% absolute and a 25% relative decrease in mortality) with supine positioning being an independent risk for mortality. Similar results were found in the Gurein et al. (2013), Taccone et al. (2009) and Fernandez et al. (2008) studies.

Mancebo et al. (2006) introduced PP early in the treatment of ARDS and maintained it for longer periods, with an average of 17 hours per day over a 10-day period compared to the rest of the studies. The briefest period of PP was in the study by Gatttinoni et al. (2001) with an average of seven hours per day for a period of ten days. In comparison, Gurein et al. maintained PP for eight hours per day for four days, Taccone et al. (2009) for 18 hours per day for eight days, and Fernandez for 18 hours daily but didn't indicate for how many days.

One study did not establish halt criteria (Gattinoni et al., 2001), but the other four studies implemented a set of measurements that included a Pa02/Fi02 Ratio and PEEP as

a guideline to halt the study. While PP was related to improvement in oxygenation, there is no standard set forth standard as to when and for how long prone therapy should be started and maintained. The subjects included in the studies were generated from patients with ARDS and respiratory failure due to various causes. The inclusion and exclusion criteria varied among the trials, making the conclusion of this review limited as to which population can benefit the most or least.

In conclusion, a total of five trials were examined to see if the use of PP reduces mortality in ARDS. Factors that were examined included days of ARDS before randomization, PaO2/FiO2 Ratio /PEEP, mean or median of PP hours per day/days, and mortality. The major finding of this systematic review is that PP in patients with severe hypoxemia in ARDS, tends to reduce mortality rates particularly when utilized in concurrence with lung protective strategies and longer duration of prone therapy. The advantageous effect of PP is probably explained by factors other than the enhancement in oxygenation, including averting ventilator-associated lung injury (VALI), which is probably a major contributing factor to the benefit of PP. As such, PP should be applied as first-line therapy to any patient with moderate or severe ARDS. Evaluation and analysis of the five studies strongly suggest that PP should be applied as early as possible and for longer duration after identification of hypoxemia to decrease the stress and strain inflicted on the entire lung by mechanical ventilation.

Recommendations and implications for advanced nursing practice will be discussed in the next section.

Recommendations and Implications for Advanced Nursing Practice

Advanced Practice Registered Nurses (APRNs) rely daily on evidence-based research. This systematic review yielded valuable information and evidence based recommendations for nurse practitioners. Current practice related to the use of PP in the intensive care units is at the discretion of the provider; usually there is not a set policy or clear direction on when to use PP. While APRNs are largely aware that prone positioning increases oxygenation in severe ARDS, there is a lack of evidenced-based knowledge related to the benefit of prone positioning and no standard for the quantity, duration and initiation time for prone positioning.

This review was able to contribute to evidence-based knowledge related to the use of PP in the intensive care unit. The outcomes of this review present an opportunity for teaching all nurse practitioners related to the use of PP in ARDS patients. Nurse practitioners are an excellent resources and are in a position to educate all providers related to evidence-based outcomes and the utilization of PP and create guidelines on PP. Continuing education is crucial to both the education of the nurse practitioners and the safety of their patients.

Additional research needs to be conducted on PP optimal duration, timing and setting in the intensive care unit. Nurse practitioners are deeply involved in patient care, creating an excellent leadership opportunity to direct and share with the rest of the intensive care unit team. Studies with larger sample sizes than were examined in this systematic review are needed.

This review was able to provide beginning evidence related to the initiation of prone positioning. In addition, it could present an opportunity to create prone positioning guidelines or policies. Most hospitals utilize electronic health care records in the

intensive care unit; the nurse practitioner could review old records and parameters

pertaining to ARDS and hypoxemia as a beginning mechanism to improving patient

outcomes.

It is imperative to recognize ARDS and to consider applying the prone maneuver

to improve oxygenation and mortality. In an effort to develop and implement definitive

treatment guidelines, further research is needed. As the research for ARDS management

grows, the therapeutic discussion for this complex condition will be more universally

understood and utilized in ARDS treatment, with the goal of improving patient outcomes.

