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Research Article

Comparison of efficacy and outcome of intravenous immunoglobulin therapy versus plasmapheresis in patients with Gullian Barre syndrome

Archana Sonawale*, Chetan Kalal

Department of Medicine, Seth G.S. Medical College and KEM Hospital, Parel, Mumbai, India

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***Correspondence:**
Dr. Archana Sonawale,
E-mail: sanjayarchana@hotmail.com

ABSTRACT

Background: Acute inflammatory demyelinating polyneuropathy (AIDP) often described as Guillain-Barre syndrome (GBS) is an ascending neuropathy involving demyelination of peripheral nerves. Very few studies on GBS have been conducted in Indian scenario in recent years. Taking into account this background, we undertook this study to have better outlook to the spectrum of disease and outcome. The objective was to study the patient's clinical profile, outcome of the disease and response to plasmapheresis (PP) versus intravenous immunoglobulin (IVIG) therapy in a case of GBS.
Methods: This was a prospective observational study. In this study 34 consecutive patients who fulfilled the inclusion and exclusion criteria and who gave a written informed consent were recruited over a period of 2 years. A detailed history and physical examination was carried out in every patient. History of preceding illnesses and clinical symptoms were recorded. End points of the study were either death during hospital stay or discharge from the hospital, whichever was early.
Results: Outcome in the present study was assessed using the modified Barthel index and modified Rankin's scale. In IVIG group both MRS and MBS showed statistically favourable outcome, at the end of study ($p<0.0001$). PP group showed no statistically significant improvement with either scale. Out of the 34 patients in the present study, 20.58% patients expired whereas 79.41% patients survived during the time of the study. 41.16% males expired while 30.43% females expired during the study.
Conclusions: Our study showed that intravenous immunoglobulins were superior to plasmapharesis both in terms of survival and outcome in contrast to other western studies which show equal efficacy of plasmapharesis and intravenous immunoglobulins. This may indicate need for more studies to clarify this aspect especially in Asian population.

Keywords: Polyneuropathy, Guillain-Barre syndrome, Plasmapheresis, Intravenous immunoglobulin

INTRODUCTION

Acute inflammatory demyelinating polyneuropathy (AIDP) often described as Guillain-Barre Syndrome (GBS) is an ascending neuropathy involving demyelination of peripheral nerves. This disease process frequently causes acute onset weakness with involvement of respiratory and/or bulbar muscles. This may lead to aspiration, respiratory failure and need for mechanical ventilation. GBS remains a diagnosis made primarily by clinical history and findings. Critically ill patients with GBS need ICU care, monitoring and ventilatory support. Successful management mandates anticipation, prompt recognition and optimal treatment of neuromuscular respiratory failure in GBS.[1]

There are two modalities of treatment for GBS: 1) plasmapheresis 2) intravenous immunoglobulin (IVIG).

Both the modalities are claimed to have equal success, but extent of recovery of patient's weakness cannot be predicted. Plasmapheresis is associated with more complications than IVIG while IVIG is very expensive. Since this study is done in a hospital where most of the patients hail from the middle to lower income group the high costs of the approved modalities of treatment makes GBS a major social problem for both the patient and the caregiver. If patient needs prolonged mechanical ventilator support; complications associated with it like ventilator associated pneumonia (VAP), sepsis syndrome, pneumothorax etc. can occur. Therefore, it is important for an ICU physician to have comprehensive control of patient's vital parameters and infection control with early and effective treatment of complications.

Very few studies on GBS have been conducted in Indian scenario in recent years. Taking into account this background, we undertook this study to have better outlook to the spectrum of disease and outcome.

Aims and objectives

To study in a case of GBS,

- The patient's clinical profile.
- Outcome of the disease.
- Response to plasmapheresis (PP) versus intravenous immunoglobulin (IVIG) therapy.

METHODS

This was a prospective observational study. In this study 34 consecutive patients who fulfilled the inclusion and exclusion criteria and who gave a written informed consent were recruited over a period of 2 years. A detailed history and physical examination was carried out in every patient. History of preceding illnesses and clinical symptoms were recorded. Every patient underwent initial scoring using the modified Rankin's scale (MRS) and modified Barthel scale (MBS).[2-5] Routine investigations like Hb, CBC, RFT, LFT, blood sugars were recorded. Details of specialized investigations nerve conduction studies and cerebrospinal fluid findings were recorded. Data pertaining to treatment details of the patient including no treatment or both (IVIG and PP) was collected. Patients were investigated and treated as per the treating physicians' decision. Patients were followed up regularly during the hospital stay. Patient outcome was assessed using the MRS and MBS. The outcome at the endpoint was analysed with respect to demographic factors, single breath count, power, response to IVIG/PP and complications during in-hospital stay. End points of the study were either death during hospital stay or discharge from the hospital.

