Rescue treatment in patients with poorly responsive Guillain–Barre syndrome

Ayman Mahmoud Alboudi[1] (iD), Pournamy Sarathchandran[2],
Samar Sameer Geblawi[3], Deeb Maxwell Kayed[4], Jihad Inshasi[2],
Sadhik Puthan Purayil[5], Abu Baker Almadani[2]
and Bashar Katirji[6]

Abstract

Objectives: To evaluate the effectiveness of rescue treatment (intravenous immunoglobulin or plasma exchange) in patients with Guillain–Barre syndrome who did not respond or deteriorated after the initial management with intravenous immunoglobulin.

Methods: We performed a retrospective review of the medical records of patients who responded poorly or did not respond to intravenous immunoglobulin treatment. The disability parameters of those who received second-line treatment with intravenous immunoglobulin or plasma exchange (20 patients) were compared with those who did not receive second-line treatment (19 patients).

Results: There was a statistically significant improvement in disability scores at 1 month in the patients who received the rescue treatment ($p = 0.033$). However, there was no significant difference in the disability scores at 3 and 6 months, or in length of intensive care unit stay.

Conclusion: Our study showed that a second course of treatment to carefully selected patients may be beneficial

Keywords

Guillain–Barre, rescue treatment, intravenous immunoglobulin, plasma changes

Introduction

Guillain–Barre syndrome (GBS) is an acute, usually symmetric, ascending, paralyzing illness.[1,2] It is the most common cause of flaccid paralysis in this era.[3] The disease has different subtypes (demyelinating vs axonal) with common pathogenesis of autoimmune inflammatory process.[1] The clinical course of the disease ranges from mild or no disability to severe with bedridden, hemodynamic instability, and respiratory failure requiring intubation in 25% of patients.[4] Mortality is high at 4%–15% within 1 year of symptom onset.[2] Among severely affected patients, 20% remain unable to walk after 6 months of disease onset.[1]

Randomized controlled trials (RCTs) have shown that plasma exchange (PLEX) and intravenous immunoglobulin (IVIG) are effective in patients with GBS.[5–7] Although no RCTs have assessed the effect of a repeated IVIG dose in GBS, treatment with a second course of IVIG in severe or worsening GBS patients is sometimes anecdotally advocated.[8]

Conflicting results have come from different studies regarding the efficacy of second course of treatment in severely affected GBS patients. An uncontrolled study in a small series of patients investigated the effect of a second course of IVIG in severe unresponsive patients with GBS and found it

[1]Neurology Department, Mercy Health Saint Mary Hospiatal, Grand Rapids, Michigan, US
[2]Neurology Department, Rashid Hospital, Dubai, UAE
[3]Pediatrics Department, Latifa Hospital, Dubai, UAE
[4]Department of Neurology, Mediclinic City Hospital, Dubai, UAE
[5]Neurophysiology Division, Neurology Department, Rashid Hospital, Dubai, UAE
[6]University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, OH, USA

Corresponding author:
Ayman Mahmoud Alboudi, Neurology Department, Mercy Health Saint Mary's Hospital, 200 Jefferson Ave SE, Grand Rapids, MI 49503, USA.
Email: alboudi.a@gmail.com

to be effective.[9] A small retrospective study reported that PLEX after IVIG did not improve the outcome measures.[10]

Severely affected GBS patients are at high risk of having long complicated hospital stays and of ending up with lasting disabilities. There is no clear evidence about the best treatment for these patients. The available data suggest that a second course of treatment could be beneficial. We did a retrospective, case-controlled study to evaluate the effect of rescue treatment in patients with severe GBS who did not respond to initial IVIG therapy.

Materials and methods

We performed an analytical cross-sectional study.

Patients

We collected the medical records of all patients admitted with a diagnosis of GBS from 1 January 2008 to 31 December 2014 from three major hospitals with neurology service in Dubai, United Arab Emirates (Rashid hospital, Latifa Hospital, and City hospital). GBS patients were identified according to International Classification of Diseases, Tenth Revision (ICD-10) coding (G 61.0, G 61.8, G 61.9, G 62.8, G 62.8, G 62.9, and G 64.x). Only patients who were diagnosed according to the NINDS criteria[11] for GBS were included.

The patients had Nerve Conduction Study/Electromyography (NCS/EMG) when needed to confirm the diagnosis. The demyelinating type was determined by increased distal latencies and conduction blocks, and the axonal type was determined by decreased amplitude without remarkable changes in the conduction velocity to explain the amplitude decrease.

The patients' medical records were reviewed retrospectively by one of the authors (A.A.) to confirm diagnosis using clinical presentation, neurological examination, NCS/EMG when needed, and treatments. The disability scale used was the Hughes disability scale (0: normal; 1: minor symptoms, but able to run; 2: able to walk 10 m or more without assistance but unable to run; 3: able to walk 10 m across open space with help; 4: bedridden or chair bound; 5: requiring assisted ventilation for at least part of the day; 6: dead). Hughes GBS scores at presentation, at the nadir, at 1 month, at 3 months, and at 6 months were collected to categorize the patients' disease severity. The response to treatment was assessed based on improvement of the Hughes disability score. Muscle strength was assessed clinically by Medical Research Council (MRC) score (range from 0 = complete paralysis to 60 = full strength).