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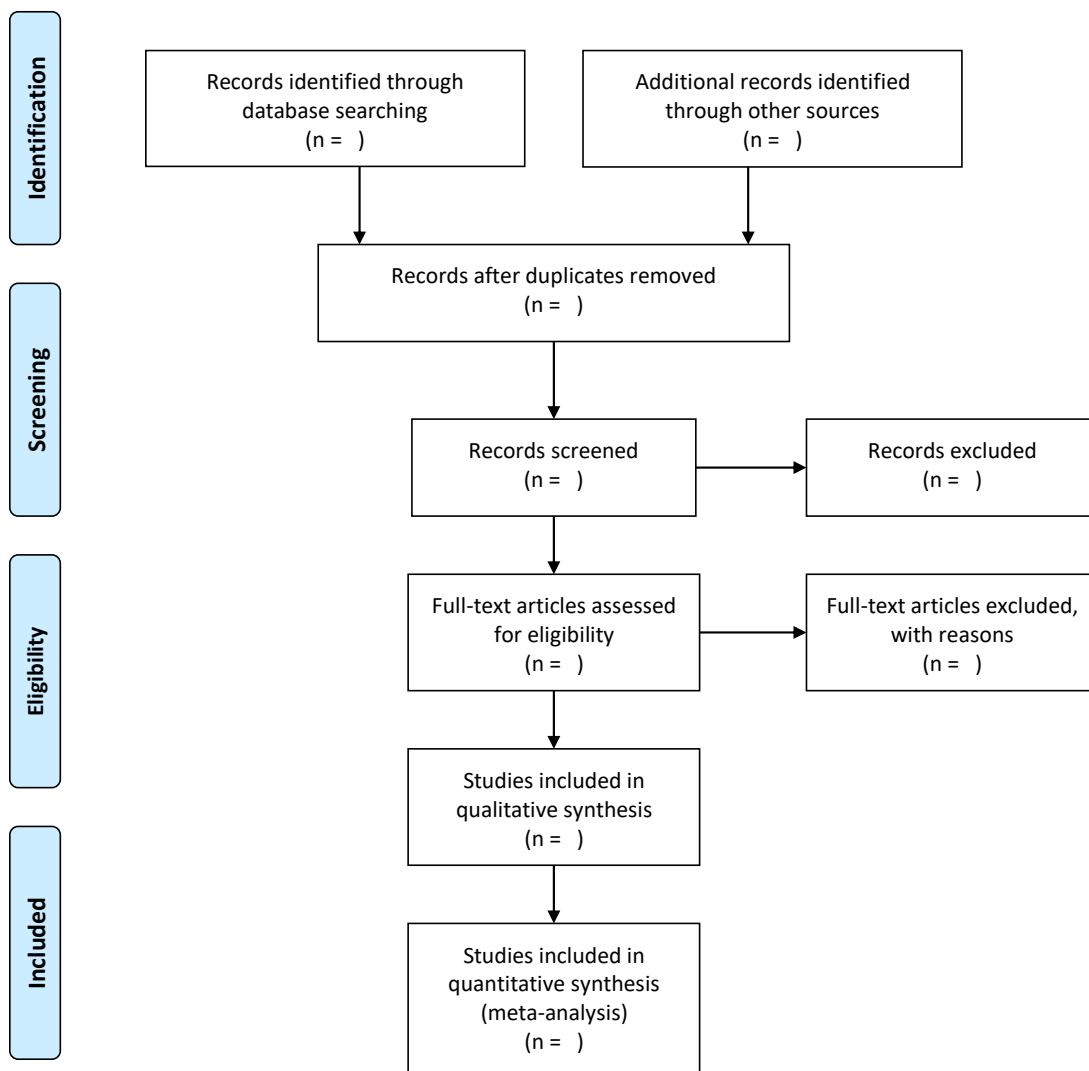
Appendix A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Appendix B

PRISMA 2009 Flow Diagram

Identification	Records identified through database searching (n =) — Additional records identified through other sources (n =)
	Records after duplicates removed (n =)
Screening	Records screened (n =) → Records excluded (n =)
Eligibility	Full-text articles assessed for eligibility (n =) → Full-text articles excluded, with reasons (n =)
	Studies included in qualitative synthesis (n =)
Included	Studies included in quantitative synthesis (meta-analysis) (n =)

Appendix C-1

Data Collection Table

Gattinoni, L. (2001). Effect of prone positioning on the survival of patients with acute respiratory failure. *The New England Journal of Medicine 345*(8), 568-573.

