The association between cumulative dose of inhaled bronchodilators and mortality in patients with severe ARDS

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Research

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Abstract

Background: The purpose of this study was to examine bronchodilator use in patients with severe acute respiratory distress syndrome (ARDS) to determine if such use affected mortality. We compared cohorts of patients receiving and not receiving bronchodilators to determine clinical differences between the groups. We then sought associations with clinical risk factors, including cumulative doses of bronchodilators, with in-hospital mortality.

Methods: This study was a retrospective analysis of patients diagnosed with severe ARDS treated at a large health care system between December 1, 2012 and February 10, 2018. From 1195 patients selected from the electronic medical records (EMR) we identified 312 patients for study after the application of inclusion and exclusion criteria. We compared cohorts of patients receiving and not receiving inhaled bronchodilators. We then performed first a univariable, followed by a multivariable analysis of clinical risk factors including the cumulative dose of bronchodilators to study their relationship with in-hospital mortality.

Results: Of the 312 patients with moderate or severe ARDS selected for this study, 260 received bronchodilators and 52 did not receive them. Most patients (n=230) received both albuterol and ipratropium. Patients receiving bronchodilators had longer intensive care unit length of stay (ICULOS; 18.6+/-14.9 days v 9.0+/-7.4 days, p=0.000) but similar mortality compared to patients not receiving bronchodilators (112/260 versus 26/52, p=0.364). Clinical risk factors significantly associated with in-hospital mortality in a univariable analysis included the mortality prediction model II score (MPM, p=0.000), age (p=0.000), the ratio of PaO_2:FiO_2 (PF, p=0.000), the cumulative amount of short acting bronchodilator (SABD, p=0.004), the maximum heart rate (HR_{max}, p=0.023), and the minimum serum potassium level (K_{min}, p=0.000). In a multivariable analysis the MPM (p=0.000, OR=7.543), PF (p=0.002, OR=0.988), cumulative SABD dose (p=0.002, OR=0.996), HR_{max} (p=0.001, OR=1.021), and K_{min} (p=0.000, OR=3.509) remained significantly associated with inpatient mortality.

Conclusions: Inhaled bronchodilators are frequently used in patients with severe ARDS despite clinical evidence that beta-agonists do not improve clinical outcome. We have demonstrated an association between the cumulative dose of SABD and decreased in-hospital mortality in patients with severe ARDS. Further study is needed to confirm these observations.

Background

Acute respiratory distress syndrome (ARDS) is a highly prevalent critical illness that represents an important cause of morbidity and mortality. Data suggest that there are more than 190,000 cases of ARDS in the United States each year with an age-adjusted incidence of 86 per 100,000 patient years [1]. A multicenter international study of ARDS found that 10% of ICU admissions are due to ARDS [2]. As many as 23% of mechanically ventilated patients may meet criteria for ARDS [2]. The incidence of ARDS increases with age and co-morbidities [1–5]. Mortality for ARDS is high, varying between 27% and 52% in

a comprehensive review of the literature [5]. The Berlin Definition of ARDS provides the current criteria used to diagnose this condition, which has been recognized since the 1960s [6, 7].

Advances in management of ARDS over more than two decades have led to the identification of interventions and treatments that improve outcomes associated with ARDS. Available evidence strongly supports the use of low tidal volumes, plateau pressures less than 30 cm H_2O, and prone positioning as ventilation strategies when treating patients with ARDS [8]. Conservative fluid management has been demonstrated to shorten time receiving mechanical ventilation and duration of ICU stays [9]. Some studies suggest that the use of higher levels of PEEP and the application of recruitment maneuvers may aid in the management of patients with ARDS [8].

Pharmacotherapeutic options for the treatment of ARDS remain extremely limited [10]. Beta-agonists are ubiquitously used in respiratory medicine with early work suggesting amelioration of physiologic derangements in ARDS. Beta-agonists have been shown to improve clearance of alveolar fluid both *in vitro* and *in vivo* through effects on sodium transport [11–13] and to reduce pulmonary capillary permeability in ARDS patients [14]. However, a prospective, randomized, placebo-controlled study of aerosolized beta agonists in patients with mild ARDS failed to demonstrate improved outcomes [15]. Despite the lack of demonstrated benefit in ARDS patients from aerosolized beta-agonists and other bronchodilators, they continue to be widely used [16].

