An Experience with Lung-Protective Mechanical Ventilation in ARDS Patients in Intensive Care Unit: Survivors vs Non-Survivors

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ABSTRACT

Introduction: ARDS i.e Acute respiratory distress syndrome is a serious clinical condition, often fatal, in which acute hypoxaemic respiratory failure occurs due to direct or/and indirect lung injury by various factors. Positive pressure mechanical ventilation is the key therapy to combat this dreaded condition in present day scenario. Study was aimed at observing the clinical profile and outcome of the ards patients on lung protective mechanical ventilation with a vis-a-vis comparison of survivors versus non-survivors of ARDS.

Material and Methods: This was a prospective observational study and conducted over a duration of one year in Emergency departmental ICU of a tertiary –care Government medical college hospital in India to have a comparative analysis of various clinical profiles of survivors and non-survivors of ARDS, undergoing lung protective mechanical ventilation protocol laid down by ARDS Network.

Results: Clinical profiles of 44 ARDS patients, satisfying Berlin Definition of ARDS, 2012 were studied. Mortality was 54.54% where sepsis was the prime etiological factor. Nonsurvivors had higher initial Plateau Pressure as well as PaO2/FiO2. Requirement of PEEP and FiO2 were also significantly higher among non-survivors.

Conclusions: Lung protective mechanical ventilation strategy with treatment of precipitating factors still remains the treatment of choice to improve the survival and reducing morbidities in ARDS patients.

Keywords: ARDS, Lung Protective Mechanical Ventilation, PEEP, Plateau Pressure, Sepsis

INTRODUCTION

Acute respiratory distress syndrome remains one of the most important and dreaded cause of acute hypoxaemic respiratory failure since its original description by Ashbaugh[1] et al in 1967 and it often leads to fatal outcome irrespective of modern progress of critical care medicine. it was not until 1994 that an international American – European Consensus Conference (AECC) laid the foundations for the definition of ARDS[2] which was further modified in Berlin,2011 which is presenty accepted as a universal definition for ARDS.[3] According to the Berlin definition[3], ARDS is defined as a syndrome characterized by (i) onset of respiratory distress within one week of a known pre-existing clinical insult, (ii) bilateral radiographic opacities, not fully explained by pleural effusions, atelectasis, or nodules, (iii) respiratory failure not fully explained by cardiac failure or fluid overload, and (iv) poor systemic oxygenation, with a PaO2/FIO2 ≤300 and a PEEP or CPAP ≥5 cm H2O. The definition also categorizes syndrome severity as mild, moderate, or severe, based on PaO2/FIO2. According to the Berlin definition, patients who previously were diagnosed with ALI, but not ARDS (i.e., PaO2/FIO2 ≤300, but >200), are referred to as having mild ARDS, with ALI now an obsolete term. Moderate ARDS is defined as PaO2/FIO2 ≤200, but >100, and severe ARDS is defined as PaO2/FIO2 ≤100.

ARDS may not be present on arrival into emergency department or hospital admission and it often occurs over a period of several hours to days following the clinical insult[4,5] which may be direct or indirect lung injury, most commonly sepsis, shock of any etiology, pneumonia, aspiration, pancreatitis, severe trauma, major surgery, multiple blood-product transfusions etc.[5,6] Clinical features of ARDS are severe dyspnoea, tachypnoea, and hypoxaemia refractory to supplemental oxygen alongwith the clinical features of the precipitating factors.[3]

The general approach to treatment of ARDS includes addressing precipitating causes and other concurrent clinical issues, ensuring adequate oxygenation, careful implementation of a lung-protective ventilator strategy, prudent fluid and hemodynamic management, and a multitude of other measures, like special patient positioning, lung recruitment maneuvers, ECMO, HFOV, TGI, pharmacologic considerations etc many of which are still in experimental phase.[7,8-10]

