A Comparative Study of IVIG versus IVIG with IV Methylprednisolone in Guillain–Barre Syndrome

Sir,

Guillain–Barre syndrome (GBS) manifests as areflexic motor paralysis with or without sensory disturbance. Usually, prognosis is good with 90% recovery.[1] Global annual incidence is reported as 0.6–2.4 cases/lakh/year.[2] Till date, there are no incidence studies in Indian population. Etiology of GBS is not known but about 70% cases were preceded 1 to 3 weeks before by respiratory or gastrointestinal infections. Theories suggest autoimmune mechanism in which antibodies are triggered to damage myelin.[3,4]

Available treatment modalities include intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) efficacy of which was already proven. The role of steroids has been a matter of debate since many decades. In a developing country like India, steroids are affordable and user friendly making them the theoretically reasonable agents. Though high-dose steroids have not produced the anticipated efficacy during their application for nearly 60 years, there is still no strong evidence demonstrating or denying their efficacy. Our study is mainly intended to know their effect when added to standard approved treatment with IVIg.

Aim is to evaluate the safety and efficacy of intravenous methylprednisolone (ivMPS) when added to IVIg in GBS patients.

This is a single-blind, placebo-controlled, randomized study conducted over 1 year from April 2018 to March 2019 with 1 month follow-up period after getting ethical clearance. A total of 46 patients equally divided into two groups by simple randomization in an alternate basis were recruited after written informed consent. Group A patients were given IVIg 0·4 g/kg/day for 5 days and placebo (normal saline). Group B patients were given IVIg along with ivMPS 1 g/d for 5 days, IVIg being started within 48 h of administration of first dose of ivMPS. If any of the exclusion criteria is met, patients were not included. Patients were blinded of the treatment they are receiving. Investigator blinding was not possible due to manpower shortage.

Patients were assessed on admission, on discharge, during the follow-up period of 1 month by

- GBS disability score
- Modified Rankin scale (mRS) score.

Primary endpoint - improvement from baseline by one or more grades after 1 month.

Inclusion criteria-Patients ≥12 years, symptoms of weakness began within 1 week before the date of admission, willing to sign the informed consent form, AIDP and AMAN variants of GBS.

Exclusion criteria-Age <12 years, previous episodes of GBS, other variants of GBS, abortive GBS, patients treated elsewhere before admission with therapies other than IVIG or ivMPS, previous severe allergic reaction to matched blood products, known selective immunoglobulin A deficiency, pregnancy, contraindications for steroids, severe concurrent disease, foreseeable difficulties precluding follow-up, patients with respiratory failure requiring mechanical ventilation, mRS score >3 before this illness.

Statistical analysis was done using SPSS 20. Quantitative variables were compared using mean and qualitative variables using proportions. Significance level is $P \leq 0.05$. Statistical tests used are Chi-square test (χ^2), Independent sample T test and Mann–Whitney U test.

Mean age of presentation was 40 [Figure 1] with Male: female ratio 2.53. Half had AIDP and the other half had AMAN variant. All variables which can affect treatment response and thereby prognosis were compared between two groups [Table 1]. comparison of various scores using Mann–Whitney Test was not significant ($P > 0.05$) [Table 2]. A number of patients achieving primary outcome in Group-A

Table 1: Variables which can affect treatment response and outcome (independent sample *t*-test)

	Group	*n*	Mean	Std. deviation	*P*
Age	IVIG+IVMPS	23	38.87	16.647	0.697
	IVIG	23	41.00	20.005	
RBS	IVIG+IVMPS	23	100.70	30.144	0.809
	IVIG	23	102.61	22.821	
TLC	IVIG+IVMPS	23	8269.57	3212.752	0.924
	IVIG	23	8343.91	1839.018	
NA	IVIG+IVMPS	23	137.00	4.200	0.365
	IVIG	23	138.17	4.499	
K	IVIG+IVMPS	23	3.878	0.3813	0.910
	IVIG	23	3.891	0.3976	
CPK-NAC	IVIG+IVMPS	23	191.17	196.639	0.057
	IVIG	23	107.87	35.253	
Age	AIDP	23	46.04	19.802	0.021
	AMAN	23	33.83	14.475	
RBS	AIDP	23	102.04	21.391	0.921
	AMAN	23	101.26	31.201	
TLC	AIDP	23	8410.87	2801.157	0.788
	AMAN	23	8202.61	2416.092	
NA	AIDP	23	137.57	3.691	0.973
	AMAN	23	137.61	4.998	
K	AIDP	23	3.848	0.4021	0.521
	AMAN	23	3.922	0.3729	
CPK-NAC	AIDP	23	132.04	65.757	0.423
	AMAN	23	167.00	196.404	