Purpose	Study Design/Setting /Treatment Protocol	Sample	Method	Data Analysis
To assess the effects of prone position-ing on the survival of patients with ALI or ARDS.	Randomized control trial. Patients recruited from 28 intensive care units in Italy and 2 in Switzerland with mild, moderate or severe ALI or ARDS.	304 patients in the ICU, 25% females and 34.2% males. 152 in the supine and 152 in prone position. Ages: supine group=57$\pm$SD16 and prone group=57$\pm$SD16. ALI patients: 6.6% supine and 5.3% prone group. ARDS patients: 93.4% supine and 94.7% prone group.	Patients randomized to one of two groups. Randomization was conducted centrally by telephone on a 24 hour/ 7day a week basis based on a permuted-block algorithm, which allowed stratification.	Calculated the sample size needed to assess a clinically relevant benefit (20% decrease mortality rate in the prone position). Survival rate analyzed according to Kaplan-Meir Method and results compared with a log-rank test. A two-tailed p value of less than 0.5 considered significant.

Appendix C-2

Study Outcome

Gattinoni, L. (2001). Effect of prone positioning on the survival of patients with acute respiratory failure. *The New England Journal of Medicine 345*(8), 568-573.

Days of ARDS before randomiz-ation	Pa02/Fi02 Ratio /PEEP	Prone Position hrs/days Mean or Median	Outcome/ Mortality	Results	Limitations
Unknown	Patients in prone position=125 Patients in supine position=130 Patients were continuously kept prone for at least 6 hours day and were assessed in the prone position. A change to the prone position was triggered by morning Pa02/Fi02 ratio of 200 or less with a PPEP of 5cm H20 or a ratio of 300 or less with a PEEP of 10cm. Ventilator settings were changed during pronation.	Patients were prone for 7 hours per day for 4.7 days.	Outcome was mortality at 10 days, discharge, and 6 months.	Mortality rate did not differ significantly between the prone and supine groups (21.1% vs. 25%). Relative risk of death in the prone group end of study 0.84 (CI=.84-1.32) 1.05 at the time of discharge from the ICU (.84-1.32) and 1.06 at six months (.88-1.28) *p*=.65 by the log rank test.	In the case of 12 patients, a decision was made despite randomization to use the prone position because of the severity of hypoxemia. Logistic problems in the prone group caused degrees of non-compliance in 41 patients.

Appendix D-1

Guérin, C (2013). Prone positioning in severe acute respiratory distress syndrome.
The New England Journal of Medicine. 368(23), 2159-2168.

Purpose	Study Design/Setting /Treatment Protocol	Sample	Method	Data Analysis
To assess the effects of early application of prone positioning on outcomes in patients with severe ARDS.	Randomized control trial. Patients recruited from 26 intensive care units in France and 1 in Spain with severe ARDS.	466 patients in the ICU, 31.8% females and 68.2% males. 229 in the supine and 237 in prone position. Ages: supine group=60±SD16 and prone group=58±SD16. ARDS patients: 49.1% supine and 50.9% prone group.	Patients randomized to one of two groups. Randomization was conducted using a centralized web-based management system (CLIN info) and stratified according to intensive care unit.	Calculated the sample size needed to assess a clinically relevant benefit (15% to 45% decrease mortality rate in the prone position). Survival rate analyzed according to Kaplan-Meir Method and results compared with a log-rank test. A two-tailed p value of less than 0.5 considered significant.

Appendix D-2

Guérin, C (2013). Prone positioning in severe acute respiratory distress syndrome.
The New England Journal of Medicine. 368(23), 2159-2168.

