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Original Article

Pharmacology Section

Prescribing Patterns of Drugs in Acute Respiratory Distress Syndrome (ARDS): An Observational Study

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ABSTRACT

Introduction: Acute respiratory distress syndrome (ARDS) is characterized by acute respiratory failure and is associated with wide range of clinical disorders. Controversy prevails over the pharmacological intervention in this disease. The aim of the study was to observe the prescribing pattern of drugs in patients with ARDS managed at a tertiary care hospital.

Materials and Methods: This observational study was conducted at tertiary care hospital in India. Data of patients admitted from January 2010 to December 2012 was collected. Patients aged more than 18 years admitted in ICU, who were diagnosed to have ARDS during the study period, were included. A total of 150 patients of ARDS were selected. Data was collected as per the pre designed proforma and it included patients' age, gender, clinical disorders precipitating ARDS, prescribing pattern of drugs and outcome. The data of the subjects was collected till discharge from hospital or death.

Results: Infection was the cause of ARDS in 81.3% (n=122) of subjects. Antibiotics were prescribed in all the subjects and beta-lactams were prescribed in 97.3% (n=146). 41.3% (n=62) were prescribed corticosteroids, 39.3% (n=59) diuretics and 89.3% (n=134) intravenous fluids.

Conclusion: The outcome of patients on different pharmacological treatment did not show any statistically significant difference.

Keywords: Antibiotics, ARDS, Corticosteroids, Intravenous fluids

INTRODUCTION

ARDS described as a clinical entity is a common disorder seen in critically ill patients [1]. It is characterized by severe inflammation which leads to diffuse alveolar damage (DAD) involving both endothelial and epithelial layers [2] resulting in hypoxemia and decreased lung compliance. Clinically, it is characterized by acute respiratory failure with severe hypoxemia and radiologically by diffuse pulmonary infiltrates on frontal chest radiograph [3].

Despite recent advances in critical care, the mortality due to ARDS varies from 35 to 45% in various studies [4]. The mortality has been reported to be associated with organ failure, sepsis, age and associated co morbid illness [4]. The treatment of ARDS involves general supportive measures, ventilator strategies and appropriate treatment of the underlying condition. Besides general supportive measures, pharmacological interventions are commonly considered throughout the course of ARDS. Despite decades of research, only a few pharmacological therapies have emerged for ARDS.

With this background, the objective of study was to study the prescribing pattern of drugs and their relation to outcome in patients with ARDS.

MATERIALS AND METHODS

The study was conducted at a tertiary care teaching hospital in South India. After taking permission from the institutional ethics committee the study was conducted in two phases. Data was collected over a period of three years from January 2010 to December 2012. It was retrospective over first two years (from January 2010 to December 2011) during which 100 patients were taken and prospective for one year (2011-2012) during which 50 patients were included.

Patients aged more than 18 years, admitted in ICU and diagnosed to have ARDS during the study period, were included. Diagnosis of ARDS was based on American/ European consensus statement for definition of ARDS which includes – PaO2/ FiO2 ratio less than or equal to 200, bilateral infiltrates on chest radiograph and absence of clinical signs of left heart failure [5]. Patients with clinical signs of left heart failure were excluded from the study.

For prospective and retrospective phase of study, a total of 150 patients of ARDS meeting the above mentioned criteria were included. For prospective phase, an informed consent was taken from patients' relatives and then the patients were enrolled in the study. Data was collected as per the proforma and included patients age, gender, past major illness, clinical disorders precipitating ARDS, presence of organ failure, clinical severity of ARDS on admission, use and duration of mechanical ventilation, length of hospital stay, presence or absence of tracheostomy, prescribing patterns of drugs and outcome. The data of the subjects was collected till discharge from hospital or death. The data for the retrospective phase of the study was collected from patient records of 2010 and 2011.The proforma used was the same as for the prospective phase of study.

STATISTICAL ANALYSIS

The data was analyzed using SPSS 16.0. The data was analysed using descriptive statistics and statistical inferences were expressed in the form of tables. P-values were calculated using chi- square test for comparing the outcomes in different drug groups. The level of statistical significance was set at p-value < 0.05.

