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Role of Adjunctive Corticosteroids Treatment in HIV Patients with Severe Pneumocystis Pneumonia; Experience from a Tertiary Care Hospital

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ABSTRACT

Background: Pneumocystis Jiroveci Pneumonia (PCP) remains a prevalent opportunistic infection in individuals with human immunodeficiency virus (HIV) infection. It is associated with a mortality rate of 10% to 20% during the initial infection, and this rate significantly escalates when mechanical ventilation is required. Earlier studies have suggested that individuals with HIV/AIDS who have PCP may benefit significantly from the combination of corticosteroid treatment with other antibiotic therapy.

Objective: This study aimed to investigate the potential role of adjunctive corticosteroid therapy in the treatment of patients with Pneumocystis jiroveci pneumonia (PCP) and HIV. The primary goal of our study was to ascertain patient survival until their discharge from the hospital and to understand their experience with respiratory failure.

Methodology: This double-blind, placebo-controlled trial study was conducted at the Department of Medical Unit, Lady Reading Teaching Hospital, Peshawar. The study spanned six months following approval from the hospital's ethical board. The sampling technique employed was non-probability convenience-based sampling. The sample size was determined using Open Epi with a confidence level of 95%, a margin of error of 2%, and a population proportion of 0.916, resulting in an estimated sample size of 86 and in this study a total of 90 study cases were enrolled.

Results: A total of 90 HIV positive cases were enrolled in this study of which 73 (81.2%) were male and 17 (18.8%) were female. The study cases were divided into two groups for study purpose. One group treated with corticosteroids and the other one is placebo groups. All patients enrolled in this study also screened for baseline blood investigations and no significant differences was found in these investigations. Among the corticosteroids group, 35 (777.8%) patients survived until hospital discharge, as compared to placebo group where 8 (17.8%) were survived until hospital discharge (CI 0.08 - 0.77: P<0.001).

Conclusions: Early adjunctive corticosteroid therapy represents a pivotal intervention for patients with AIDS suffering from severe Pneumocystis carinii pneumonia. This treatment not only enhances survival rates but also significantly reduces the incidence of respiratory failure.

Keywords: Pneumocystis Jiroveci Pneumonia; HIV: Trials: Corticosteroids; Placebo; Peshawar

Introduction

Since the identification of the first AIDS case in 1981, approximately 20 million deaths have been attributed to the disease. The global number of individuals infected with HIV has been steadily increasing and is currently estimated at 37.9 million.[1] The HIV virus causes a long-lasting infection that weakens the immune system, with some individuals developing severe immunosuppression within 2 to 3 years, while others can remain symptom-free for up to 10 to 15 years. Untreated, symptomatic HIV progresses to AIDS, often accompanied by opportunistic infections (OI) or malignancies.[2] Among immunocom-promised individuals, the lungs are frequently affected, with infections accounting for 75% of cases and neoplastic causes accounting for 25%.[3]

Pulmonary complications in immunocompromised individuals often lead to death unless medical intervention occurs. The differential diagnosis for diffuse pulmonary disease in this population includes opportunistic infections, extension of the underlying disease to the lungs, adverse drug reactions, unrelated diseases like pulmonary oedema or pulmonary emboli, and combinations thereof. Up to one-third of these patients may experience multiple complications, such as pneumonitis caused by different opportunistic organisms or a combination of opportunistic infections and drug-induced pulmonary complications.[4]

Pneumocystis jirovecii pneumonia (PCP) is a severe lung infection that often leads to respiratory failure and death in people with weakened immune systems. Conditions like cancer treated with chemotherapy, autoimmune diseases managed with corticosteroids, and organ or bone marrow transplant recipients are at high risk of getting PCP.[5,6] The mortality rate for PCP in non-HIV patients remains high, despite effective drugs available. In HIV-positive patients, corticosteroids treatment alongside other medications have shown to decrease PCP mortality. However, it's not clear if this approach works as well in non-HIV patients due to differences in the disease's nature. Some studies have explored using additional therapies to lower PCP mortality in non-HIV patients, but the results are conflicting and not well-established.[7]

The corticosteroids therapy is recommended in the treatment of Pneumocystis Pneumonia patient who desaturate. We have no local studies on it. We have good bulk of patient of pneumocystis pneumonia, so this study planned to conduct.

Objective

The primary objective of this study was to investigate the potential role of adjunctive corticosteroid treatment in HIV patients suffering from severe Pneumocystis pneumonia (PCP). Specifically, we aimed to assess whether corticosteroids could offer supplementary benefits in the management of severe PCP cases among individuals living with HIV.