We postulated that the use of aerosolized bronchodilators in patients with severe ARDS may be associated with improved mortality. We retrospectively studied patients with ARDS and compared characteristics of patients who received aerosolized bronchodilators with those who did not receive them. We then examined the population of patients with ARDS to determine mortality risk factors and to study the effects of bronchodilator administration upon mortality.

Methods

Study patients

This is a retrospective cohort study. The subjects were treated in a large Southeast Michigan health care system that included one tertiary care hospital and four community hospitals. This study was deemed exempt by the Henry Ford Health System institutional review board (IRB #11795).

Design

Potential subjects were selected from the electronic medical record (EMR) of patients hospitalized between December 1, 2012 and February 10, 2018 using a search engine employing the terms “acute respiratory distress” and “acute respiratory distress syndrome”. Subjects were excluded from the study cohort if they did not meet the Berlin criteria for moderate-to-severe ARDS [6], were under 18 years of age, or were transferred into or out of the healthcare system during their hospital treatment (Table 1).

A database for subjects in the study cohort was created including demographics and clinical variables. Severity of illness was assessed by determining a mortality prediction model II score (MPM) [17]. The age at ARDS onset was determined by the day of intubation. For those patients who were initially intubated for airway protection or pre-operatively, the day of ARDS onset was defined by the day when the PaO_2 to FiO_2 ratio (PF) fell below 200. The maximum heart rate was determined as the maximum heart rate observed in the EMR over the hospital stay (HR_{max}). Similarly, we determined the lowest potassium level recorded in the EMR for each patient over the hospital stay (K_{min}).

The cumulative amount of albuterol and ipratropium given to each patient during the hospital stay for ARDS was recorded. We assessed whether the bronchodilator was administered before or after onset of ARDS and whether the patient had been prescribed a bronchodilator prior to hospitalization (prescribed longer than one month prior to hospitalization and not discontinued prior to hospitalization). The total number of doses of short acting bronchodilator was calculated for each patient (SABD). One dose of albuterol was 2.5 mg of albuterol base, and one dose of ipratropium was 0.5 mg of ipratropium. We used the cumulative SABD doses for each patient instead of the amounts of albuterol or ipratropium administered because most patients in our study received both medications when they received nebulized bronchodilators.

We studied in-hospital mortality (defined as the patient not surviving to discharge from the hospital). We also measured ICU length of stay (ICULOS), hospital length of stay (HLOS), and days requiring mechanical ventilation or with tracheostomy during the index hospitalization (VD). All numeric data is reported as mean, plus or minus standard deviation, if applicable.

Statistical analysis

Comparisons between dichotomous variables were performed using Fisher's exact test. Comparisons between continuous variables were performed by a two-sided student t-test or the Mann Whitney U test. Corrections were not made for multiple comparisons. Risk factors for mortality were first assessed by univariable analysis. If risk factors were significantly associated with mortality, had data present in at least 80% of subjects, had a frequency between 10–90% in subjects (for dichotomous variables), and were not collinear with other variables, they were included in a model examined by multivariable analysis to determine the degree of independent association with mortality. Analyses were considered significant when p-values were < 0.05. Statistical analysis was conducted using a statistical software package (SPSS 27, International Business Machines).

Results

A total of 312 patients were included in the study with 260 receiving bronchodilators during the hospitalization (83.3%). Of the 260 patients receiving bronchodilators, 230 received both albuterol and ipratropium, 27 received only albuterol, and 3 received only ipratropium. The gender distribution was not different between the groups receiving and not receiving bronchodilators (55.4% v 51.9%, p=0.651). The distribution of blacks (33.5% v 46.2%, p=0.112) and whites (54.2% v 40.4%, p=0.094) was also not

different between the groups receiving and not receiving bronchodilators. Other races constituted less than 15% of either group.

