PLASMAPHERESIS VERSUS INTRAVENOUS IMMUNOGLOBULINS IN GUILLAIN BARRE SYNDROME, THE THERAPEUTIC OUTCOMES

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ABSTRACT

Objective: To compare the therapeutic outcomes of plasmapheresis with intravenous immunoglobulins (IVIG) for Guillain Barre syndrome.

Study Design: Randomized controlled trial.

Place and Duration of Study: Medicine department; PNS Shifa Hospital Karachi from Jan 2011 to Jun 2012.

Patients and Methods: Adult patients admitted to internal medicine department with the diagnosis of Guillain Barre Syndrome (GBS) fulfilling the inclusion and exclusion criteria were included after taking ethical approval and informed consent. They were randomly assigned to plasmapheresis and IVIG treatment groups. Their presenting features, investigations and management plan were followed over 6 months duration. Hughes disability scale for Guillain Barre syndrome was documented and compared at admission, 4 weeks, 12 weeks and 6 months by non-parametric tests via SPSS version 17.

Results: Total 36 patients (31 males & 5 females) were included. Mean age was 37 ± 15 (18-70) years, mean duration of symptoms 11.6 ± 12.7 days. Plasmapheresis and IVIG groups were comparable with respect to age and gender ($p>0.05$). Significant improvement of mean disability score was observed in each group from baseline score ($p<0.0005$). At specified intervals, comparison between the two groups in terms of mean improvement in disability scores showed significant improvement at 4 weeks ($p<0.05$) in IVIG group as compared to plasmapheresis group; however on further observation at 12 weeks and 6 months, mean improvement was comparable between two groups with no significant difference ($p>0.05$). There was no significant difference in need for assisted ventilation between two groups ($p>0.05$). Variants of GBS observed were AIDP (50%), AMAN (31%) and AMSAN (19%).

Conclusion: Our study suggests that both plasmapheresis and intravenous immunoglobulins are useful and effective modes of treatment for Guillain Barre Syndrome. Significant short term improvement was observed in the IVIG group at 4 weeks of treatment; however no significant difference in therapeutic outcome observed between the two groups on further follow up of 6 months. Thus focusing the need of further large scale regional studies to analyze various factors contributing to this short term but significant improvement with IVIG treatment observed in this study.

Keywords: Guillain Barre syndrome, Intravenous immunoglobulins, Plasmapheresis.

INTRODUCTION

Guillain Barre syndrome (GBS) is an acute onset inflammatory demyelinating polyneuropathy, characterized by symmetrical ascending flaccid paralysis and absent reflexes[1]. There may be numbness of the limbs & weakness of facial, deglutition and respiratory muscles. In most of the cases myelin sheaths are involved, but in few cases axons are also involved. Weakness gradually increases to its maximum in 4 weeks[2]. In 25-30% patients assisted ventilation may be required[3]. Almost 2.8% patients die during the early stage of illness[4]. Recovery may take several weeks to months; however fatigue is a common complaint. Despite adequate treatment, 4% of patients remain bed bound and 9% are unable to walk without support after a year of onset of illness[5].

Regarding the clinical course of illness, weakness starts in proximal part of lower limbs that may progresses to upper limbs. However, in 10% cases weakness may start from upper limbs or facial muscles. The Miller-Fisher variant of GBS is its subtype that begins with cranial nerve deficits. Cranial nerve involvement is seen in 45-75% of patients with GBS[6]. Facial muscles are involved in 50% of patients with severe disease, dysphagia in 50%,

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third cranial nerve involvement in 15% and autonomic involvement in 70%. This may include labile blood pressure, arrhythmias, loss of sweating or paralytic ileus[7-8]. Other features are mental state changes like hallucinations, delusions and abnormalities in REM sleep

Plasmapheresis and IVIG in terms of improvement in functional status over six months duration in patients from our region.

PATIENTS AND METHODS

These randomized controlled trials were

Table-1: Comparison between IVIG and plasmaphresis group according to different variables and clinical parameters.

Variables	All patients (n=36)	Plasmaphresis group (n=18)	IVIG group (n=18)	*p*-value
Age (years) mean + SD (range)	37 + 15 (18-70)	37.94 + 15.5 (18-70)	36.7 + 16.6 (18-65)	0.29
Males (%) Females (%)	31 (86%) 5 (14%)	16 (88.9%) 2 (11.1%)	15 (83.3%) 3 (16.7%)	0.63
Duration of symptoms (days)	11.6 + 12.7 (1-60)	12.8 + 11.3 (3-45)	10.4 + 14.3 (1-60)	0.49
Bowel Diarrhea (%) Constipation (%)	6 (16%) 4 (11%)	5 (27.8%) 4 (22.2%)	1 (5.6%) 0 (0%)	0.10
Fever (%)	14 (38.8%)	8 (44.4%)	6 (33.3%)	0.49
RTI (%)	4 (11%)	3 (16.7%)	1 (5%)	0.28
Sensory symptoms (%)	9 (25%)	5 (27.8%)	4 (22.2%)	0.70
Cranial nerve involvement	6 (17%)	1 (5.6%)	5(28%)	0.16
Reflexes Diminished Absent	19 (53%) 17 (47%)	12 (66.7%) 6 (33.3%)	7 (38.9%) 11 (61%)	0.09
EMG / NCS AIDP AMAN AMSAN	18 (50%) 11 (31%) 7 (19%)	9 (50%) 5 (28%) 4 (22%)	9 (50%) 6 (33%) 3 (17%)	0.89
Assisted ventilation	5 (14%)	2 (11.1%)	3 (16.6%)	0.63

$p < 0.05$ is significant

particularly in critically ill patients[9].