Modified Rankin scale (MRS)[2]

Score description

- 0: No symptoms at all
- 1: No significant disability despite symptoms; able to carry out all usual duties and activities
- 2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3: Moderate disability; requiring some help, but able to walk without assistance
- 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6: Dead

Total (0–6):____

The MBI is a measure of activities of daily living, which shows the degree of independence of a patient from any assistance. It covers 10 domains of functioning (activities): bowel control, bladder control, as well as help with grooming, toilet use, feeding, transfers, walking, dressing, climbing stairs, and bathing.

Each activity is given a score ranging from 0 (unable to perform task) to a maximum of 5, 10, or 15 (fully independent- exact score depends on the activity being evaluated). A total score is obtained by summing points for each of the items. Total scores may range from 0 to 100, with higher scores indicating greater independence. It should be noted, however, that dependency scores have been established for stroke populations, so they do not necessarily transfer to persons with spinal cord injury (SCI). Scores based on the past 48 hours are preferred.[4,5]

RESULTS

The mean age in study group was 35.24 years & SD 15.61. Highest numbers of patients were present in the age group of 15-45 years i.e. young adults (73.52%). The age of the youngest patient in the study was 15 years and eldest 68 years.

Of the total 34 patients in the study, 21 (61.8%) were males and 13 (38.2%) were females. The male to female ratio was 1.6:1. Various clinical symptoms reported by the patients at presentation are mentioned in Table 1.

Table 1: Clinical presentation.

Paraparesis (P)	8 (23.52%)
Quadriparesis (Q)	7 (20.58%)
Paraparesis + extra bulbar (P+EB)	5 (14.70%)
Quadriparesis + extra bulbar (Q+EB)	3 (8.82%)
Quadriparesis + bulbar + respiratory (Q+B+R)	3 (8.82%)
Paraparesis + bulbar + respiratory (P+B+R)	2 (5.88%)
Quadriparesis + bulbar + extra bulbar + respiratory (Q+B+EB+R)	3 (8.82%)
Paraparesis + bulbar + extra bulbar + respiratory P+B+EB+R	2 (5.88%)

Respiratory muscle involvement i.e SBC <15 was seen in 11 (32.4%) patients.

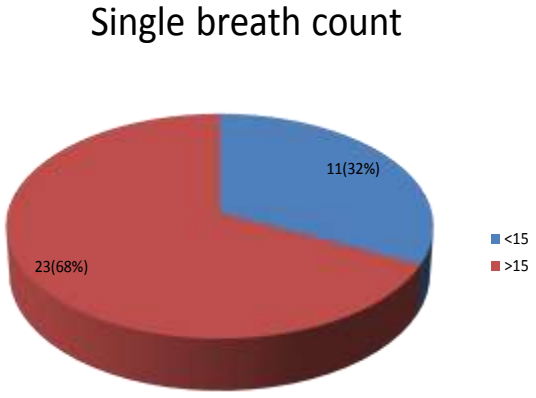

Figure 1: Respiratory muscle involvement i.e SBC <15.

Various antecedent illnesses were reported by patients as follows (Table 2).

Table 2: Antecedent illness.

	No. of patients
Diarrhoea	6 (17.6%)
U.R.T.I.	5 (14.7%)
No triggering illness	23 (68%)
Total	34

Various associated features noted which are described in Table 3.

Nerve conduction velocity NCV finding showed demyelination in 23 (67.8%), axonal in 7 (20.6%), mixed variety in 4 (11.8%) (Table 4).

Table 3: Associated features.

	No of patients
Sensory	9 (26.4)
Dysautonomia	5 (14.7%)
Sensory + dysautonomia	3 (8.9%)
No associated features	17 (50%)
Total	34

Table 4: Nerve conduction velocity (NCV).

	No. of patients
Axonal	7 (20.6%)
Demyelinating	23 (67.7%)
Mixed	49 (11.80%)
Total	34

Analysis of cerebro spinal fluid CSF showed classical albuminocytological dissociation in 12 (35.3%) patients (Table 5).

Table 5: Cerebro spinal fluid analysis.