Among thirteen conditions identified as being a cause for ARDS, only three were present in more than 5% of our population (Table 2). Patients receiving bronchodilators were slightly more likely to have pneumonia as a cause for ARDS than those not receiving bronchodilators (155/260 v 23/52, 59.6% v 44.2%, p=0.047) but less likely to have non-pneumonia sepsis causing ARDS (52/260 v 19/52, 20.0% v 36.5%, p=0.017). ARDS as a post-operative complication occurred with similar frequency in the two groups (51/260 v 6/52, 19.6% v 36.5%, p=0.237).

Patients receiving bronchodilators had a similar age, severity of illness, HR_{max} and K_{min} compared to patients not receiving bronchodilators, but had longer mean ICULOS, HLOS, and VD (Table 3). Among patients not receiving bronchodilators during the hospitalization, three had been prescribed inhaled bronchodilators as an outpatient prior to their hospitalization, whereas 83 of 260 patients receiving bronchodilators had them prescribed prior to hospitalization (p=0.000). Of the 260 patients receiving bronchodilators in hospital, 160 had them initiated prior to intubation. Among the 52 patients who did not receive bronchodilators, the mortality rate was 50% (26/52), which was not significantly different than the rate of 43.1% (112/260) among the 260 patients receiving bronchodilators (p=0.364, Fisher's exact test).

We then studied clinical risk factors for mortality across the population of patients with ARDS. Risk factors significantly associated with mortality in univariable analysis included MPM, age, PF, cumulative amount of SABD, HR_{max}, and K_{min} (Table 4). Additionally, we found that ICULOS (14.57+/-14.67 days for expired patients, 18.95+/-13.86 for survivors, p=0.000, Mann Whitney U test) and HLOS (17.09+/-17.8 days for expired patients, 24.98+/-16.20 days for survivors, p=0.000, Mann Whitney U test) were each positively associated with decreased mortality in our patients.

We performed a multivariable analysis of clinical risk factors associated with mortality in the univariable analysis to include MPM, PF, cumulative SABD, HR_{max}, and K_{min} . We controlled for the ICULOS by incorporating this risk factor in the multivariable analysis model. We excluded age which was collinear with MPM, and HLOS which was collinear with ICULOS. Of the 312 patients, 311 were included in the analysis (one patient had missing MPM data). ICULOS was not independently associated with mortality. All of the remaining clinical risk factors remained significantly and independently associated with mortality, with the cumulative amount of SABD demonstrating an inverse association with mortality (Table 5).

Discussion

The most important finding from our study is that an increasing cumulative dose of SABD was significantly associated with reduced mortality. Patients in our study with ARDS were frequently treated with bronchodilators even though current guidelines do not propose their use [8, 18]. Other risk factors independently associated with mortality included higher MPM scores, lower PF, higher HR_{max}, and higher

K_{min}. We did not see a significant difference in the HR_{max} or the K_{min} between patients receiving versus those not receiving bronchodilators. Most patients receiving bronchodilators received both albuterol and ipratropium via nebulization.

Multiple studies suggest mechanisms by which bronchodilators may lead to physiologic improvements in patients with ARDS. Beta-2 receptor stimulation has been found to increase alveolar fluid resorption and decrease capillary permeability, thereby reducing alveolar edema [19, 20]. Other studies have also shown that beta-agonists stimulate repair of the alveolar-capillary barrier and epithelial wound repair [21, 22]. Treating patients with IV albuterol appeared to decrease capillary membrane permeability, and *in vitro* studies showed that albuterol administration causes human lung epithelium to heal more quickly [22].

Less evidence is available to support a role for ipratropium in ARDS. In a rat model of acute pulmonary inflammation caused by cadmium inhalation, ipratropium diminished neutrophil numbers in bronchoalveolar lavage and reduced pulmonary edema as determined by lung weight [23]. Rolla and colleagues administered inhaled ipratropium to a small cohort of patients with pulmonary edema due to congestive heart failure, demonstrating improved airflow attributed to amelioration of airway edema [24]. The mechanism by which ipratropium might improve clinical outcomes in ARDS remains speculative. In addition to bronchodilation, physiologic studies suggest that muscarinic antagonists may affect mucus secretion, water and electrolyte secretion from epithelial cells, release of inflammatory mediators from airway epithelium, and fibroblast proliferation [27].