Days of ARDS before randomization	Pa02/Fi02 Ratio /PEEP	Prone Position hrs./days Mean or Median	Outcome/ Mortality	Results	Limitations
≤ 2.5	Patients in prone position=237 Patients in supine position=229 Patients were continuously kept prone for at least 16 hours per day and were assessed in the prone position. A change to the prone position was triggered by improvement in oxygenation Pa02/Fi02 ratio of ≥ 150 with a PPEP of ≤510cm H20 and an Fi02 of ≤0.6; in the prone group.	Patients were prone for 17 hours per day for 4 days.	Outcome was 16% mortality at 28 days and 23.6% at 90 days.	Mortality rate did differ significantly between the prone and supine groups (16% vs. 32.8%) (P<0.001). Relative risk of death in the prone group end of study The hazard ratio for death with prone positioning was 0.39 (95% confidence interval [CI], 0.25 to 0.63). Unadjusted 90-day mortality was 23.6% in the prone group versus 41.0% in the supine group (P<0.001), with a hazard ratio of 0.44 (95% CI, 0.29 to 0.67)	Few ICUs complied with recording the data of patients who were eligible but not included making it impossible to fully appreciate the physiological condition of the excluded patients. Fluid balance and the cumulative dose of catecholamines were not assessed.

Appendix E-1.

Fernandez, R. (2008). Prone positioning in acute respiratory distress syndrome:
A multicenter randomized clinical trial. *Intensive Care Medicine*, *34*(8), 1487-1491.

Purpose	Study Design/Setting /Treatment Protocol	Sample	Method	Data Analysis
To assess the effect on survival of ARDS patients when prone positioning is used as an early and continuous therapy.	Randomized control trial. Patients recruited from 17 intensive care units in Spain with moderate to severe ARDS despite protective ventilation in the supine position.	42 patients in the ICU, 37.5% females and 62.5% males. 19 in the supine and 21 in prone position. Ages: supine group=55.3±SD 14.6 and prone group=53.9±SD 17.9.	Patients randomized to one of two groups. Patients were randomized via a centralized call center that hosted the computer-generated random sequence. Randomization was stratified according to the level of severity.	The estimated sample size required to confirm a 15% absolute reduction in mortality rate in the prone position with an α error of 0.05 and a power of 80% was 250. The rate of enrollment was steadily dropping, and for this reason the Steering Committee decided to stop the study prematurely at 30 days.

Appendix E-2

Fernandez, R. (2008). Prone positioning in acute respiratory distress syndrome:
A multicenter randomized clinical trial. *Intensive Care Medicine*, *34*(8), 1487-
1491.

Days of ARDS before randomiz-ation	Pa02/Fi02 Ratio /PEEP	Prone Position hrs/days Mean or Median	Outcome/ Mortality	Results	Limitations
≤ 2	Patients in prone position=114 Patients in supine position=122 Patients were continuously kept prone for at least 18 hours per day and were assessed in the prone position. A change to the prone position was triggered Pa02/Fi02 ≥ 250 or with a PPEP ≤ 8cm H20 for 12 hrs.	Patients were prone for 18 hours per day with unknown number of days.	Outcome was mortality at 60-day survival.	A 15% reduction in mortality was observed in the prone group compared with supine (38% vs. 53%); however, although this difference fits the projected survival advantage, it did not reach statistical significance due to the small sample.	Only 42 patients had been enrolled, and the rate of enrollment was steadily dropping.

Appendix F-1

Taccone, et al., (2009). Prone positioning in patients with moderate and severe acute respiratory distress syndrome. *JAMA, 302*(18), 1977.

Purpose	Study Design/Setting /Treatment Protocol	Sample	Method	Data Analysis
To assess possible outcome benefits of prone positioning in patients with moderate and severe hypoxemia who are affected by ARDS.	A multicenter, unblinded, randomized controlled trial conducted in 23 centers in Italy and 2 in Spain. Patients with ARDS receiving mechanical ventilation.	342 patients in the ICU, 28.7% are females. 174 in the supine and 168 in prone position. Ages: supine group=60±SD16 and prone group=60±SD16. 192 patients were stratified into the subgroup of patients with moderate hypoxemia (94 prone, 98 supine) and 150 into the subgroup with severe hypoxemia (74 prone, 76 supine). .	Patients randomized to one of two groups. Randomization was conducted centrally by telephone on a 24 hour/ 7day a week basis based on a permuted-block algorithm, which allowed stratification.	Calculated the sample size needed to assess a clinically relevant benefit (15% decrease mortality rate in the prone position). Survival rate analyzed using the procedure of Peto. A two-tailed p value of less than 0.5 considered significant.