	No. of patients
Albumin cytological dissociation	12 (36.3%)
No albumin cytological dissociation	22 (64.7%)
Total	34

Treatment wise distribution

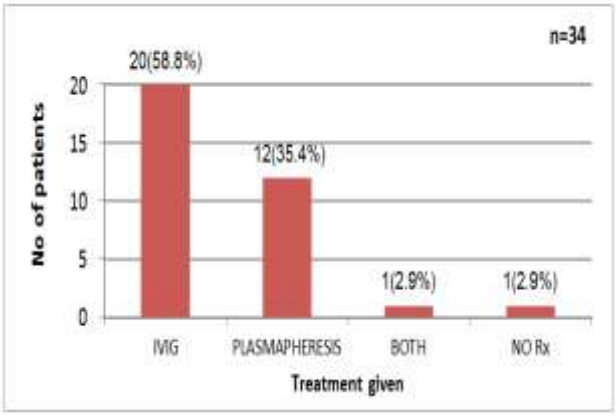

Figure 2: Treatment wise distribution.

Mean single breath count at the time of discharge was statistically significant in IVIG group versus in plasmapheresis (Table 6).

4 out of 23 of demyelinating variety required intuation while 3 out of 7 of axonal required intubation as follows (Table 7).

Table 6: Improvement in single breath count (SBC).

	IVIG		PP	
Single breath count	Admission	Discharge	Admission	Discharge
	24.2	37.3	17.67	23.17
	P=<0.0001 i.e. statistically significant		P=<0.08 i.e. statistically not significant	

Table 7: NCV finding and intubation.

	Intubated	Non intubated
Demyelinating	4	19
Axonal	3	4
Mixed	3	1

Both total ICU stay and days on ventilator was significantly low in IVIG group (Table 8).

Table 8: Days on ventilator.

	PP	IVIG
Days on ventilator	7	1.6
Days off ventilator	17	9.2
Total ICU stay	24	10.8

P= <0.001 i.e. statistically significant

Power improvement

P=<0.0001 i.e. statistically significant, statistically significant improvement in power was seen in IVIG group.

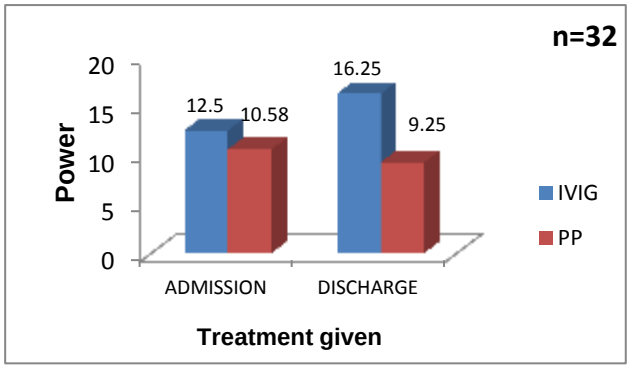

Figure 3: Power improvement.

Table 9: Improvement in MBS and MRS.

	MBS		MRS	
	Admission	Discharge	Admission	Discharge
IVIG	58	78	3.12	1.72
PP	42	48	3.5	2.88
	P=<0.0001 statistically extremely significant		P=<0.0001 statistically significant	

There was statistically significant improvement in both the scores in IVIG group.

Complications

There were no complications found in 59% of cases. Complications like VAP, pneumothorax, sepsis were more in PP group (Figure 4). Death was more in the PP group (33.33%) compared to the IVIG group (10%). (Figure 5).

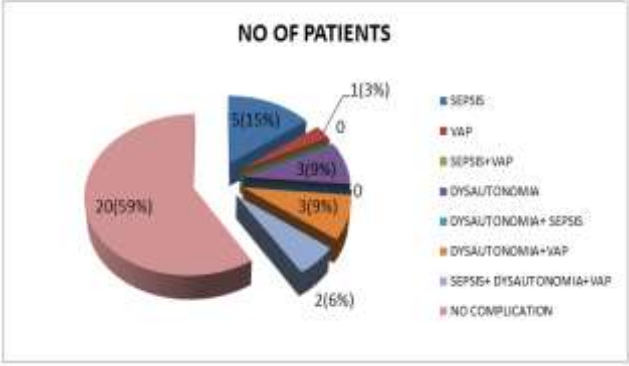

Figure 4: Complications.