Despite preliminary data supporting a role for beta-agonists in the treatment of ARDS, the results of clinical trials have been disappointing. The BALTI-1 [25] and BALTI-2 [21] trials investigated the use of intravenous salbutamol in the treatment of patients with ARDS. In BALTI-1 results suggested a reduction of extravascular lung water in the treatment arm, but there was no difference in mortality between the treatment and placebo groups, and more patients in the treatment group had supraventricular dysrhythmias [25]. The larger BALTI-2 trial was stopped early because of increased mortality in the treatment group [21]. Treatment group patients in BALTI-2 also had longer ventilator times and increased risk of tachycardia and dysrhythmias [21]. The ALTA trial [15] was a randomized, double-blind, placebo-controlled trial where nebulized albuterol was compared with placebo for the treatment of patients with acute lung injury using a primary outcome of ventilator-free days. The ALTA trial was stopped early because of futility. One important difference between ALTA and the current work is that our study examined patients with moderate to severe ARDS whereas ALTA targeted patients with mild disease. A metanalysis including these three trials demonstrated that beta-agonist treatment was not associated with improved mortality but was associated with decreased ventilator-free days and organ-failure free days [26].

Our finding of a strong association between cumulative SABD use and decreased mortality in ARDS patients has to our knowledge not been previously reported. Our study may have different results compared to previous work in this area because we studied patients with more severe disease. We chose to study cumulative SABD use in our multivariable analysis because most patients received both

medications and the effects of each individually could not be distinguished. It is also conceivable that combination therapy of beta-agonists and muscarinic antagonists has salutary effects not seen with either agent alone. We considered that increased duration of treatment would affect cumulative SABD dose, and that the cohort receiving bronchodilators may be different than the cohort not receiving bronchodilators with respect to other factors. When we controlled our analysis for ICULOS that was different between the two cohorts, our findings remained robust.

We studied the difference in HR_{max} and K_{min} between patients receiving and not receiving bronchodilators to assess whether there was evidence of adverse effects from albuterol in the cohort receiving this medication. There was no difference in these two parameters between the two cohorts of patients that we studied, although each risk factor was significantly associated with mortality. Among the risk factors that we found to be associated with mortality other than the cumulative use of SABD, the MPM is a validated severity of illness score [17], and derangements of oxygenation status, serum potassium, and heart rate are well known factors associated with mortality in the critically ill patient [28].

There are several limitations to our work. Our study is a retrospective, observational, single center study and our results may not be universally applicable. Bronchodilators were widely used among patients in our study, so that the cohort of patients not receiving bronchodilators was small compared to the group receiving bronchodilators and not equivalent in some respects. Most patients received both albuterol and ipratropium so that we could not distinguish whether the effects noted were due to one agent or the other, or both.

The finding of an association of the cumulative dose of SABD with decreased mortality in patients with severe ARDS is novel and provocative. These results should also be considered as preliminary and hypothesis generating, rather than definitive. Further prospective study of beta-agonist and muscarinic antagonists separately and in combination should be considered in patients with severe ARDS to learn if this intervention will change important patient outcomes to include mortality.

Conclusions

Inhaled bronchodilators are frequently used in patients with severe ARDS despite clinical evidence that beta-agonists do not improve clinical outcome. We have demonstrated an independent association between the cumulative dose of SABD and decreased in-hospital mortality in patients with severe ARDS. Further study is needed to confirm these observations.

Abbreviations

ARDS: Adult respiratory distress syndrome

IRB: institutional review board

EMR: electronic medical record

MPM: mortality prediction model II score

PF: PaO_2 to FiO_2 ratio

HR_{max}: maximum heart rate observed in the EMR over the hospital stay

K_{min}: lowest potassium level recorded in the EMR

ICU: intensive care unit

ICULOS: intensive care unit length of stay

HLOS: hospital length of stay

VD: days requiring mechanical ventilation or with tracheostomy

SABD: short acting bronchodilator

Declarations

Ethics approval and consent to participate:

This study was reviewed and approved by the Henry Ford Health System Institutional Review Board (IRB #11795). The study was considered exempt from the need to obtain informed consent.

Consent for publication:

Not applicable.

Availability of data and materials:

A de-identified data base of all study data will be made available upon request to the corresponding author. A non-disclosure statement will be required from the requestor.