RESULTS

The study population consisted of 150 patients meeting the AECC (American/ European consensus conference) criteria for definition of ARDS. [Table/Fig-1] shows the baseline characteristics of the study population. The mean age of the study population was 42.92±13.916. 48% of the patients (n=72) were less than 40 years of age. 9.3% (n=14) of the subjects were both smokers and alcoholics. 5% (n=3) of the female subjects were pregnant. Among causes of ARDS, pneumonia comprised 23.35% (n=35), scrub typhus 22% (n=33) and leptospiral infection 7.3% (n=11) of the total patient population. 61.3% (n=92) of the patients were on mechanical ventilation.

		n (%)
Age	< 40 years	72 (48)
	years	60 (40)
	> 60 years	18 (12)
Gender	Male	90 (60)
	Female	60 (40)
Smoker	Yes	23(15.3)
	No	127(84.7)
Alcohol consumption	Yes	21(14)
	No	129(86)
Blood Transfusion	Yes	43(28.7)
	No	107(71.3)
Aetiology of ARDS	Infectious	122 (81.3)
	Non-infectious	28 (18.7)
Co-morbidities	Yes	36 (24)
	No	114 (76)

[Table/Fig-1]: Baseline characteristics of the study population (N=150)

Drugs prescribed to patients are shown in [Table/Fig-2].

Drugs		Number, (%)
Corticosteroids	Methyl prednisolone	43 (28.7)
	Hydrocortisone	18 (12)
	Dexamethasone	1 (0.6)
	No steroids	88 (58.7)
Neuromuscular blocking agents	Pancuronium	2 (1.3)
	Vecuronium	9 (6)
	Noneuromuscular agents	139 (92.7)
IV fluids	Dextrose Normal Saline	120 (80)
	Normal Saline	6 (4)
	Ringer lactate	2 (1.3)
	5% dextrose	6 (4)
	No Fluids	16 (10.7)
Diuretics	Furosemide	59 (39.3)
	No diuretics	91 (60.7)

[Table/Fig-2]: Different classes of drugs (other than antibiotics) and fluids prescribed for management of ARDS. (N=150)

41.3% (n=62) patients were on corticosteroids. Among them 69.3% (n=43) were on methylprednisolone and 29.1% (n=18) were on hydrocortisone. One subject was on intravenous dexamethsone (4mg/day). 54.8% (n=34) of the cases were on divided dose of steroids. Minimum dosage of methylprednisolone used was 24mg/day while the maximum dosage was 500mg/day. Minimum dosage of hydrocortisone used was 150mg/day while maximum dosage was 600mg/day [Table/Fig-3].

Among the subjects who were prescribed corticosteroids (n=62), 54.84% (n=34) were administered steroids in divided doses and 45.16% (n=28) as infusion.

Steroid	Dosage per day	n (%)
Methyl prednisolone (mg/day)	≤40	4 (6.5)
	41-80	20 (32.2)
	81-120	3 (4.8)
	≥120	16 (25.9)
Hydrocortisone (mg/day)	≤200	11(17.7)
	> 200	7 (11.2)
Dexamethasone	4mg	1 (1.6%)

[Table/Fig-3]: Dosage of steroid administered per day (N=62)

39.3% (n=59) patients were administered diuretics and 89.3% (n=134) intravenous fluids.

Among the 59 patients who were on furosemide, majority (76.3%, n=45) were on dosage of ≤40mg/day. The rate of fluid administration was less than 50ml per hour in 41.3% (n=62) of subjects, 50-100 ml per hour in 45.3% (n=68) and more than 100ml per hour in 2.7% (n=4).

Microbiological cultures were positive in 28.6% (n=43) of the cases Antimicrobials were prescribed to all the patients. [Table/Fig-4] shows the different antimicrobials prescribed in patients with ARDS

Antimicrobials		n (%)
Piperacillin-tazobactam		112 (74.7)
Doxycycline		85 (56.7)
Macrolides		48 (32)
Cephalosporins	Cefoperazone-sulbactam	16 (10.7)
	Ceftriaxone	13 (8.7)
	Cefepime	4 (2.7)
	Ceftazidime	2 (1.3)
Nitroimidazole		31 (20.7)
Meropenem		26 (17.3)
Aminoglycosides	Netilmicin	10 (6.7)
	Amikacin	10 (6.7)
Fluoroquinolones	Levofloxacin	18 (12)
	Ciprofloxacin	1 (0.7)
	Prulifloxacin	1 (0.7)
Linezolid		18 (12)
Teicoplanin		9 (6)
Other beta-lactams	Amoxicillin-clavulanic acid	4 (2.7)
	Crystalline penicillin	3 (2)
	Faropenem	1 (0.7)
Clindamycin		7 (4.7)
Polymyxin		4 (2.7)
Cotrimoxazole		2 (1.3)
Vancomycin		2 (1.3)
Tigecycline		1 (0.7)

[Table/Fig-4]: Antimicrobials prescribed in patients with ARDS Piperacillin–tazobactam was most frequently prescribed antimicrobial combination, followed by doxycycline and then macrolides

The outcome of patients on different groups of drugs is shown in [Table/Fig-5]. There was no statistically significant difference between the patient outcome in patients who were administered corticosteroids, diuretics or i.v. fluids. WHO prescribing indicators have been shown in [Table/Fig-6].