Mechanical ventilation is the key-step in the management of ARDS patients.[11] We now know that mechanical ventilation itself can aggravate lung injury, referred to as ventilator-associated or –induced lung injury (VALI/VILI), through several mechanisms eg barotrauma, volutrauma, and biotrauma.[12] The lung protective mechanical ventilation by providing low tidal volume of 6 mL/kg IBW and limiting the inspiratory plateau pressure to <28–30 cmH2O is now accepted as standard of care for patients presenting with ARDS.[7] Latest studies suggest that reducing further ventilator associated / induced lung injury (VALI/VILI) is

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one of the main resort to further decrease the mortality in ARDS.[13] Monitoring tools such as oesophageal pressure or lung volume measurements may also help to set the ventilator.[14,15]

Keeping in mind of all these facts and data-sheets our study hereby aimed at observing the clinical profile and outcome of the ards patients on lung protective mechanical ventilation with a vis-a-vis comparison of survivors versus non-survivors of ARDS.

MATERIAL AND METHODS

After taking prior institutional ethical committee approval, this prospective observational study was conducted among the admitted patients in Emergency ICU of Department of Emergency Medicine, Gauhati Medical College and Hospital, Assam, India. Inclusion criterias were adult patients (aged 18 years or elder) fulfilling the defining criteria of ARDS according to the Berlin definition, 2012[3] whereas patients of known bronchial asthma, COPD, interstitial lung disease, active pulmonary TB, congestive heart failure, chronic liver disease, chronic kidney disease, and patients with pregnancy were duely excluded from the study.

Clinical history in details were obtained and thorough physical examination were done for each and every patient on admission to the ICU and all necessary investigations like Chest X-ray, ABG, ECG, blood tests for haematological and relevant biochemical assessments and cultures of appropriate specimens etc were sent. Chest X-ray and ABG were performed every 24 hourly as a routine basis and also additionally whenever clinically indicated till the patients were weaned from the ventilators and therafter as indicated. for every patient on mechanical ventilation, Lung protective mechanical ventilation protocol by ARDS Network was followed and relevant parameters were noted properly. Initial ventilatory parameters like mode, FiO2, Positive End Expiratory Pressure (PEEP), Plateau Pressure (Pplat), Peak Inspiratory Pressure (Ppeak), Respiratory Rate (RR), Tidal Volume (Vt) were noted after 20 minutes of initiation of mechanical ventilation. Daily SOFA scoring was done for every patient for signs of organ failure.

Primary outcome variable in our study was mortality while undergoing lung protective mechanical ventilation during ICU stay. secondary outcome variables studied were ventilatory parameters, organ dysfunction parameters, time duration on mechanical ventilation, clinical parameters during discharge from ICU etc.

STATISTICAL ANALYSIS

Results of categorical variables in the study were expressed in numbers and percentages whereas numerical variables were presented as mean ± Standard Deviation (SD). To test the significance of comparison between categorical data Fisher exact test was applied while for numerical data, Student's t or Kruskal-Wallis test was used. SPSS 16.0 software was used for all statistical analyses.

RESULTS

clinical profiles of 44 patients of ARDS after application of the inclusion and exclusion criteria, were studied, which was 6.3% of the total number of patients admitted to THE emergency ICU during the study period. There was Male predominance (n = 28, 64%) with male to female ratio 1.75:1. The mean age in this study was 40.4 ± 14.12 years (Mean ± SD), with majority of the patients in relatively younger (<48years) age group.

Majority of the patients were presented with breathlessness (n = 36, 82%), fever (n = 29, 66%) and altered sensorium (n=28, 63.6%). However, Among the etiological factors of ARDS in our study, commonest cause was non-pulmonary sepsis (n= 13, 29.5%) which was followed by direct respiratory insult due to aspiration (n=10, 22.7%). In several cases there were more than one etiological factors for developing ARDS. Onset of ARDS following exposure to these known clinical insults is shown in table 1, with a mean onset of 3.59 ± 1.56 days. Most of the patients fell into the category of Moderate ARDS as per the PaO2/FiO2 criteria (100<PaO2/FiO2 <200) [Figure 1].