Competing interests of authors:

AMS: None

RAF: None

EDAA: None

IOM: None

JLB: None

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Authors' contributions:

AMS: participated in the design of the study, was involved in the acquisition of data, analyzed and interpreted the data, and helped draft the manuscript.

RAF: was involved in the acquisition of data and helped draft the manuscript.

EDAA: was involved in the acquisition of data and helped draft the manuscript.

IOM: was involved in the acquisition of data and helped draft the manuscript.

JLB: was involved in the acquisition of data and helped draft the manuscript.

DRO: participated in the design of the study, analyzed and interpreted the data, and helped draft the manuscript.

All authors read and approved the final manuscripts.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

TABLE 2 Conditions Leading to ARDS

ARDS-Associated Diagnosis	Population Frequency, %
Bacterial Pneumonia	57.1
Influenza	4.8
Non-pneumonia Sepsis	22.8
Caustic Ingestion, Inhalational Injury	<1
Transfusion Related Acute Lung Injury	1.2
Aspiration Pneumonitis	3.3
Acute Eosinophilic Pneumonia	<1
Acute Pancreatitis	3.5
Post-Operative Complication	18.3
Post Bronchoscopy	<1
Perinatal, Post-partum	<1
Alcohol Withdrawal	<1
Trauma	3.5

TABLE 3 Comparison of Patients Receiving Bronchodilators with Patients Not Receiving Bronchodilators

Variable (n_{BD}, n_{No})	Mean+/-SD, BD	Mean+/-SD, No BD	p-value
Age (260, 52)	56.2+/-16.8	53.4+/-18.6	0.288#
HR_{max} (260, 52)	144+/-22 min^{-}	147+/-27 min^{-}	0.444#
K_{min} (260, 52)	3.22+/-0.45 mEq/L	3.24+/-0.61 mEq/L	0.740#
MPM (259, 52)	0.376+/-0.269	0.452+/-0.322	0.149*
PF (260, 52)	85.1+/-36.3	85.9+/-40.8	0.683*
ICULOS (260, 52)	18.6+/-14.9 days	9.0+/-7.4 days	0.000*
HLOS (260, 52)	23.2+/-17.8 days	12.8+/-11.4 days	0.000*
VD (260, 52)	14.1+/-13.0 days	7.4+/-7.36 days	0.000*

*Mann Whitney U test

#Student t-test

TABLE 4 Univariable Analysis of Mortality Risk Factors

Risk Factor	Died	Died, mean	Survived	Survived, mean	P value
MPM	138	0.469+/-0.288	173	0.324+/-0.257	0.000*
Age	138	60.4+/-16.9	174	52.0+/-16.5	0.000#
Gender M/F	81/57		90/84		0.252**
Black y/n	49/89		62/112		1.000**
White y/n	73/65		89/85		0.820**
Pneumonia causing ARDS y/n	83/55		95/79		0.358**
Non-pneumonia sepsis causing ARDS y/n	33/105		38/136		0.685**
Post-operative Comp. causing ARDS y/n	19/119		38/136		0.077**
PF	138	77.5+/-35.0	174	91.4+/-37.5	0.000*
Bronchodilator given Yes/no	112/26		148/26		0.364**
Cumulative SABD received, doses	138	62.28+/-83.53	174	109.85+/-136.63	0.004*
Outpatient bronchodilator prescription y/n	41/97		45/129		0.524**
HR_{max}	138	147.6+/-24.6	174	141.7+/-21.2	0.023#
K_{min}	138	3.35+/-0.55	174	3.12+/-0.39	0.000#

*Mann Whitney U test

#Student t-test

**Fisher's Exact test

TABLE 5 Multivariable Analysis of Mortality Risk Factors

Mortality Risk Factor	P value	Odds Ratio	CI of Odds Ratio
MPM Score	0.000	7.543	2.958-19.237
PF	0.002	0.988	0.981-0.996
Cumulative SABD received	0.002	0.996	0.993-0.998
HR_{max}	0.001	1.021	1.009-1.033
K_{min}	0.000	3.509	1.878-6.555
ICULOS	0.924	1.001	0.978-1.024

Supplementary Files

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- Table1.png