GBS has been found to be associated with history of infection (respiratory or gastrointestinal). Various associations and pathogens involved are *Campylobacter Jejuni*, Cytomegalovirus, Human Immunodeficiency virus (HIV), *Mycoplasma pneumonia*, Lyme's disease and rarely lymphoma or connective tissue disorders[10]. Asbury diagnostic criterion is used all over the world for GBS.

GBS being a rare disease with reported incidence of 0.89 to 1.89 cases (median, 1.11) per 100,000 persons per year[1]. There has been limited number of studies conducted in our region in this context. Purpose of this study is to compare the therapeutic outcomes of

conducted at the Internal Medicine Department of Pakistan Navalship (PNS) Shifa Hospital Karachi (January 2011 to June 2012). Adult patients, age > 18 years fulfilling the Asbury diagnostic criteria of GBS[11].

Previously treated and partially treated cases of GBS. Patients having the electrolyte and metabolic derangements suggesting other causes of muscle weakness were also excluded. Approval from ethical committee was obtained and patients admitted with diagnosis of Guillain Barre Syndrome, that fulfilled the inclusion and exclusion criteria were included after taking the informed consent, demographic details including name, age, and gender were obtained. Presenting complaints and detailed

history inquired. Clinical examination was performed including neurological and systemic examination. Laboratory investigations were parameters. All the details were documented on a specially designed performa.

SPSS version 17 was used to analyze the

Table-2: Mean disability Scale at admission and further follow up in Plasmaphresis and IVIG group; demonstrating significant within group improvement in disability scale.

Study Groups	Disability Scale mean ± SD				Within group improvement in mean Disability Scale from admission (by Wilcoxon signed rank test)		
	Admission	4 weeks	12 weeks	6 months	at 4 weeks	at 12 weeks	at 6 months
Plasmapheresis group	3.56+0.76	2.67± 0.75	1.67+0.59	1.06+0.63	0.88 +0.83 *p*<0.005	1.88+0.75 *p*<0.0005	2.50+0.86 *p*<0.0005
IVIG group	3.78+0.87	2.17± 0.62	1.67+0.90	0.83+0.78	1.61+0.60 *p*<0.0005	2.11+0.47 *p*<0.0005	2.95+0.72 *p*<0.0005

p < 0.05 is significant

Table-3: Comparison of mean improvement in Disability Scale between Plasmapheresis and IVIG group.

No of weeks	Disability Scale mean improvement ± SD	*p*-value (by Mann-Whitney U test)	Interpretation- (degree of improvement between two groups)
At 4 weeks IVIG Plasmapheresis	 1.61 ± 0.60 0.88 ± 0.83	*p*<0.05 (0.04)	Significant difference in improvement in IVIG as compared to plasmapheresis group
At 12 weeks IVIG Plasmapheresis	 2.11 ± 0.47 1.88 ± 0.75	*p*>0.05 (0.89)	No significant difference in improvement between two groups
At 6 months IVIG Plasmapheresis	 2.94 ± 0.72 2.50 ± 0.86	*p*>0.05 (0.33)	No significant difference in improvement between two groups

advised accordingly that included complete blood picture, serum electrolytes, urea and creatinine. Lumbar puncture was performed with all the prerequisites and cerebrospinal fluid was examined. Nerve conduction studies were performed and variants of GBS observed documented.

Thirty six patients were randomly assigned to two modes of therapy i.e. plasmapheresis and intravenous immunoglobulins (IVIG) with the help of random number generator. On the basis of clinical evidence and laboratory evaluation, treatment plan was discussed with patients and their families in detail. GBS disability scale by Hughes was calculated at admission, 4 weeks, 12 weeks and 6 months. Patients were followed for the changes in symptoms, clinical signs and biochemical data. Frequencies and percentages were calculated for quantitative variables like age, gender, history of diarrhea, fever, respiratory tract infection and cranial nerve involvement. Mean and standard deviation were calculated for quantitative variables like age, disability score at specified intervals. Wilcoxon-signed rank test was used to compare the mean disability scores at specified intervals to assess the improvement from baseline within each group. Mean improvement in disability score was compared between two groups at each specified interval by Mann-Whitney U test. A *p*-value < 0.05 considered as significant.

RESULTS

Thirty six patients were included. The plasmapheresis and IVIG group contained 18 patients each. Both groups were comparable in

terms of demographic and baseline characteristics. Mean disability score at baseline between group insignificant with *p*-value 0.427. Mean disability score calculated at admission, 4 weeks, 12 weeks and 6 months is shown in the table below. Improvement in the disability scores at specified intervals showed significant improvement in each group from the baseline disability scores ($p<0.0005$) (table-1).