Methodology

This double-blind, placebo-controlled trial was conducted at the Department of Medical Unit, Lady Reading Teaching Hospital, Peshawar. The study spanned six months following approval from the hospital's ethical board. The sampling technique employed was non-probability convenience-based sampling. The sample size was determined using OpenEpi with a confidence level of 95%, a margin of error of 2%, and a population proportion of 0.916,[8] resulting in an estimated sample size of 86.

Specific inclusion and exclusion criteria were applied for participant selection. Inclusion criteria encompassed individuals diagnosed with both HIV infection and PCP, who were adults aged 18 years and above, with documented medical records verifying their HIV status. Additionally, participants should not have any contraindications or known allergies to corticosteroid medications. Exclusion criteria excluded individuals with incomplete medical records, insufficient data on HIV status, those under 18 (i.e., children and adolescents), and patients with a history of Pneumocystis pneumonia unrelated to HIV. Pregnant women with HIV were also excluded due to potential confounding factors related to pregnancy-related changes.

Data were collected using a specifically designed proforma for the study, which included brief demographics such as age, gender, duration of HIV, and detailed questions regarding the role of adjunctive corticosteroid treatment in HIV. This proforma was annexed with the study proposal. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 25.0. Categorical variables were presented as frequencies and percentages, while numerical variables were presented as Mean ± SD.

Oral informed consent was obtained from study participants, and the study was conducted after receiving approval from the Institutional Review Board (IRB) at LRH. The confidentiality of the data was strictly maintained, and permission from the head of the department was obtained prior to data collection. Data were stored on a password-protected computer.

The study focused on individuals initially diagnosed with severe Pneumocystis carinii pneumonia (PCP) with HIV/AIDS who had received less than 72 hours of antibiotic treatment. Severe PCP was characterized by specific criteria, which included a resting respiratory rate exceeding 30 breaths per minute, an alveolar-arterial

oxygen difference greater than 30 mm Hg while breathing room air, and an arterial partial pressure of oxygen below 75 mm Hg when using a 35 percent oxygen face mask. However, this level improved to above 60 mm Hg when using a 100 percent oxygen face mask. Trimethoprim-sulfamethoxazole was administered for a duration of 21 days at a dosage of 15 mg of the trimethoprim component per kilogram of body weight per day.

The present study was planned as clinical trial, for which the study cases were divided into two groups, i.e., PB and CT groups. For this, all cases were randomly selected for each group and each group received their respective treatment.

A special situation occurred in few cases where some patients experienced relapse after seven days of treatment. For such cases according to standard guidelines, 2nd course administered with same drugs. After this therapy, all patients were offered prophylactic treatment for PCP, in addition to anti-HIV treatment.

Results

A total of 90 patients were enrolled in this study, of whom 78 were men and 12 were women. The study cases were divided into two groups for study purpose. One group treated with corticosteroids (CT group) and the other one is placebo groups (PB group). Mean age for PB group was 42.68 with SD ±44.9, where mean age for CT group was 43.65 ±42.8. In this study we also tried to know the possible route for HIV infection and the results showed that the main possible reason for acquiring HIV infection was sexual contact, 33% percent through intravenous drug use, and 4% might be due to infected blood. Baseline demographic characteristics of study cases had no research bias.

For the purpose of our study, we ensured that both groups consisted of an equal number of patients, with 45 individuals in each group. All patients in both groups received identical treatment as part of their routine care, and there were no significant differences observed between the groups in terms of any pretreatment characteristics.

Our primary focus was to investigate the ultimate patient outcomes, specifically their survival until hospital discharge. Therefore, factors such as individual CD4-cell counts, levels of lactate dehydrogenase, and initial findings on chest radiographs did not exhibit any significant correlation with the final clinical outcomes.

The mean weight for PB group was 40.78±9.2 and that for CT group was 40.93±8.9. The duration of symptoms also varied between the two groups. In the CT group, the average duration of symptoms was 3.7±1.9 weeks, while in the PB group, it was 2.9±1.4 weeks. This study also showed that patients in both groups also used antibiotics before enroll into this study for different days and in PB, patients used antibiotics for 1.2±0.9 days where in CT group these days were 1.7 (0-5) (Table 1).