Appendix F-2

Taccone, et al., (2009). Prone positioning in patients with moderate and severe acute respiratory distress syndrome. *JAMA*, *302*(18), 1977.

Days of ARDS before randomiz-ation	Pa02/Fi02 Ratio /PEEP	Prone Position hrs/days Mean or Median	Outcome/ Mortality	Results	Limitations
≤ 3	Patients in prone (moderate hypoxemia subgroup) position=94 Patients in supine position=98 Patients in prone (severe hypoxemia subgroup) position=74 Patients in supine position=76 Patients were continuously kept prone for at least 17 hours day and were assessed in the prone position. A change to the prone position was triggered if Fi02 ≤40% and PPEP ≤ 10cm H20	Patients were prone for 18 hours per day for 8 days.	Outcome was mortality at 28- days, discharge, and 6 months.	Mortality rate did not differ significantly between the prone and supine groups (21.1% vs. 25%). Relative risk of death in the prone group end of study 0.84 (CI=.84-1.32) 1.05 at the time of discharge from the ICU (.84-1.32) and 1.06 at six months (.88-1.28) *p*=.65 by the log rank test. Prone and supine patients from the entire study population had similar 28-Day mortality (31.0% vs 32.8%; relative risk of death 0.97; interval (CI= 0.84-1.13; *P*=.72) and 6-month (47.0% vs 52.3%; RR, 0.90; 95% CI, 0.73-1.11; *P*=.33).	To standardize the severity of hypoxemia, the author assessed the arterial oxygenation while keeping the PEEP between 5 and 10 cm H2O; therefore, in patients treated with a higher level, the author decreased the PEEP to 10 cm H2O (unless the PaO2:FIO2 ratio was already less than 100)

Appendix G-1

Mancebo, J. (2006). A multicenter trial of prolonged prone ventilation in severe acute
    respiratory distress syndrome. *American Journal of Respiratory and Critical Care*
    Medicine, *173*(11), 1233-1239.

Purpose	Study Design/Setting /Treatment Protocol	Sample	Method	Data Analysis
To assess the effects of early prone position-ing and for a longer period on the survival of patients with ALI or ARDS.	Randomized control trial. Patients were recruited from 13 intensive care units: 12 in Spain and 1in Mexico. With mild, moderate or severe ALI or ARDS with four quadrant infiltrates on X-ray.	142 patients in the ICU. 60 in the supine (18 females) 76 in prone position (32 females). Ages: supine group=54±SD16 and prone group=54±SD17. .	Patients randomized to one of two groups. A sequence of random numbers was computer-generated. This sequence was partitioned into blocks of different size according to the expected number of inclusions at each participating center.	Mortality in patients ventilated supine would be 50%, and calculated a need to enroll 200 patients, 100 in each arm, to detect a decrease in mortality rate from 50% (supine group) to 30% (prone group). Survival rate analyzed according to Kaplan-Meir Method and results compared with a log-rank test. A two-tailed p value of less than 0.5 considered significant.

Appendix G 2

Mancebo, J. (2006). A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, *173*(11), 1233-1239.

Days of ARDS before randomiz-ation	Pa02/Fi02 Ratio /PEEP	Prone Position hrs/days Mean or Median	Outcome/ Mortality	Results	Limitations
≤ 2	Patients in prone position=132 Patients in supine position=161 Patients were continuously kept prone for at least 16 hours day and were assessed in the prone position. A change to the prone position was triggered if Fio2 ≤45%, PEEP≤ 5cm of H2O	Patients were prone for 17 hours per day for 17 days.	Outcome variable was intensive care unit mortality reduction Outcome was mortality at 20 days.	The intensive care unit mortality was 58% (35/60) in the patients ventilated supine and 43% (33/76) in the patients ventilated prone (p =0.12). number of days elapsed between ARDS diagnosis and inclusion (OR, 2.83; p _ 0.001), and randomization to supine position (OR, 2.53; p =0.03) were independent risk factors for mortality.	Includes the facts that it was stopped due to decreased patient accrual and the fact that it was is underpowered.

