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Original Research Article

Outcome of hypoxic COVID-19 patients treated with dexamethasone-based treatment protocol in a designated COVID center

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ABSTRACT

Background: Managing severe COVID-19 is a difficult situation in resource limited settings. With the inclusion of steroid based treatment guidelines, this can be made feasible in such settings.
Methods: This was a hospital record based retrospective cohort study done at a designated COVID hospital. Data of all patients who were 18 years and above, hypoxic and required initiation of dexamethasone-based protocol were analysed. Hypoxia was defined as a finger pulse oximeter value less than 95%. The primary outcome was the percentage of patients who required a referral to the higher centre or died in hospital.
Results: 109 patients with hypoxia with a mean age of 55.2±13.5 years and a median symptom duration of 4 days were analyzed. Seventy-eight (71%) patients were male and 81 (74.3%) had other comorbid illnesses. Of the 109 patients, 5 (4.6%) patients died in hospital, 22 (20.2%) patients were referred to higher center for further management and 82 (75.2%) patients could be treated and discharged. Those who were referred or died had lower SpO_2, reduced time to initiation of protocol, more severe pneumonia, lower absolute lymphocyte count and lower platelet count. New onset diabetes was detected in 20 (18.3%) patients.
Conclusions: Detection of hypoxia early and initiation of dexamethasone-based treatment protocol with timely referral of worsening patients can help to improve outcome in COVID-19 patients. This model can be effectively constructed in limited resource settings and can be of much help to the struggling health infrastructure.

Keywords: COVID-19, Dexamethasone, Hydroxychloroquine, Hypoxia, Pneumonia

INTRODUCTION

Since its onset in December 2019, COVID-19 has ravaged across the countries breaking down many economies, health care infrastructure and millions of human lives. The health infrastructure in least developed countries and developing countries are finding it hard to cope-up with the rising number of COVID-19 patients. There is a huge shortage of hospital beds in these countries.[1] To keep up the pace with rising patient load, the governments across are relying on temporary infrastructures. This was the case with state of Kerala, India. With the number of patients raising, the existing healthcare facilities became inadequate in our state. Designated COVID hospitals were set up to cater these patients. First line and second line treatment centers were set up to support these COVID hospitals.[2] Patients who were mildly symptomatic without any comorbidities were monitored in the treatment centers and category C symptomatic patients were shifted to these designated COVID centers. Patients who have multiorgan failures were identified early and referred to tertiary care

hospitals. The course of COVID-19 is characterized by viremia and dysregulated immune reaction. Specific treatment options are limited at present. The evidences for effectiveness of antiviral therapy are inconclusive.[3-5]

Dexamethasone was shown to have a mortality benefit in RECOVERY trial.[6] Its benefit was also supported by CoDEX trial.[7] The meta-analysis by REACT working group has shown the efficacy of glucocorticoids with no severe adverse events.[8] Based on these encouraging results, most of the guidelines incorporated dexamethasone for hypoxic COVID-19 patients.[9-12] A short course of steroid therapy is easily accessible, the adverse events can easily be monitored, and the administration requires only basic infrastructure. For developing economies, where other treatment options were inaccessible due to financial constraints and lack of proper laboratory backup, this is a feasible treatment option. In the COVID centers set up in our state, this was very feasible. Asymptomatic and mildly symptomatic patients were monitored closely in first and second-line treatment centers as well as at home. On detection of hypoxia, they were shifted to the COVID centers and a steroid based protocol was initiated that had dexamethasone and prophylactic anticoagulation. In this study we analyzed the outcome of these patients whom such a protocol was initiated in our COVID center.

METHODS

Study design, setting and participants

This was a hospital record based retrospective cohort study done at a designated COVID hospital in North Kerala, India. Data of all patients who were 18 years and above, hypoxic and required initiation of dexamethasone-based protocol, admitted from 1st July 2020 to 15th October 2020 was analysed for the study. The patients were diagnosed at screening centres by RT-PCR (SARS-CoV-2 RT-PCR Kit, Altona diagnostics, Germany) from oropharyngeal swabs. Asymptomatic and mildly symptomatic patients were monitored closely in first and second-line treatment centers as well as at home. On detection of hypoxia, they were shifted to the index hospital which is a third line COVID care hospital and have basic infrastructure, lab investigations that included hemogram, renal function test, blood sugar testing and a non-portable roentgenogram.

