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Nephrology

A STUDY ON PLASMAPHERESIS IN ANCA ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS AND ITS SHORT-TERM OUTCOME IN A TERTIARY CARE CENTER IN NORTH EAST INDIA

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ABSTRACT
Introduction- ANCA associated rapidly progressive glomerulonephritis is a group of disorders characterized by the presence of circulating ANCA antibodies and a rapid loss of kidney function, often accompanied by oliguria or anuria, and by features of glomerulonephritis, including dysmorphic erythrocyturia, erythrocyte cylindruria, and glomerular proteinuria. Plasmapheresis by removing these antibodies may help in treatment of the disorder. **Materials and methods-** All the patients with RPGN presentation with positive ANCA serology and with creatinine of more than 5.7 mg/dl and/ or diffuse alveolar hemorrhage with hypoxemia were included in the study. Patients meeting the criteria were treated with plasmapheresis for a total of 7 sessions over a period of 14 days. The immunosuppressive therapy like steroids, cyclophosphamide and rituximab were continued as per standard protocol. **Results and conclusion-** Of the 19 ANCA positive patients, 13 met criteria for plasmapheresis. However only 7 patients gave consent for plasmapheresis. Of these 7 patients, there were 2 males (28.57%) and 5 females (71.43%). The mean age was 29.86 ± 10.41 years, the mean hemoglobin being 7.17 ± 1.85 g/dl and mean creatinine being 9.77 ± 3.89 mg/dl. All of the patients had undergone renal biopsy with the mean number of glomeruli being 14.28 ± 4.03, the mean percentage of glomeruli with crescents being 70.761 ± 30.90, the mean percentage of cellular, fibrocellular and fibrous crescents being 39.49 ± 37.50, 29.53 ± 27.27, and 30.96 ± 35.30 respectively. The mean IFTA was 15.4 ± 13.02. Of the 7 patients who underwent plasmapheresis, 4 (57.14%) patients were independent of HD at a follow up of 6 months. The were no significant correlation between dialysis independence and baseline creatine (p 0.172) or the percentage of crescents (p 0.931). 2 patients were HD dependent and 1 patient expired as complication of pneumonia with sepsis.

INTRODUCTION:

The term rapidly progressive glomerulonephritis (RPGN) refers to a clinical syndrome characterized by a rapid loss of kidney function, often accompanied by oliguria or anuria, and by features of glomerulonephritis, including dysmorphic erythrocyturia, erythrocyte cylindruria, and glomerular proteinuria.[1] Aggressive glomerulonephritis that causes RPGN usually has extensive crescent formation.[2] Hence crescentic glomerulonephritis is taken as the pathological equivalent to the clinical syndrome of rapidly progressive glomerulonephritis.

Crescentic glomerulonephritis is classified into the following types:[3]
- Type 1 (anti-glomerular basement membrane [GBM] disease)
- Type 2 (immune-complex mediated)
- Type 3 (pauci-immune)
- Type 4 includes combinations of types 1 and 3
- Type 5 is ANCA-negative, pauci-immune renal vasculitis (5% to 10% of cases)

The rationale for the use of plasmapheresis for ANCA associated glomerulonephritis was initially based on the fact that the histopathology of ANCA vasculitis was similar to that of anti GBM disease. In the study by CD Pusey et al[4], it was found that focal necrotizing glomerulonephritis related to systemic vasculitis responds well to immunosuppressive drugs when treatment is started early, and suggest that plasma exchange is of additional benefit in dialysis-dependent cases.

In the Canadian Apheresis Study Group[5], no demonstrable benefit of therapeutic plasma exchange (TPE) in non–dialysis dependent patients was found, however, 3 of 4 dialysis-dependent patients who received TPE were able to come off dialysis compared with only 2 of 7 patients who did not receive TPE.

Jayne et al[6] studied whether the addition of plasma exchange was more effective than intravenous methylprednisolone in the achievement of renal recovery in those who presented with a serum creatinine 5.8 mg/dl. A total of 137 patients with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine 5.8 mg/dl were randomly assigned to receive seven plasma exchanges (n=70) or 3000 mg of intravenous methylprednisolone (n=67). Plasma exchange increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure when compared with intravenous methylprednisolone. Patient survival and severe adverse event rates were similar in both groups.

A meta-analysis by Walters et al[7] had found that plasma exchange as adjunctive therapy significantly reduces the risk of end-stage kidney disease at three months (2 studies: RR 0.43, 95% CI 0.23 to 0.78) and 12 months (6 studies: RR 0.45, 95% CI 0.29 to 0.72).

However, the recently concluded PEXIVAS trial[8] found that among patients with severe ANCA-associated vasculitis, the use of plasma exchange did not reduce the incidence of death or ESKD.

AIMS AND OBJECTIVES:
To study the short-term outcome of patients with ANCA associated rapidly progressive glomerulonephritis who receive plasmapheresis with immunosuppressants.