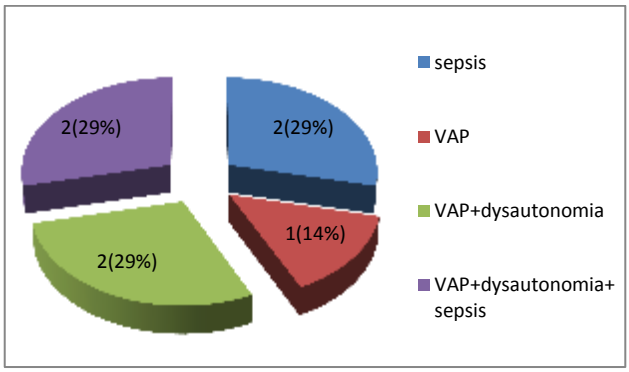

Figure 5: Causes of death.

DISCUSSION

In this study, 34 consecutive patients were recruited over a period of 2 years. Data collected from these patients was analyzed to find the clinical profile, and outcome and response to plasmapheresis and intravenous immunoglobulins in patients with Guillain Barre syndrome.

Age

Bouglin et al have found that incidence increases with advancing age from less than 1/100,000 in younger than

30 years to about 4/100,000 in those older than 75 years.[6] In our study we found the mean age of the patients included in the present study was 35.24 years with a Standard deviation of 15.61 highest number of patients were present in the age group of 15-45 years (young adults (73.52%)). The age of the youngest patient in the study was 15 years and eldest 68 years.

Sex

Of the total 34 patients in the present study, 61.8% were males and 38.2% were females. The Male to Female ratio was 1.6:1which parallels that reported in literature (men about 1.5 times more likely to be affected. Literature has given the incidence of GBS as approximately 0.6 to 4 per 100000 throughout the world The high number of GBS cases (34) presenting to a tertiary care hospital within a short span of nine months could reflect rise in environmental infections known to be associated with GBS as well as a referral preference.

Antecedent illness

Approximately 70% patients of GBS occur 1- 3 weeks after an acute infectious process usually respiratory or gastrointestinal. Evidence of preceding *Campylobacter jejuni* infection has been found in 25-30 % of cases Hadden et al reported recent infection by *C. jejuni* (23%), *Cytomegalovirus* (8%), *Epstein Barr* (2%) in cases of GBS. Other viruses, mycoplasma and even parasites like malaria have been identified as agents involved in antecedent infections, as have recent immunizations. Kanjalkar M, Karnad DR have reported 11 cases of GBS following malarial infection. Rabies vaccination is followed by GBS in about one in thousand (risk being higher compared to influenza vaccination).[7]

Variants of GBS like Miller-Fischer are much less common and Bouglin et al have reported incidence of 0.1 per 100000. In our study out of 34 patients we have 1 patient with classic Miller-Fischer variant (2.96%).

In our study, we found that 5 cases (14.7%) had preceding upper respiratory tract infections, while 6 patients (17.6%) had diarrheal illness. None had received a vaccine prior to illness.

In our study the predictors of intubation and mechanical ventilation were taken as clinical presence of bulbar weakness and presence of respiratory muscle weakness (SBC<15).

Out of 34 patients 8 (23.52%) patients had paraparesis while 7 (20.58%) presented with quadriparesis. All the patients who had bulbar involvement also had respiratory muscle weakness (that is SBC<15) and 8 out of 10 (80%) of these patients required intubation and mechanical ventilation. Similarly only 2 patients out of remaining 24 (8.33%) who had no bulbar weakness and respiratory muscle weakness (that is SBC<15) required intubation and mechanical ventilation.

Dade Fletcher et al conducted an analytical survey of 114 patients with GBS over period of 20 years. They found incidence of mechanical ventilation to be 81%. Martin Kohrmann et al in their study reported incidence of intubation and mechanical ventilation to 81.25% when they studied 32 patients of GBS.[8,9]

In our study of 34 patients 10 patients required intubation, that is 29.6%. This may be because of small sample size or may indicate need for more conservative protocols for intubation in GBS patients.

Regarding EMG NCV studies, Hadden et al in North America found majority of patients to have demyelination as the underlying subtype and only 5% as the axonal subtype.[10] However various studies done in Asian countries have found axonal variant in 30-47% of cases.

EMG NCV studies were obtained in all our 34 patients. We found that 67.8% of them have demyelinating type of GBS, 20.6% were of axonal variant and 11.8% had mixed variant.