A high dependency unit was set up with provision for continuous central oxygen supply and hypoxic patients were monitored using fingertip pulse oximetry. Out of the healthcare workers 10% had critical care training, but all were given basic training to manage COVID-19 that included infection control practices. All patients who required any mode of mechanical ventilation or with organ dysfunction other than hypoxia were referred to the tertiary care hospital which was located at a 2 hour distance. An ambulance equipped with a portable ventilator and an emergency medical technician was kept ready round the clock. The hospital followed the treatment guidelines as issued by the Government of Kerala with modifications adjusting to the available infrastructure.

Definitions and treatment protocol

Hypoxia was defined as a finger pulse oximeter value less than 95%. The symptom based categories and severity of pneumonia were defined according to the Government of Kerala guidelines.[13] As per the treatment protocol, Dexamethasone 6 mg was given once daily if SpO_2 was 90-95% and twice daily if SpO_2 was less than 90%. Dexamethasone was given for 7 days and was extended to 10 days if the hypoxia persisted. Supplemental oxygen was given if SpO_2 was less than 95 to maintain SpO_2 of 92-95%. Low molecular weight heparin was given to all patients at a dose of 0.4 ml once daily throughout the stay. A third generation cephalosporin along with azithromycin was given to all patients with severe pneumonia and on a case to case basis in others. Hydroxychloroquine was given to few patients at the beginning and later withheld in view of lack of evidence.[12]

Data collection and analysis

Details regarding age, clinical history, treatment history, duration of hospital stay, lab parameters and outcome at the end of hospital stay were collected from case records on a predesigned proforma. The primary outcome was the percentage of patients who required a referral to the higher centre or died in hospital. Data was analysed using SPSS software 22. Categorical variables were expressed using frequencies and continuous variables were expressed as median and interquartile ranges or mean and Standard deviation.

Bivariate analysis was done to find out factors related to primary outcome. Chi-square test was used to assess association between categorical variables and outcome. Binary logistic regression was performed using the factors found to be significant in the bivariate analysis. A p value of <0.05 was taken as significant level for all calculations. The study was conducted in accordance with the ethical standards of the committee on human experimentation by ICMR and with the Helsinki Declaration of 1975, as revised in 2000 norms of declaration of Helsinki. Ethical clearance for the study was obtained from Institutional Ethical Committee, GMC Kannur (IEC No.102/2019/GMCK dated 17.09.20). A waver for taking patient consent was allowed as the study involved anonymous retrospective data analysis.

RESULTS

During the study period 109 patients with hypoxia were admitted in the center. The mean age was 55.2±13.5 years with a median symptom duration of 4 days. Seventy-eight (71%) patients were male and 81 (74.3%) had any other

comorbid illnesses. The baseline characteristics are given in Tables 1 and 2. Of the 109 patients, 5 (4.6%) patients died in hospital, 22 (20.2%) patients were referred to higher center for further management and 82 (75.2%) patients could be treated and discharged. On univariate analysis, lowest recorded SpO_2, time to protocol initiation, severity of pneumonia, median absolute lymphocyte count and median platelet count were significantly different among those discharged and those who were referred or died (Table 2). Those who were referred or died had lower SpO_2, reduced time to initiation of protocol, more severe pneumonia, lower absolute lymphocyte count and lower platelet count.

Table 1: Baseline characteristics.