24 patients in our study died out of total 44 patients causing a mortality of 54.5%. Non-Pulmonary Sepsis was also the major cause (n=10 out of 24, 41.7%) for mortality followed by Shock (n=5,20.8%) and Pneumonia (n=4,16.7%). Table 2 also describes the individual cause-wise mortality which shows 100% mortality in drug induced ARDS patient, and majority of the sepsis patients (76%) also died.

Furthermore we have done a comparative analysis between survivor and non-survivor group about general clinical

Time of onset (in days)	No. of patients	Percent (%)
1	4	9.1
2	9	20.5
3	8	18.2
4	8	18.2
5	11	25.0
6	3	6.8
7	1	2.3
Total	44	100.0

Table-1: Frequency distribution of time of onset of ARDS from the inciting event

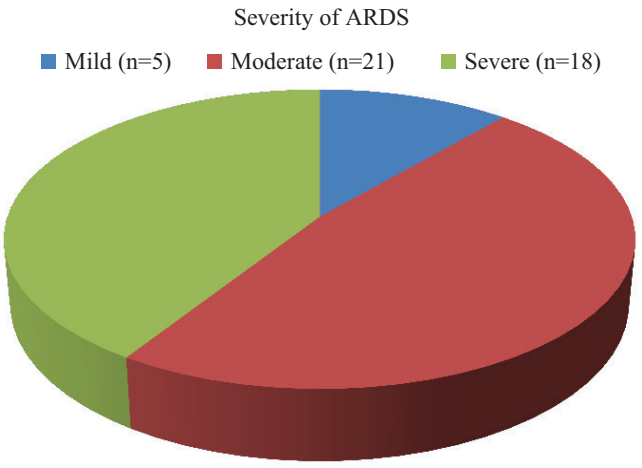

Figure-1: Pie diagram showing the severity categories of ARDS patients

parameters as well as crutial parameters of lung-protective mechanical ventilation and its complications and outcome (Table 3-4). In general, severe ARDS, SEPSIS as initial diagnosis were significantly associated with higher mortality. Non-survivors in our study required significantly higher amount of FiO2 and PEEP. First day Plateu pressure and Peak Inspiratory pressure generated while all the patients were put on low tidal volume strategy, was significantly high in non-survivor group.

DISCUSSION

A prospective study by Heffernan et al[16] showed that females were more likely to develop ARDS (35 % versus 25%, p=0.02) wheras our study exhibited a male predominance. Maximum number of patients belonged to the age group of 38-48 years (27.2%) followed by 25% in the age group of 18-28 years. Only about 30% patients were more than 48 years of age. In our study, Mean age was 40.4 years (SD ± 14.12). In a study by Bhadade et al[17] in Maharashtra, the mean age of ARDS patients was 37.9 years. Singh et al[18] had shown that the mean age in ARDS patients was 44.8 ± 15.5 years. Hence it seems that ARDS is more frequently observed in younger age group.

Cause	Total patients	Nonsurvivors
Non pulmonary sepsis	13	10 (76%)
Aspiration	10	3 (30%)
Shock	9	5 (55%)
Pneumonia	6	4 (67%)
Acute pancreatitis	5	3 (60%)
Malaria	4	2 (50%)
Major Trauma	3	1 (33%)
Fat Embolism	2	0 (0%)
Drug overdose	1	1 (100%)
Anaphylaxis	1	0 (0%)

Table-2: Etiologies of ARDS and etiology-wise mortality in our study

In our study, non-pulmonary sepsis (29.5%) was the commonest causative factor for developing ARDS, followed by aspiration in 22.7% cases and shock in 20.4% cases, which was nearly similar to the observations of gajic et al.[19] However, Study by Rubenfeld[20] et al Showed most common cause was severe sepsis due pulmonary infections (46%). Agarwal et al[21] also showed pneumonia to be the commonest etiology for ARDS.