Also at specified intervals the comparison between the two groups in terms of mean improvement in disability scores showed significant difference in improvement at 4 weeks ($p=0.04$) in IVIG group as compared to plasmpheresis group; however on further follow up at 12 weeks and 6 months the mean improvement was comparable between two groups with no significant difference ($p>0.05$) (table- 3).

Assisted ventilation was required in 2 (11.1%) patients in plasmapheresis group as compared to 3 (16.6%) in IVIG group with no significant difference ($p=0.63$). Various variants of GBS found on of EMG and NCS were Acute Inflammatory Demyelinating Polyneuropathy (AIDP) in 18 (50%), Acute Motor Axonal Neuropathy (AMAN) in 11 (31%), Acute Motor Sensory Axonal Neuropathy (AMSAN) in 7 (19%) patients.

DISCUSSION

Along with the supportive care, plasma exchange and IVIG are the mainstay of treatment in GBS. In plasma exchange, blood is taken from one vein, followed by separation of plasma from blood cells, and then replacement with albumin, fresh frozen plasma or other fluids. During plasmapheresis, antibodies are removed from the body at the rate of 200-250 ml /kg body weight. The recommended dose of IVIG is 0.4 gm/kg/day for five consecutive days[12].

While comparing both procedures, each has its own benefits and risks. IVIG is considered to be non-invasive, comparatively safer and easy to administer with minimum delay, though expensive. In contrary, plasmapheresis is difficult to carry out, can't be given to all ages, has risk of cardiovascular instability and transmission of viral and other infections, however comparatively less expensive[14].

We conducted this study to compare therapeutic outcomes of these two different modes of therapy. The male to female ratio observed in our patients was 6:1, hence larger number of male patients as compared to other regional studies that show the male to female ratio of 3:1[14].

Regarding the history and presenting complaints, 27% patients had history of diarrhea as compared to figure of 33% in other South Asian studies. Also the sensory symptoms were seen in 25% patients as compared to 35-64% in regional studies[15]. In our study 16% patients had cranial nerve involvement that is comparable to the figure of 11% in other local studies[16].

We assessed the functional status by using Hughes disability scale. In a study conducted at Military Hospital Rawalpindi by Muhammad et al, London Scale was used for assessment of functional status and patients were followed up to 4 weeks[14]. We preferred following the patients for prolonged duration to compare not only immediate, but also long term effects. Further observation up to 5 years in future regional studies is suggested.

Regarding the need for assisted ventilation, it was required in 33% patients. This figure is in concordance with figure of 30% documented by international studies[3]. Thus indicating same incidence of assisted ventilation requirement in both modes of therapy. The death rate observed in other regional studies was 8%, however none of our patients died during study duration[16].

Various variants of GBS labeled on the basis of NCS and EMG studies showed that most common variant seen was AIDP that comprised almost half of the patients. AMAN was next common followed by AMSAN. However, other local and international studies show prevalence of AIDP (47%), followed by AMSAN (21%) and AMAN (15%)[17,18].

In each group, significant within group improvement in disability scale from admission till six months duration suggests that both

modes of therapy are effective and beneficial. Randomized controlled trials conducted by Hughes et al and Raphael et al also showed similar results[2,19],

While comparing the mean improvement between the two groups at specified intervals, mean disability scale was comparable between two groups at admission. However, at 4 weeks duration there was significant improvement in IVIG as compared to plasmapheresis group. This is contrary to results of a study conducted by Muhammad et al that showed no difference at this duration of treatment[14]. Another study conducted by Yakoob et al on 34 patients at Agha Khan University Hospital Karachi showed no significant difference between two modes of therapy[20]. Though this short term improvement was seen in IVIG group, when we followed the patients up to 6 months duration, this difference disappeared and both the groups had comparable improvement. The international studies conducted on smaller sample size show no difference in the treatment outcomes. However, several studies conducted on larger sample size show earlier recovery with IVIG as compared to plasmapheresis[21].

One of the limitations of this study is comparatively smaller sample size. The reason being very low incidence of Guillan Barre Syndrome (reported to be 0.89 to 1.89 per 100,000 persons per year), with fewer patients available over a specified time duration of 18 months that includes a follow up of 6 months[1]. Also, we haven't exposed our patients to combination therapy of plasmapheresis and IVIG, and that should be considered in future studies.

There is limited number of studies available from Pakistan regarding the therapeutic outcomes of Guillain Barre Syndrome. Hence, this study adds to current available literature from our region. Also, other local studies have followed patients up to 3 months, while we followed our patients for comparatively longer duration of 6 months. In view of these, we recommend a multicentre trial with longer duration follow up to achieve a larger sample size and prolonged follow up duration for future regional studies.

CONCLUSION

Both IVIG and plasmapheresis are equally effective for the treatment of Guillain Barre Syndrome. The therapeutic outcome in terms of need for ventilator assistance, functional improvement and mortality is similar between two groups. However, IVIG therapy has better short term improvement in terms of functional status.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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