Variables	Total (n=109)	Discharged (n=82)	Referred or died (n=27)	P value
	N (%)	N (%)	N (%)	
Age (in years)	55.2 (13.5)	54.3 (13.1)	58.2 (14.4)	0.19
Male:female	78:31	56:26	22:5	0.2
Median duration of symptoms (IQR) in days	4 (2-7)	4 (3-7)	3 (1-7)	0.12
Lowest SpO_2	91 (87-92)	91.0 (88.7-92)	86 (80-90)	0.001
Time to Protocol initiation from diagnosis in days (IQR)	2.5 (1-4)	3 (2-5)	1.0 (0.1-3.2)	0.005
Severe pneumonia*	46 (42.2)	27 (32.9)	19 (70.3)	0.001
Ever smoker	12 (11)	10 (13.8)	2 (9.5)	0.72
Duration of stay	12 (11-14)	13 (11-14)	5 (2-9)	0.001
Fever	88 (80.7)	68 (85)	20 (74.0)	0.20
Breathlessness	83 (76.1)	59 (72.8)	24 (88.8)	0.12
Cough	75 (68.8)	53 (65.4)	22 (81.4)	0.15
Extreme tiredness	37 (33.9)	28 (37.8)	9 (40.9)	0.80
Any comorbidity	81 (74.3)	61 (74.4)	20 (74.0)	0.99
HTN	41 (37.6)	29 (35.4)	12 (44.4)	0.49
Diabetes mellitus	63 (57.8)	46 (56.1)	17 (62.9)	0.65
Cardio vascular disease	28 (25.7)	18 (21.9)	10 (37.0)	0.13

*$SpO_2 \leq 90$.

Table 2: Baseline biochemical investigations.

Variables	Total (n=109)	Discharged (n=82)	Referred or died (n=27)	P value
	N (%)	N (%)	N (%)	
Mean haemoglobin (SD)	12.5 (1.8)	12.6 (1.8)	12.4 (1.9)	0.73
Median total leucocyte count/mm^3	6600 (5100-9800)	6700 (5100-9725)	6500 (4600-12000)	0.76
Median absolute lymphocyte count/mm^3	1100 (794-1442)	1117 (825-1507)	975 (624-1174)	0.04
Median absolute neutrophil count/mm^3	5003 (3430-8010)	4986 (3451-7835)	6058 (3307-10472)	0.51
Median platelet count*10^3/mm^3	203.0 (148.5-256.0)	210.5 (160.7-272.2)	163.0 (119.0-235.0)	0.02
Median ESR (mm in first hour)	56 (30-93.7)	54.5 (25.8-95)	59.5 (43-91.3)	0.49
Serum Creatinine (mg/dl)	1.0 (0.8-1.1)	0.95 (0.8-1.1)	1.0 (0.9-1.3)	0.34

Table 3: Treatment received during hospital.

Variables	Total (n=109)	Discharged (n=82)	Referred or died (n=27)	P value
	N (%)	N (%)	N (%)	
HCQ use	31 (28.4)	23 (28.0)	8 (29.6)	0.80
Antibiotic use	103 (94.5)	78 (95)	25 (92.5)	0.64
ACEI use	11 (10.1)	8 (9.7)	3 (11.1)	0.99
New onset diabetes	20 (18.3)	16 (19.5)	4 (14.8)	0.99
Insulin requirement	64 (58.7)	48 (58.5)	16 (59.2)	0.21

Table 4: Binary logistic regression of factors in patients who were referred/died.

Variables	Adjusted OR (95% Confidence interval)	P value
Lowest SpO_2 at room air	1.34 (1.04-1.73)	0.02
Time to initiation of dexamethasone therapy from diagnosis	1.02 (0.82-1.290	0.82
Absolute lymphocyte count	1.0 (1.00-1.002)	0.16
Platelet count	1.0 (1.00-1.00)	0.06

Nagelkerke R square = 0.348.

Table 5: Characteristics of patients who died in hospital.