All enrolled patients underwent baseline blood investigations at the time of admission, and these assessments were regularly conducted throughout the study period. In the PB group, patients had an average hemoglobin (Hb) level of 11.3 g/dl, while in the CT group, it was slightly higher at 11.9 g/dl. The mean corpuscular volume (MCV) was notably higher in the CT group, measuring 103.9 fl, as compared to the patients in the PB group. Platelet counts were higher in the PB group and lower in the CT group. White blood cell counts were similar in both groups, whereas CD4 counts were higher in the PB group. C-reactive protein (CRP) levels were higher in the PB group compared to the CT group. On the other hand, lactate dehydrogenase (LDH) levels were higher in the CT group, reaching 973 U/l. Alanine aminotransferase (ALT) levels were also higher in the PB group at 61 U/l, and total protein levels were elevated at 71 g/l in the PB group. Similarly, albumin and globulin levels were higher among

Table 1. Clinical characteristics of the study cases (N=90)

Characteristics	Placebo Group	Corticosteroids Group
Mean age in months (SD)	42.68 (44.9)	43.65 (42.8)
Gender (N (%))		
Male	35 (77.8)	38 (84.5)
Female	10 (22.3)	07 (15.6)
Weight (kg) (mean (SD)	40.78 (9.2)	40.93 (8.9)
Respiratory rate (bpm) (mean (SD)	77(14.0)	74 (13.0)
Peripheral oxygen saturation in room air (%) (mean (SD)	71 (14.9)	75 (13.9)
Use of Antibiotics before enrolment (Days)	1.2±0.9 (0-4)	1.5-1.7 (0-5)

Table 2. Investigations at baseline among study cases (mean (SD))

Investigation	Placebo Group	Corticosteroids Group
Haemoglobin (g/dl)	11.3 (1.9)	11.9 (2.1)
MCV (fl)	84.8 (6.9)	103.7 (11.9)
Platelets (×109 /l)	342 (152)	328 (147)
White cell count(×109 /l)	16.6 (7.6)	16.9 (10.5)
CD4 count (×106 /l)	991 (847.1)	969 (873)
CRP (mg/l)	27 (85.9)	17.4 (31.7)
LDH (U/l)	894 (501)	973 (902)
AST (U/l)	88 (59)	79.8 (47)
ALT (U/l)	61 (49)	53 (61)
Total protein (g/l)	71 (12.7)	59 (17.1)
Albumin (g/l)	31 (5.09)	29 (3.9)
Globulin (g/l)	41 (12.1)	39 (11.9)
Blood culture no growth (N (%))	37 (59%)	39 (61%)
PCP IF positive (N (%))	5 (11.2%)	7 (15.6%)
PCP PCR sputum positive (N (%))	6 (13.4%)	4 (8.9%)
CXR findings		
Hyperinflation (N (%))	17 (37.8%)	11 (24.5%)
Infiltrate present (N (%))	39 (86.7%)	41 (91.1%)
Interstitial infiltrate (N (%))	37 (82.3%)	39 (86.7 %)
Acinar infiltrate (N (%))	13 (28.9 %)	17 (37.8%)

Table 3. Outcome of study cases

End Point	Placebo Group	Corticosteroids Group	95% CI	p-value
Survival to discharge	8 (17.8%)	35 (77.8%)	0.08- 0.77	<0.005
Respiratory Failure	39 (86.7%)	10 (22.3%)	0.11- 0.24	<0.005
Complition of Antibiotics therapy	14 (31.2%)	40 (88.9%)	0.05- 0.64	<0.005

patients in the PB group. Furthermore, different chest X-ray (CXR) findings were observed in patients of both groups (Table 2).

All of the patients received treatment with trimethoprimsulfamethoxazole, and none of them needed an alternative treatment like pentamidine due to drug-related side effects. Out of total of 43 (47.8%) survived to hospital discharge, including 35 (77.8%) in the CT group and 8 (17.8%) in the PB group and significant positive association was found among the two groups at this end point (CI 95% 0.08 – 9.77: P<0.005) (Table 3).

Out of total, 49 (54.5%) experienced respiratory failure, and here 39 (86.7%) were form PB group and 10 (22.3%) from CT group and here also strong significant association was found among the two groups at this study end point (CI 95% 0.111 – 0.24: P<0.008). Antibiotics were also

used by these patients for different duration. A total of 54 (60.0%) patients were used antibiotics and completed their treatment which consists of 40 (88.9%) of CT group and 14 (31.2%) of PB group patients (Table 3).

The average duration of hospitalization for all patients in the study was 21 days, with a range spanning from 2 to 71 days. Specifically, patients in the PB group had a mean hospital stay of 17 days, whereas those in the CT group stayed for an average of 23 days. It's noteworthy that this difference did not reach statistical significance ($P<0.21$).

When looking at time spent in the intensive care unit (ICU), patients in the PB group spent an average of 7.1 days in the ICU, while those in the CT group had a shorter average stay of 2.1 days. This disparity in ICU duration was statistically significant ($P<0.005$).

It is noteworthy that all patients who survived until their discharge from the hospital showed evident clinical and radiological improvement within a span of 23 days. Furthermore, their arterial blood gas measurements demonstrated improvement, with 69 percent of these survivors attaining normal arterial partial pressures of oxygen while breathing room air by the 19th day.