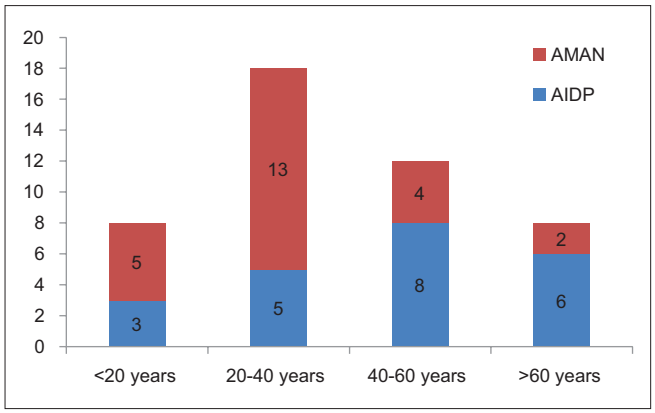

Figure 1: Age distribution of various types of GBS variants

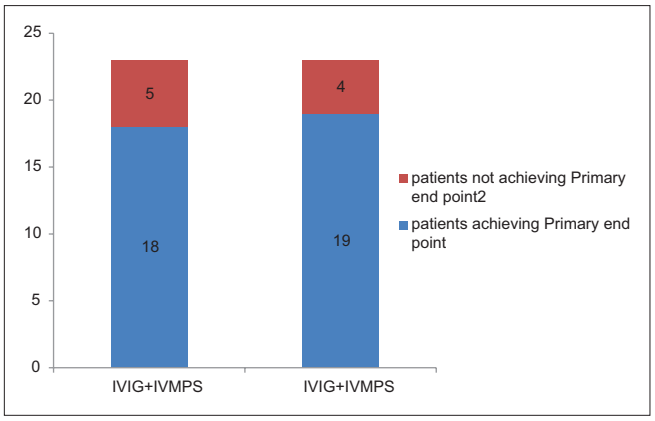

Figure 2: Number of patients achieving primary end point

Table 2: Comparison of outcome scores between the two treatment groups (Mann-Whitney test)

	Group	*n*	Mean	Std. deviation	*P*
GBS disability score on admission	IVIG+IVMPS	23	3.39	1.270	0.382
	IVIG	23	3.70	0.974	
GBS disability score on discharge	IVIG+IVMPS	23	2.96	1.022	0.079
	IVIG	23	3.43	0.728	
GBS disability score during 1 month follow-up	IVIG+IVMPS	23	2.04	1.296	0.471
	IVIG	23	2.30	1.259	
mRS score on admission	IVIG+IVMPS	23	3.74	1.137	0.055
	IVIG	23	4.35	0.935	
mRS score on discharge	IVIG+IVMPS	23	3.57	1.273	0.733
	IVIG	23	3.74	1.010	
mRS score during 1 month follow-up	IVIG+IVMPS	23	2.43	1.674	0.703
	IVIG	23	2.65	1.526	

were 18 (78%) and Group-B were 19 (82%) which was not significant ($P > 0.05$) [Figure 2]. None of our patients developed treatment-related fluctuations within the follow-up period.

Various immunosuppressive treatments were tried with variable success rate.[5] Outcome is generally favorable with mortality seen in <5%. No difference was found between IVIg and PLEX with respect to improvement in disability grade after 4 weeks, duration of mechanical ventilation, mortality, or residual disability. As IVIg is safer and more convenient than PLEX, IVIg became the treatment of choice for GBS.[6] Trials till date have not studied the effect of IVIg or PLEX in mildly affected patients. In our study, we had included patients with mild disease also and did not find any added benefit of steroids. Cochrane meta-analysis of six randomized trials indicated no beneficial effect of corticosteroids.[7] The guideline on GBS treatment in 2003 recommended PLEX and IVIg solely but no steroids.

In 1994, Dutch Guillain-Barre Study Group reported a before-after trial in 25 patients on effect of high-dose ivMPS when added to IVIg indicating a beneficial effect at 4 weeks as measured with the GBS disability score.[8] So, a multi-center clinical randomized controlled trial by van Koningsveld *et al*. was initiated and results were published in 2004.[9] The reasons for considering steroid therapy in our study includes: previous open label studies and pilot study showed their effectiveness in GBS, steroids are effective in CIDP which is immunologically similar to GBS, no prior Indian studies done to know synergistic effect of combined treatment, easy availability, and cost-effectiveness of steroids in India.

In our study, male to female ratio was 2.53:1 comparable with other Indian studies in which ratio ranged from 1.5:1 to 3.5:1.[10] Mean age of presentation in our study was 40 years similar to studies by Shrivastava *et al*.[11] and Habib *et al*.[12] Previous Indian studies showed AIDP to be common variant, but our study had equal occurrence of both AIDP and AMAN variants [Table 3]. Unfortunately, there were no previous large Indian studies comparing the available immunosuppressant modalities. In present study, we had compared treatment outcome between two predefined groups. Although the proportion of patients achieving primary end point were more in Group B, difference was not significant ($P > 0.05$). Our findings were similar to study by van Koningsveld *et al*.[9] Even today, about 15% of patients with GBS die or are left disabled even after administration of approved therapies. Though our study did not indicate significant outcome difference, these two drugs might work synergistically to influence the disease outcome. Limitations may reduce validity of this study include: Small sample size, quasi randomization, and single blinding leading to various biases.

We conclude that ivMPS along with IVIg offers no added benefit in GBS. Due to lack of previous studies in India, limited side effects, easy availability, and cost-effectiveness of steroids, our study highlights the need for further investigation of this combined treatment in GBS patients. Also, our study highlights the need for newer immunosuppressive agents, such as mycophenolate, rituximab, and others in GBS. Large sample size and double blinding might have improved the validity of the results.

Table 3: Comparison of outcome scores between AIDP and AMAN variants of GBS (Mann-Whitney test)

	Group 2	*n*	Mean	Std. deviation	*P*
GBS disability score on admission	AIDP	23	3.17	1.072	0.389
	AMAN	23	3.91	1.083	
GBS disability score on discharge	AIDP	23	2.87	0.815	0.079
	AMAN	23	3.52	0.898	
GBS disability score during 1 month follow-up	AIDP	23	1.74	1.137	0.471
	AMAN	23	2.61	1.270	
mRS sum score on admission	AIDP	23	3.78	0.951	0.055
	AMAN	23	4.30	1.146	
mRS sum score on discharge	AIDP	23	3.26	1.010	0.733
	AMAN	23	4.04	1.147	
mRS sum score during 1 month follow-up	AIDP	23	2.09	1.535	0.703
	AMAN	23	3.00	1.537	

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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