Characteristics	Died (n=5)	Discharged (n=82)	P value
	N (%)	N (%)	
Mean age in years (SD)	75.2 (11.3)	54.3 (13.1)	0.002
Mean hemoglobin in gram/dl (SD)	11.6 (3.2)	12.6 (1.8)	0.2
Median total leucocyte count/mm^3	14500 (8050-17350)	6700 (5100-9725)	0.02
Median Absolute lymphocyte count/mm^3	474.8 (301-1615)	1117 (825-1507)	0.09
Median Absolute neutrophil count/mm^3	13557 (7578-15198)	4986 (3451-7835)	0.01
Median platelet count*10^3/mm^3	116.0 (73.5-137.7)	210.0 (160.7-272.2)	0.003
Lowest SPO_2	80 (75-84)	91.0 (88.7-92)	0.001
Time to protocol initiation from diagnosis in days (IQR)	1 (1-1)	3 (2-5)	0.001
Duration of stay	5 (3-9.5)	13 (11-14)	0.01
Duration of symptoms	1 (1-2)	4 (3-7)	0.001

On binary logistic regression analysis, lowest SpO_2 was significantly lower among the referred/died (Table 4). Five patients died in hospital. All of them had severe pneumonia at admission and at least one non-pulmonary co-morbid illness with diabetes in four. Compared to those who were discharged, their mean age, median TLC and median ANC were higher, while median platelet count and median lowest SpO_2 were low. They had rapid progression of disease with shorter duration of symptoms and required early initiation of dexamethasone (Table 5). New onset diabetes was detected in 20 (18.3%) patients and 64 (58.7) patients required insulin use to control blood sugars.

DISCUSSION

With a dexamethasone-based protocol, 75% of the hypoxic patients could be treated and discharged in our setting. The efficacy of dexamethasone-based protocol has been already established and our results are corroborating with these.[6,7,10] Those patients who died in hospital or referred to higher centers had severe hypoxia at admission and significant hematological involvement. Lymphopenia and low oxygen saturation were previously shown to be risk factors for poor outcome in severe COVID-19.[14,15] The patients who were referred also had rapid progression of the disease as evidenced by a shorter time to initiation of protocol. This suggests that those patients who have rapid progression and have severe hypoxia should be closely watched and referred early. Few previous cohorts have suggested older age and presence of comorbidities as risk factors for severe disease but age and presence of comorbidities did not affect the referral decision in our study.[16-18] This may be probably due to that our patients had severe disease at inclusion itself and comorbidities might have predisposed to severe hypoxia, which was the most important factor that decided referral.

The patients who died were more aged and had multiple co-morbid conditions. This is in accordance with the mortality data from the state. The case fatality rate among lab confirmed cases was 0.34 as on 2nd December 2020 and most of them were aged above 60 years and had multiple other comorbid illnesses.[19] The patients admitted with us were older, had other comorbid illnesses and severe pneumonia at admission suggesting that these patients were at high risk for mortality at admission. Rather than a case to case based decisions on referral, an institution-based referral policy taking these characteristics of admitted patients needs to be prepared. Such referral protocols may help in reducing mortality, streamlining the care and help the health care workers in such centers to function at their best.

The evidences for effectiveness of antiviral therapies are inconclusive with the enormous cost attached, they were considered on an experimental basis in the state.[3-5] Their administration and monitoring required more infrastructure and was available only in referral center. Since three fourth of hypoxic patients could be discharged without the use of such experimental

therapies, it seems that with close watch for hypoxia and a steroid based protocol much of these patients can be managed in resource limited settings. One major issue with such designated COVID centers is the difficulty in getting multidisciplinary help and allied infrastructure. This can create issues if unforeseen complications especially adverse drug events occur. The common adverse event observed with the treatment was new onset dysglycemia. This is a known side effect of dexamethasone. This can be detected early by regular blood sugar monitoring which is a bedside investigation and can be managed in this setting. Other adverse events like dyselectrolemia, gastritis and steroid induced psychosis can also be effectively managed in such a setting.

Limitations

The study has few limitations of a retrospective design. Few clinical features were not completely recorded. Detailed records of referred patients were not available for analysis. A referral bias might have occurred as some of the critically ill patients and those with multiple comorbidities were referred directly to the higher centers from the first-line treatment centers.

CONCLUSION

In conclusion, detection of hypoxia early and initiation of dexamethasone-based treatment protocol with timely referral of worsening patients can help to improve outcome in COVID-19 patients. A decision to refer can be made based on patient characteristics and disease progression. This model can be effectively constructed in limited resource settings and can be of much help to the struggling health infrastructure.

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