Discussion

This study provides compelling evidence that the inclusion of corticosteroid therapy as an adjunctive treatment can effectively prevent respiratory failure and enhance survival rates when administered promptly to individuals with severe Pneumocystis carinii pneumonia (PCP). The findings underscore the significant role that corticosteroids can play in the management of AIDS patients, potentially leading to remarkable improvements in their outcomes. It's important to note that our study focused on a specific subset of patients who were at a critical juncture, where the onset of respiratory failure was imminent but had not yet occurred. These patients had received antibiotic treatment for less than 72 hours. The introduction of adjunctive intravenous methylprednisolone contributed to increased survival rates, primarily by reducing the occurrence of respiratory failure.

Prior studies with a similar objective have explored the potential benefits of adjunctive corticosteroid therapy, reporting varying survival rates ranging from 0 to 65 percent.[9-12] It's important to note that the study designs of these previous investigations differ from the current study.

In contrast, a study led by Montaner et al. conducted similar designed study with the same objective of the use of corticosteroids in the treatment of PCP.[13] Notably, the patients in their study had less severe pulmonary disease compared to those included in our current study. Furthermore, due to the crossover design of their study, it was not feasible to assess the impact of corticosteroids on respiratory failure or survival in their patient cohort.

Corticosteroids, however, exhibited an association with reduced early respiratory deterioration during antibiotic therapy in patients with moderately severe disease. These findings align with the results obtained in our study.

It's worth noting that several studies involving non-AIDS patients have demonstrated no discernible effect of corticosteroid therapy in individuals with adult respiratory distress syndrome (ARDS). To address this, our study focused on a patient population that had not yet developed ARDS. We intentionally excluded patients with mild Pneumocystis carinii pneumonia (PCP), as they typically experience favorable survival outcomes without the need for corticosteroid intervention. Additionally, we imposed a 72-hour limit on the duration of antibiotic treatment for entry into the study for practical reasons and to ensure a consistent study population. The terminology "early" in reference to adjunctive corticosteroid treatment remains somewhat ambiguous in our study, as it could pertain to the duration of antibiotic therapy or simply denote the period before the onset of ARDS.

The clinical progress noted in our patients was marked by substantial enhancements in temperature, dyspnea assessments, and arterial blood gas readings. These improvements exhibited significant distinctions between the two groups receiving different treatments during the initial week of therapy.

Among the study cases, when corticosteroid treatment was stop, 25% of the study cases achieved relapse treatment outcome. However, according to study protocol when corticosteroid treatment was reintroduced and gradually tapered, all except one of these patients' showed improvement and ultimately had positive outcomes. These findings suggest the potential effectiveness of a tapering schedule, although they do not establish the optimal duration for the tapering process.

Significantly, our research noted rare occurrences of severe adverse effects related to antibiotics, and none of the patients required switching from intravenous pentamidine to trimethoprim-sulfamethoxazole. The usage of corticosteroids may have played a role in mitigating the severity of the most frequently observed adverse effects associated with trimethoprim-sulfamethoxazole. This probably allowed patients to finish their treatment with a single medication, thereby preventing the adverse effects and complications typically associated with pentamidine.

It's important to note that our study utilized an initial dose of trimethoprim-sulfamethoxazole with lower dosage as compared with standard dosage of these drugs but its effectiveness was very high and this also showed by

another study.[9]

One important finding of the current study was that there was no significant difference in the duration of hospital admission between both groups. However, a significant difference was observed in the time spent by patients from both groups in the hospital's ICU, with the PB group experiencing a longer duration compared to the CT group.

Our study underscores the significant advantages of early corticosteroid intervention in AIDS patients with severe Pneumocystis pneumonia (PCP), leading to higher survival rates and reduced levels of respiratory failure. Additionally, this study highlights the effectiveness of this treatment approach, resulting in a decreased need for ICU care among patients.

Based on these findings, we propose early initiation of supplementary corticosteroid therapy for a minimum of seven days in non-ventilated patients with severe Pneumocystis pneumonia (PCP), followed by a gradual reduction in corticosteroid dosage. Although we have not identified the optimal corticosteroid dosage or type, we observed that intravenous administration of 40 mg of methylprednisolone every six hours was highly effective in our patients. Further exploration of corticosteroid mechanisms of action in the lungs of such patients may offer additional insights into which other groups of PCP patients could potentially benefit from adjunct corticosteroid treatment.

Conclusion

In conclusion, early adjunctive corticosteroid therapy represents a pivotal intervention for patients with AIDS suffering from severe Pneumocystis carinii pneumonia. This treatment not only enhances survival rates but also significantly reduces the incidence of respiratory failure. These findings underscore the importance of considering corticosteroid therapy as a vital component of the treatment regimen for such patients.

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