MATERIALS AND METHODS
STUDY DESIGN- A single center prospective observational study
STUDY AREA: Department of Nephrology, GMCH, Guwahati
STUDY POPULATION: Admitted patients in the department of Nephrology
STUDY PERIOD: February 2022 to January 2023

Inclusion criteria
- Patients with RPGN presentation, with ANCA positivity on serology
- Patients with creatinine of more than 5.7 mg/dl and/ or diffuse alveolar hemorrhage with hypoxemia
- Patients of both sexes
- Patients of all age groups

Exclusion criteria

• Patients not giving consent for plasmapheresis therapy

METHOD
All the patients with RPGN presentation with positive ANCA serology and visiting the Department of Nephrology, GMCH and fulfilling the inclusion criteria were included in the study. Ethical clearance was taken from the institutional ethics board before conducting the study. After taking informed consent, a detailed history was be taken with particular focus on the renal symptoms like duration of illness, swelling of lower limbs or whole body, reduced urine output, cola colored urine, or symptoms which may be associated with an underlying disorder like epistaxis or hemoptysis. The baseline characteristics like age, sex, blood pressure, weight was noted.

The patients were then be evaluated with routine laboratory investigations like complete blood count, random blood sugar, renal function test, electrolytes, serum albumin, lipid profile, and urine routine examination and 24-hour urine protein quantification, ECG, chest X-ray and serological tests like ANCA.

Patients meeting the criteria were treated with plasmapheresis for a total of 7 sessions over a period of 14 days. The immunosuppressive therapy like steroids, cyclophosphamide and rituximab were continued as per standard protocol.

Patients were followed up for 6 months. They were evaluated for disease remission i.e. absence of features of vasculitis and stable or improved GFR, and for dialysis independency in patients who were on dialysis previously.

RESULTS-
A total of 21 pauci immune crescentic glomerulonephritis cases were found during the study period. Of the 21 patients, 4 were male and 17 were female, with females being 80.95 % of the cases. The mean age was 33.61 ± 15.95 years.

Of these 19 were ANCA positive and 13 of these patients met criteria for plasmapheresis. However only 7 patients gave consent for plasmapheresis. All of these patients were on dialysis at study enrollment and none had hemoptysis. Of these 7 patients, there were 2 males (28.57%) and 5 females (71.43 %). The mean age was 29.86 ± 10.41 years, the mean hemoglobin being 7.17 ± 1.85 g/dl and mean creatinine being 9.77 ± 3.89 mg/dl. All of the patients had undergone renal biopsy with the mean number of glomeruli being 14.28 ± 4.03, the mean percentage of glomeruli with crescents being 70.761 ± 30.90, the mean percentage of cellular, fibrocellular and fibrous crescents being 39.49 ± 37.50, 29.53 ± 27.27, and 30.96 ± 35.30 respectively. The mean IFTA was 15.4 ± 13.02.

Of the 7 patients who underwent plasmapheresis, 4 (57.14%) patients were independent of HD at a follow up of 6 months. The were no significant correlation between dialysis independence and baseline creatine (p 0.172) or the percentage of crescents (p 0.931). 2 patients were HD dependent and 1 patient expired as complication of pneumonia with sepsis.

DISCUSSION
This was an observational descriptive study of 7 patients of ANCA vasculitis with severe renal dysfunction who were treated with plasmapheresis. We found that, 4 patients (57.14%) were dialysis independent at the end of the 6 months of follow up.

Jayne et al[1] had found that, renal recovery had occurred in 33 (49%) of 67 of the intravenous methylprednisolone group and 48 (69%) of 70 of the plasma exchange group. Szpirt et al[9] found that of all patients who were on dialysis when recruited were dialysis dependent 5 years later. There was no difference in morbidity or mortality between PE and control groups. Multivariate analysis demonstrated that PE improved renal survival (P<0.01) at initial plasma creatinine levels >250 µmol/L (2.85 mg/dL). Change from CYC to CsA did not influence rate of relapses or time to relapse.

The enthusiasm regarding the role of plasmapheresis was, however, dampened with the results of the large PEXIVAS trial[8] where death or ESKD occurred in 100 of 352 patients (28.4%) in the plasma-exchange group and in 109 of 352 (31.0%) in the control group (hazard ratio with plasma exchange, 0.86; 95% confidence interval [CI], 0.65 to 1.13; P=0.27) thus showing no benefit of plasmapheresis with regard to death or ESKD.

There is a knowledge gap in the role of plasmapheresis in the management of patients of ANCA glomerulonephritis, which will perhaps be clarified in the future with further studies.

Table 1: Baseline characteristics of patients

Baseline characteristics	Total no of patients (n=7)
Age [mean ± SD]	29.86 ± 10.41 years
Male [No. (%)]	2 (28.57)
Female [No. (%)]	5 (71.43)
Hemoglobin [mean ± SD]	7.17 ± 1.85 g/dl
Creatinine [mean ± SD]	9.77 ± 3.89 mg/dl

Table 2: Renal biopsy characteristics

Renal biopsy characteristics	Mean ± SD
No of glomeruli	14.28 ± 4.03
Percentage of total glomeruli with crescents	70.761 ± 30.90
Percentage of cellular crescent (of the total crescent)	39.49 ± 37.50
Percentage of fibrocellular crescent (of the total crescent)	29.53 ± 27.27
Percentage of fibrous crescent (of the total crescent)	30.96 ± 35.30
IFTA	15.4 ± 13.02

Table 3: Outcome of patients

Outcome	Frequency (%)
HD independence	4 (57.14)
HD dependent	2 (28.57)
Mortality	1 (14.29)

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