A recent multicentre observational study had shown that ARDS develops mostly within 2 days of admission and thereby increases in-hospital mortality significantly.[4] The mean time of onset of refractory hypoxemia after exposure to a known clinical insult was 3.59 ± 1.56 days (Mean±SD) in our study. Two studies have reported the average time of onset of ARDS from a known clinical insult to be within 3 to 7 days.[6,19] Ferguson et al[22] observed that diagnosis of ARDS was done after a median of 1 day from the onset of known clinical insult in them. Ferguson et al[23] observed that late onset ARDS (onset after >48 hrs of mechanical ventilation;) was an independent factor for higher mortality (odds ratio = 2.09).

In this study, out of 44 patients, there was incidence of mild ARDS in only 5 patients (11.3%) while severe ARDS occurred in 18 patients (40.9%) and moderate ARDS in 21 patients (47.7%). In a study by Thille et al[24] also, incidence of mild ARDS was less (14%), most of them were in moderate (40%) and severe (46%) group. The ALIVE study[19] reported that the incidence of mild ARDS was only 30% on admission but half of them developed moderate or severe ARDS afterwards.

Parameters	Survivors (n=20)	Non-survivors (n=24)	P Value
Male gender (n, %)	12 (60%)	16 (66.7%)	0.75
Age in years (mean ± SD)	39.2 ± 17.3	41.3 ± 11.4	0.64
Direct lung insults (n,%)	10 (50%)	7 (29.2%)	0.21
Primary diagnosis as SEPSIS (n,%)	3 (15%)	13 (54.2%)	0.007
onset of ARDS in days from initial insult (Mean ±SD)	3.4 ± 0.3	3.7 ± 1.5	0.59
Severe ARDS (n,%)	3 (15%)	15 (62.5%)	0.001
Metabolic Acidosis(n, %)	4 (20%)	9 (37.5%)	0.17
Number of nonpulmonary Organ failure (Mean±SD)	2.75±1.61	3.87±1.36	0.009
Length of ICU stay in days (Mean ±SD)	12.9 ± 2.8	4.8 ± 2.7	< 0.001

Table-3: Comparison of over-all parameters of survivors and non-survivors of ARDS

Parameters	Survivors (n=20)	Nonsurvivors (n=24)	P Value
Tidal Volume (ml/Kg IBW)	6.018± 0.0622	5.984 ± 0.1832	0.43
RR	26 ± 2.53	25.79 ± 2.3	0.77
PEEP	6.6 ± 1.81804	9.875 ± 2.0916	<0.0001
P_{PEAK} (Peak Inspiraory Pressure)	28.1 ± 4.85473	32.25 ± 4.8297	0.0071
FiO2	0.465 ± 0.08751	0.7375 ± 0.1883	<0.0001
Day 1 Plateau Pressure	21.16±4.19	26.02±4.38	0.0005
Day1 Static Lung Compliance (Cs)ml/cm H2O	27.2±7.76	25.7±5.83	0.47
Initial PaO2/FiO2	162.8± 41.89	88.9± 7.71	<.0001
Duration of Ventilation in days (mean ±sd)	9.2±2.04	4.79 ± 2.68	< 0.0001

Table-4: Comparison of mechanical ventilatory parameters of survivors and non-survivors of ARDS

Despite recent advances in critical care ARDS is associated with significant mortality, which was 54.54% in our study. In studies by Agarwal et al[21] and Rubenfeld et al[20], the hospital mortality rate for ARDS was 47.8% and 41.1% respectively. Esteban et al[25] observed that overall ICU mortality was 30.7% whereas mortality was much higher (52%) in the patients undergoing mechanical ventilation for ARDS. Recent studies show a decreasing mortality trend in ARDS patients which may be explained by the widespread following of lung protective ventilation protocol. The ARMA trial showed reduced mortality(21%) in patients with lung protective mechanical ventilation whereas 40% mortality with conventional ventilation strategies in ARDS patients.[26] In a recent prospective, multicenter observational study by Villar et al[27], it was observed that even with the use of lung protective mechanical ventilation, the mortality of ARDS cases in ICU was still above 40%.