Appendix H-1

Gattinoni, L. (2001). Effect of prone positioning on the survival of patients with acute respiratory failure. *The New England Journal of Medicine 345*(8), 568-573.

1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	**Yes**	Can't tell	No
4	Were patients, health workers and study personnel 'blind' to treatment?	Yes	Can't tell	**No**
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? **Mortality rate measured-Prone group 21.1% (32 death) vs supine group 25% (38 death)**	**Yes**	Can't tell	No
8	How precise was the estimate of the treatment effect? **The relative risk of death in the prone group vs the supine group was 0.84 (95% CI, 0.56 to 1.27)**	**Yes**	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

Appendix H-2

Guérin, C (2013). Prone positioning in severe acute respiratory distress syndrome.
The New England Journal of Medicine. 368(23), 2159-2168

1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	**Yes**	Can't tell	No
4	Were patients, health workers and study personnel 'blind' to treatment?	Yes	Can't tell	**No**
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? **The 28-day mortality was 16.0% in the prone group and 32.8% in the supine group (P<0.001).**	**Yes**	Can't tell	No
8	How precise was the estimate of the treatment effect? **The hazard ratio for death with prone positioning was 0.39 (95% confidence interval [CI], 0.25 to 0.63).**	**Yes**	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

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Appendix H-3

Fernandez, R., Trenchs, X., Klamburg, J., Castedo, J., Serrano, J. M., Besso, G., …
Lopez, M. J. (2008). Prone positioning in acute respiratory distress syndrome: A
multicenter randomized clinical trial. *Intensive Care Medicine, 34*(8), 1487-1491.

1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	**Yes**	Can't tell	No
4	Were patients, health workers and study personnel 'blind' to treatment?	Yes	Can't tell	**No**
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect?? **60 -day survival reached the targeted 15% absolute increase in prone patients (62% vs. 47%)**	**Yes**	Can't tell	No
8	How precise was the estimate of the treatment effect? **This study failed to reach significance due to the small sample (42 patients). No confidence limits, no statistical significance**	**Yes**	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

Appendix H-4

Taccone, et al., (2009). Prone positioning in patients with moderate and severe acute respiratory distress syndrome. *JAMA, 302*(18), 1977.

1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	**Yes**	Can't tell	No
4	Were patients, health workers and study personnel 'blind' to treatment?	Yes	Can't tell	**No**
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? **Prone group 49.1% (168/342), supine group 50.9% (174/342). Moderate hypoxemia group-prone 49% (94/192), supine 51% (98/192). Severe hypoxemia group- prone 49.3% (74/150) and supine 51.7% (76/150).**	**Yes**	Can't tell	No
8	How precise was the estimate of the treatment effect? **95% confidence interval [CI], 0.84-1.13; *P*=.72)**	**Yes**	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

Appendix H-5

Mancebo, J. (2006). A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine, 173*(11), 1233-1239.

1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	**Yes**	Can't tell	No
4	Were patients, health workers and study personnel 'blind' to treatment?	Yes	Can't tell	**No**
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? **The ICU mortality was 58% (35/60) in the supine patients and 43% (33/76) in the prone patients.**	**Yes**	Can't tell	No
8	How precise was the estimate of the treatment effect? **A 15% absolute and 25% relative decrease that was not statistically significant (p =0.12).**	**Yes**	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

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Appendix I

Cross Study Analysis

Author, Year	PEEP at inclusion	Duration of PP hr/day	Mortality
(Gattinoni et al., 2001)	PEEP > 5 cm of water	7hrs./day for 10 days.	23% during the 10-day, 49.3% at discharge and 60.5% at discharged
(Guérin et al., 2013)	PEEP > 5 cm of water	17hrs./day for 4 days	(28-day mortality rate)16% in the prone vs. 32.8% in supine position
(Fernandez et al., 2008)	Unknown	18 hrs./day	60-day survival after ICU discharge-15% reduction in mortality was observed in the prone group compared with supine (38% vs. 53%)
(Taccone et al., 2009)	PEEP > 5 cm of water	18 hrs./day for 8 days	28-day mortality rate 31% prone vs. 32.8% supine
(Mancebo et al., 2006)	Unknown	17hrs./day x 10 days	43% in prone vs. 58% in supine