DISCUSSION

In ARDS, the impairment of gas exchange and hypoxemic respiratory failure can be refractory and life threatening. Pharmacological interventions are used throughout the course of ARDS, in addition to ventilator support. In this study the various drugs being prescribed to these patients have been evaluated and discussed.

A considerable number of patients in this study were less than years. Other Indian studies also show a mean age of around 39 years [6]. However, studies done in Boston and Australia show that mean age of patients with ARDS was 60 years [7,8]. This lower mean age of ARDS patients may be explained by the higher percentage of tropical infectious diseases as a cause of ARDS in our study population.

An independent dose-response association is seen between current cigarette smoking and the subsequent hospital presentation of ARDS. This predictive association may be explained by the fact that cigarette smokers are more likely to develop acute precipitating factors of ARDS such as pneumonia, sepsis syndrome etc [9]. In addition to the effect mediated through precipitating factors, smoking causes alveolar damage and thus directly contributes to respiratory insufficiency and ARDS [9]. No association was found

Outcome	Corticosteroids			Diuretics			IV fluids		
	Yes	No	Chi-square p-value	Yes	No	Chi-square p-value	Yes	No	Chi-square p-value
Recovered	27	39	0.013 1.000	31	35	4.041 0.142	61	5	2.556 0.329
Died	32	45		27	50		66	11	
DAMA	3	4		1	6		7	0	
Total	62	88		59	91		134	16	

[Table/Fig-5]: Outcome in relation to the use of various therapeutics agents used in patients with ARDS
DAMA- discharged against medical advice

Average number of drugs prescribed	4.56
Percentage of drugs prescribed as generics	91%
Percentage of drugs prescribed from national Essential Drug List	67.007%
Percentage of drugs prescribed as antibiotics	59.56%
Percentage of drugs prescribed as injections	86.86%

[Table/Fig-6]: WHO prescribing indicators assessed

between alcohol consumption and ARDS incidence in our study. Similar results were seen by authors in a 15 years cohort study in Northern California [9]. However, another review put forth that history of chronic alcohol abuse is associated with increased incidence and severity of ARDS in critically ill patients [10]. Alcohol abuse alters lung structure and function making lung susceptible to edematous injury in presence of inflammatory stress [11].

The aetiology is infection in 81% of patients and pneumonia is the most common underlying condition with 23.35% of the total cases suffering from pneumonia. In another study from India, 30% of total cases had pneumonia [6].

In our study, majority of the patients were on intravenous fluids (89.3%, n=134). A large percentage of patients were on corticosteroids (41%, n=62) and diuretics (39.3%, n=59). Only 7.3% (n=11) cases were on neuromuscular blocking agents. All the patients were on antibiotics.

Corticosteroids by inhibiting neutrophil activation, suppressing synthesis of phospholipase A_2, cyclooxygenase and inducible nitric oxide synthase, inhibit the host defences [12]. So, corticosteroids in high doses for a short period are proposed in the early phase of ARDS for quick resolution and to prevent progression to lung fibrosis. Methylprednisolone administered to patients with intermediate and late ARDS is associated with improved oxygenation and reduced dead space to tidal volume ratio as early as four days following initiation [13]. In a prospective, randomized trial of methylprednisolone therapy which included 99 patients the investigators concluded that the outcome was not affected in patients with ARDS receiving high-dose methylprednisolone [14]. Although preventive steroid therapy in critically ill patients may have been associated with detrimental effects on the incidence of ARDS and subsequent mortality, a trend was found to benefit when steroids were given after the onset of ARDS [15]. Another study stated that starting methylprednisolone therapy more than two weeks after the onset of ARDS may increase the risk of death [16]. The results of various studies have been quite variable and hence, the role of corticosteroids in ARDS is not clear. In our study a considerable number of patients (41%, n=62) received corticosteroids [Table/Fig-3]. In these patients the mean duration of corticosteroid use was approximately half that of the mean duration of hospital stay [Table/Fig-7]. The contradictory findings of various studies make it difficult for a clinician to decide regarding prescription of corticosteroids in patients with ARDS. This explains the findings of our study in which approximately 60% patients were not prescribed corticosteroids. Moreover, it was also observed that there was no significant difference in the outcome between the group that received corticosteroids and one that did not [Table/Fig-5].