In our study mortality in ARDS varied according to the causative factor. 76% of patients with non-pulmonary sepsis, 67% of the pneumonia patients, 60% of the pancreatitis patients 55% of shock patients and 50% of the malaria patients, 33% of the patients with aspiration and 33% of the major trauma patients with ARDS died. Rubenfeld et al[20] also showed mortality in ARDS varied from 24.1% among patients with severe trauma to 40.6% among patients with severe sepsis with a suspected pulmonary source, to 43.6% among patients with witnessed aspiration.

Bhadade et al[17] found mortality in females to be higher than males (73% vs 51%) but our series showed higher incidence of mortality in males (16/ 28, 57%) compared to females (8/16, 50%). However, these gender differences were not statistically significant. The study by Luhr et al[28] also demonstrated that gender was not independently associated with mortality.

The mean age of the survivors in our study was 39.25 years (SD ± 17.39) and for non-survivors it was 41.3 years (SD ± 11.45) which was statistically not significant (p=0.644). However, the overall higher mean age in non-survivors was also reported by Singh et al.[18] Several studies like Rubenfeld[20] and Suchyta et al[29] have shown increased risk of ARDS and increased mortality in the elderely age group.

Another cause of increased mortality in ARDS is sepsis as has been reported in studies. Sheu et al[30] concluded in their prospective study that Sepsis-related ARDS had a higher overall severity of the disease, poorer recovery, less successful weaning rate, and higher mortality than non-sepsis-related ARDS In this study the percentage of patients with sepsis (pulmonary and non-pulmonary) at presentation was 36.4% (16 out of 44 patients) among whom 13 patients with sepsis died showing that ARDS patients with sepsis were twice more likely to die than patients with ARDS without sepsis (Relative risk 2.1 with 95%Cl 1.2 to 3.5; p =0.011). Montgomery et al in a prospective study reported that only 16% of deaths in the ARDS were due to irreversible respiratory failure. Most of the deaths in the first 3 days after enrollment into the study were due to the pre-existing illness or background pathology. Sepsis was the major cause of late deaths in ARDS patients. Among the non-survivors of ARDS who died after 3 days 73% met criteria for sepsis syndrome[31] Suchyta et al[29] found survivors had statistically less incidence of sepsis than did nonsurvivors.

We further analyzed the severity of hypoxemia as reflected by PaO2 /FiO2 ratio and its early response to conventional therapy. It was observed that incidence of mortality in severe ARDS patients were much higher than the mild/ moderate ARDS patients (p<0.0002). Similar findings was also noted by Rubenfeld et al.[20] The ARDS task force conducted a meta analysis during preparing the draft of Berlin Definition during which they noted that in in mild ARDS the mortality was 27% (95%CI 24%-30%), in moderate ARDS 32% (95%CI 29%-34%) but in severe ARDS it was 45%(95%CI 42%-48%) and this difference was highly significant (p<0.001).[3] Also, there was significant difference in the initial Pa02 / Fi02 ratio (indicating the severity of ARDS on presentation) in survivors (162.8±41.89) than nonsurvivors (88.9± 27.71) (p <0.0001) in our study Esteban et al[25] reported mortality of 25% in the group of patients with Pa02 /Fi02 of 200-300, 31% with Pa02 /Fi02 150-199, 47% with Pa02 iFi02 of 100-149 and 83% with Pa02 /Fi02 of less than 100.Villar et al[27] observed that Pa02 /Fi02 ratio at the time of ARDS identification had an inverse relationship to mortality. Again, mean Pa02 /Fi02 on day 7 between survivors and non-survivors was compared.In survivors the mean Pa02 /Fi02 on day 7 was 171.8 ± 48.67 (Mean±SD) and in non-survivors 95.85 ± 34.73(Mean±SD). The difference between the two groups was statistically significant (p<0.0001).Hence we agree with R C Bone et al[32] that the early response to conventional therapy is a marker of good prognosis and thus can be used as a tool for likely survival of ARDS patients.

All of the ARDS patients have undergone low tidal volume ventilation in our study, hence there was no difference in mean tidal volume (per kg ideal body weight) or respiratory rate between two groups but Non-survivors in our study required significantly higher amount of FiO2 and PEEP to maintain adequate oxygenation goals.