Durand et al conducted a study in 60 patients in France to determine whether electrophysiological features could predict endotracheal intubation and mechanical ventilation in GBS patients. They found pure demyelination in 62% of patients, of which 46% required mechanical ventilation. Axonal variant was found in 8% of patients and none of them required ventilation. They also found equivocal results in 30 patients of which 17% required mechanical ventilation

Our study of 34 GBS patients revealed that 4 out of 23 patients (17.39%) of demyelination group required intubation and mechanical ventilation. Regarding axonal variant, a much higher proportion of patients, 3 out of 7 (43%) required intubation and mechanical ventilation. Mixed variety on other hand showed intubation and mechanical ventilation rate of 75%, that is 3 out of 4 patients. This data is compared in the table above.

However in a study done by Chowdhury et al in Indian patients found that axonal variant has a more severe course, with frequent respiratory involvement, ventilator dependence and significant residual weakness.[11] Lawn ND et al in their study have found that bulbar dysfunction and upper limb paralysis were significant predictors of requirement of mechanical ventilation.[12]

In patients with GBS definitive treatment should be initiated as soon after diagnosis as possible. In a large series reviewed by Raphael et al in 204 GBS patients found plasma exchange to be beneficial in 55% of patients, but randomized control trial by Van der Meche et al found equal efficacy with IVIG and plasma

exchange.[13,14] A combination of two therapies is not significantly better than either alone. IVIG is often the initial therapy chosen because of its ease of administration and good safety record.

Meta- analysis of randomized clinical trials indicate that definitive treatment reduces need for mechanical ventilation by nearly half (from 27% to 14%) and increases the likelihood of full recovery at 1 year (from 55% to 68%).

In our study every (except one) patient was given definitive treatment after confirmation of diagnosis. Out of 33 patients 20 patients (60.6%) received Intravenous Immunoglobulin and 18 (54.54%) of them recovered well, 12 (36.36%) patients received plasmapheresis and 8 (24.24%) of them recovered well and 1 patient received both plasmapheresis and Intravenous Immunoglobulin. One of the patients has not received any treatment. With IVIG survival rate was 90% and with plasmapheresis it was 66.33%. Our study showed better treatment success with IVIG vs. plasmapheresis.

Lawn ND et al did a study to find out predictors of mechanical ventilation in GBS patients and concluded that presence of bulbar dysfunction, bilateral facial weakness or dysautonomia along with rapid progression of the disease are associated with high probability of mechanical ventilation.[12]

Fletcher D et al conducted an analytical survey of 114 patients with GBS over period of 20 years. They found incidence of mechanical ventilation to be 81%.[8] Kohrmann M et al in their study reported incidence of intubation and mechanical ventilation to 81.25% when they studied 32 patients of GBS.[9] In our study the incidence of intubation and mechanical ventilation was 29.41%.

GBS being a purely neurological disease, the complications associated with it are related to mechanical ventilation.

Fish M in his review article has claimed dysautonomia may be present in 20% of GBS patients. Our study showed dysautonomia in 8(23.5%) patients.[15] Kohrmann M et al reported 56%incidence of dysautonomia in their study with 75% of mortality amongst those patients with dysautonomia.[9]

Infection is probably the most common medical complication that develops in GBS patients in the ICU. The major sources of infection are the lungs, urinary tract, and central intravenous catheters. Infections of the trachea or sinuses are other considerations in patients who are on a ventilator. Ventilator-associated pneumonia is a constant risk in patients whose normal airway defenses have been bypassed; this risk increases progressively as the duration of intubation increases. Other nosocomial infections, including urinary tract infections and infections through intravenous access lines, are also a common occurrence. Even with meticulous care, several of these complications cannot be prevented in a patient requiring prolonged mechanical ventilation. Deaths resulting from GBS are nowadays uncommon, because of advances in all the aspects of intensive care. Mortality rates vary widely, ranging from 1% to 18% in various reports. Patients requiring mechanical ventilation may have higher mortality rates.[16,17]

Death in GBS usually result from, sepsis, VAP, adult respiratory distress syndrome, and less frequently, from autonomic instability or pulmonary embolism; most of these patients are on ventilatory support.[18,19] Old age and associated co morbidities increase the risk of death.[20] In our study we found that out of 34 patients 7 patients developed sepsis and 4 died due to it. 1 out of 4 patients of VAP without sepsis survived. One patient during treatment period developed pneumothorax but he survived. Thus our study has overall mortality of 20.5% dysautonomia alone was present in 3 patients and did not cause any mortality.

CONCLUSIONS

The present study showed that intravenous immunoglobulins was superior to plasmapharesis both in terms of survival and outcome in contrast to other western study which shows equal efficacy of plasmapharesis and intravenous immunoglobulins. This may indicate need for more studies to clarify this aspect especially in Asian population.

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