89% (n=134) of patients in our study were on intra-venous fluids. The early phase of ARDS with septic state is responsible for hypovolemia where early fluid loading will improve prognosis [17]. In a study, conducted by the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network, the investigators compared a conservative and a liberal strategy of fluid management. They found that the conservative strategy improved lung function and reduced the number of days on mechanical ventilation without increasing non-respiratory organ failures. The use of conservative strategy of fluid management in patients with acute lung injury was supported by these results [18]. Some studies associate positive fluid balance with development of ARDS. In an observational cohort study from 198 European ICUs reported that patients who subsequently developed ARDS received more fluids during the first four days of their ICU stay compared to patients who did not develop ARDS [19]. Thus, minimal positive fluid balance can be targeted in these patients. In our study though majority of the patients received intravenous fluids but only a very small percentage received fluids at a rate of more than 100ml per hour. The mean duration of intravenous fluid use was approximately only half that of the mean duration of ICU stay. Investigators have also recommend conservative strategy for patients with acute lung injury (ALI)/ARDS as they found that it improved lung function and shortened the duration of mechanical ventilation and ICU stay without increasing non-pulmonary organ failures or increasing the risk of death [20]. Liberal and conservative fluid strategies are therefore complementary and should ideally follow each other in time in the same patient whose hemodynamic state progressively stabilizes [21].

As for other infections, in these patients as well the choice of antimicrobial treatment is much easier when the specific aetiological agent is identified by a reliable diagnostic technique like pulmonary specimens obtained, for direct examination and cultures, from patients [22]. Also, the range of bacteria and their susceptibility patterns vary widely among hospitals and different countries, selection of initial antimicrobial therapy thus depends on the prevalent pattern of microbes and antimicrobial resistance.

Outcome	Subjects on corticosteroids (n=62)		Subjects on diuretics (n=59)		Subjects on intravenous fluids (n=134)	
	Mean duration of ICU stay (days)	Mean duration of corticosteroid usage (days)	Mean duration of ICU stay (days)	Mean duration of diuretic usage (days)	Mean duration of ICU stay (days)	Mean duration of intravenous fluids usage (days)
Recovered	11.97 ± 4.575	5.59 ± 2.030	11.07 ± 4.287	2.67±1.922	11.73±4.552	5.33±3.105
Died	7.44 ± 5.820	3.63± 2.097	7.45 ± 5.732	3.00±2.295	7.43±5.676	3.87±2.298
Discharge against medical advice	10 ± 4.583	4.00±1.732	6	1.00	13.00±7.234	8.43±5.563
All	9.90 ± 5.539	4.66± 2.239	9.08 ± 5.354	2.81±2.113	9.84±5.656	4.83±3.118

[Table/Fig-7]: Mean duration of ICU stay and mean duration of corticosteroid, diuretic and intravenous fluid use in relation with outcome

Antimicrobials were prescribed in all the patients, as majority of the cases of ARDS were secondary to an infectious aetiology. The beta lactam antibiotics were the most commonly prescribed antimicrobials followed by doxycycline. Almost 30% of cases were secondary to scrub typhus or leptospirosis. This high percentage of tropical diseases in our set up explains the use of doxycycline in 56.7% of the cases. A study showed that of 381 antibiotic treatments, 198 (52%) were empirical, 66 (17%) were based on microbiological identification and 117 (31%) were based on antibiotic susceptibility [23]. In our study microbiological culture was positive in 28.6% cases and rest 71.3% were on empirical therapy.

Secondary analysis of multicenter randomized control trial from ARDS and ALI which collected data regarding antibiotic use in ALI found that antibiotics were administered in 99% of patients. Of these cephalosporins were used in 39.5%, fluoroquinolones in 38% and macrolides were used in 20% [24].

Neuromuscular blockers agents (NMBA) in ARDS facilitate mechanical ventilation and control patient/ventilator asynchrony [25]. In comparison with placebo or no intervention, systematic review and meta-analysis of RCTs examining the effect of using NMBA (cisatracurium) resulted in a significant reduction in risk of death at 28 days and at ICU and hospital discharge [26]. Improvements in mortality and gas exchange by NMBs could be related to a decrease in ventilator induced lung injury, as suggested by the decreased incidence of barotrauma and pneumothoraces in the cisatracurium group [27], One of the main complications of corticosteroid treatmentis ICU acquired weakness [28], which is responsible for difficulty in weaning from ventilator. The risks associated with the use of NMBAs can be limited by shortening the duration of administration to the first 48 hours of ARDS. Some authors are of the opinion that administration of NMBAs for 48 hours in patients with early and severe ARDS is beneficial and can be included in future recommendations [29]. In addition to the above drugs, cell-based therapy with mesenchymal stem cells [30], statin therapy [31], anti-inflammatory drugs, such as aspirin [32] are being tried and are in various phases of development.

CONCLUSION

Infection was the most common aetiology of ARDS and beta lactams were the commonest antibiotics prescribed. A significant number of patients received corticosteroids and diuretics. Intravenous fluids were received by most of the patients. The outcome of patients on different pharmacological intervention did not vary. Though there are many pharmacological interventions in ARDS, but none of them seem to be effective and improving the disease outcome.

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