Hager et al[33] had reported that increased day 1 plateau pressures(Pplat) in ARDS was associated with increased risk of mortality. In our study also, mean Day 1 Pplat as well as Ppeak were significantly higher in Non-survivors than in survivors reflecting high airway pressures generated due to stiffer lungs in more severe ARDS patients. This fact was reinforced by direct measurements of the static lung compliance (Cs) at initiation of mechanical ventilation and afterwards. There was higher mean static lung compliance (27.1+7.76 ml/cm H20 in survivors than in non-survivors (25.7±5.83 ml/lcm H2O) in our study. However, this difference was not statistically significant and Kangelaris et at[34] also observed similar non-significant difference in lung compliance among survivors and non-survivors of ARDS. But then, An increase in lung compliance alone can be a sign of improved lung distensibility. We noted significant improvement in the mean Cs at initiation of mechanical ventilation (27.1+7.76 ml/cm H20) and prior to discontinuation of mechanical ventilation (36.6±5.9

mllcm H_2O) (p=0.0001) in the survivor group. Improving compliance can be a good indicator of improvement in lung function provided there is decreasing need of PEEP to maintain desired oxygenation.[35]

Metabolic acidosis has been found to correlate with inceased mortality in some studies on ARDS. Brun-Buisson[36] et al observed that ph <7.3 was associated with mortality in ARDS. Bhadade et al[17] found that acidosis is an independent factor associated with mortality. Present study observes increased incidence of metabolic acidosis among nonsurvivors on admission to ICU, though it was statistically not significant (p=0.1753)

Another important factor for mortality is the presence of non-pulmonary organ failure in ARDS patients.[35] In my study all the non-survivors had more than one non-pulmonary organ dysfunction. In this study a comparison between the mean number of non-pulmonary organ dysfunction between survivors and non survivors on second day of admission was done. In the survivors the mean number of non-pulmonary organs in failure was 2.75 ± 1.6 1 (Mean±SD) and in non-survivors it was 3.87±1.36 (Mean± SD) which was also statistically significant (p=0.0092). Villar et al[27] and Suchyta et al[29] also observed that more the number of failing organs, the greater was the mortality in ARDS patients.

Survivors had significantly high duration of Mechanical ventilation and ICU stay than non-survivors in our study most probably due to early mortality resuting from more severe disease in non-survivors. Rios et al[37] in 2009 observed that in survivors of ARDS mechanical ventilation was required for an average of 11 days (6-19days).

In our study, mean duration of survival was 4.8 days (SD ± 2.7) which was quite similar with the observation (4.55 days) by Bhadade R et al.[17]

There was no significant variation in the duration of mechanical ventilation among survivors whether they had mild, moderate or severe ARDS (p=0.907). How long a critically ill patient needs ventilation varies from one. patient. to another, eg. course of the underlying disease process, comorbidities and organs involved etc.

The mean duration of ICU stay in survivors was 12.95±2.85 days (Mean±SD). In a study by Kangelaris et al[34] observed that median length of ICU stay in survivors of mild ARDS was 9 days (IQR 6 to 15) in moderate ARDS 9 days(IQR 6 to 16) and in severe ARDS 10 days(IQR 7 to 19). There was no incidence of barotraumas due to mechanical ventilation in our study. Most of the survivors were discharged in stable condition without any significant organ dysfunction.

CONCLUSION

Early detection of the critically ill patients who are at risk of developing ARDS and timely initiation of appropriate preventive strategies have become an important aspect in critical care medicine, particularly in patients receiving mechanical ventilation. The lung protective ventilation protocol using low tidal volume and limiting plateau pressure, thereby preventing VILI as much as possible, is the mainstem therapy to improve survival in patients with ARDS. At the same point of time treating precipitating factors, maintaining hemodynamic stability and tissue oxygenation, judicious use of advanced strategies coupled with time-to-time monitoring of ventilatory and clinical parameters are essential steps to reduce the mortality as well as the morbidity from this life-threatening syndrome.

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