The patients who responded poorly to initial treatment with IVIG were assessed separately. Their files were reviewed for demographic and clinical data and were confirmed by another author (P.S.). Patients were eligible for the study if they were severely affected (Hughes 3 or more) and did not respond to initial treatment (or the improvement was less than one grade on the Hughes scale). This was determined by the responsible physician during the course of treatment. At that time, the decision was made to give or not give the rescue treatment. Of these patients, those who had rescue treatment with IVIG/PLEX were identified. The rescue treatment was given after a median = 17 days (range = 12–48 days). Patients who did not receive any additional treatment were managed conservatively (either because the decision of the primary physician or the patient's choice or because of financial constraints) and were selected as controls. The benefit of the rescue treatment in improving the disability scores was compared between the cases and controls.

Treatment

IVIG with a dose of 0.4 g/kg/day for 5 days was administered as first-line treatment for all patients. The rescue treatment was either (1) IVIG (0.4 g/kg/day for 5 days) or (2) PLEX (five sessions over 1–2 weeks with 40 mL/kg per PLEX). The rescue treatment was given after a median of 17 days (range = 12–48 days) from the first-line treatment. Both groups offered similar supportive management, including physiotherapy.

Outcome

The primary outcome measure was Hughes GBS disability at 1, 3, and 6 months from the disease onset and at discharge. The secondary outcome measures included duration of intensive care unit (ICU) stay, intubation period, and total hospital stay.

Standard protocol approvals and registration

The study was approved by the Dubai Scientific Research Approval Committee (DSRAC)

Statistics

Normality was checked by SPSS version 22 for Windows, and nonparametric distribution was found for most variables. As a result, we used the Mann–Whitney U test to compare the two groups (with and without rescue treatment). In addition, we ran a comparison between the two types of rescue treatment (PLEX and IVIG). Descriptive data were expressed as the median and standard deviation.

Results

We identified 116 patients who were diagnosed with GBS from 2008 to 2015. Male patients were 71.6% of patients, and the age ranged from 1 to 82 years (median = 37.5 years). Of those, 20 (17.2%) had rescue treatment, and the male

Table 1. Demographic and basic characteristic of patients analyzed.

	Treatment group	Control group	p value
Gender (M:F)	12:8	16:3	0.204
Age at onset (median ± SD)	43.5 ± 19.6	43 ± 19.65	0.235
Duration from symptoms onset to treatment (median ± SD), days	2.5 ± 2.42	3 ± 3.4	0.857
MRC at nadir (median ± SD)	22 ± 17.2	20 ± 13	0.627
Hughes at nadir (median ± SD)	5 ± 1.03	3 ± 0.87	0.204
NCS type (axonal %)	50%	42.1%	0.857

MRC: medical research council, NCS: nerve conduction study; SD: standard deviation.

Table 2. Outcome measures.

	Rescue treatment (median/SD)	Control group (median/SD)	p value
Hospital stay (days)	55/76 (19)	11/34 (16)	0.005
ICU stay (days)	5/17.5 (17)	0/25.5 (18)	0.318
Intubation period (days)	0/12.8 (17)	0/24.6 (18)	0.483
Hughes score at 1 month	3/1.94 (19)	5/1.24 (17)	0.033
Hughes score at 3 months	3/2.04 (15)	4/1.48 (12)	0.732
Hughes score at 6 months	1/1.49 (8)	3/1.75 (7)	0.230
Hughes score at discharge	2/1.67 (19)	4/1.3 (17)	0.390

ICU: intensive care unit; SD: standard deviation.

to female ratio was 1.5:1. The age range was 8-81 years (median = 43.5 years). The MRC score for those patients at nadir ranged between 0 and 40, with a median of 22 (SD = 17.2), which was not different from the time of rescue treatment. In addition, the median Hughes score at nadir for this group was 5 (SD = 1.03). Eight patients (40%) needed ICU admission.

There were two groups of patients divided by the rescue treatment given: 7 patients (35%) had IVIG and 13 (65%) had PLEX.

This group was compared with a control group of 19 patients (described in the "Materials and methods" section). There was no significant difference between the two groups regarding the age of onset of the disease (p = 0.23), gender (p = 0.2), and duration from symptom onset to the initiation of treatment (p = 0.8). Furthermore, there were no significant differences in the severity of the disease course as was expressed by the clinical situation at the nadir of the disease based on MRC (p = 0.6) and Hughes (p = 0.2). In addition, there was no significant difference regarding the GBS type (axonal vs demyelinating), which was determined from a single NCS/EMG study in the majority of patients. It is important to note, that the percentage of the axonal type among our selected group of patients (who had a poor prognosis and received rescue treatment) was 50%, while the percentage of patients with the axonal type in the whole group (39 patients) was 46.2% (Table 1).

The median hospital stay for patients who had rescue treatment was 55 days (range = 8–369 days). The functional

disability at discharge ranged between 1 and 5, with approximately 41% of patients severely affected (4–5); however, there were no deaths. When compared with the control group, the median hospital stay was = 11 days (range = 4–115), and the duration of the hospital stay was significantly longer in the treatment group (p = 0.005). The Hughes scores at 1 month were significantly better in the treatment group (p = 0.033) but not at 3 or 6 months (Table 2).

There were no deaths in the control group, and five patients needed ICU admission (26%). The functional disability at discharge ranged between 0 and 5 in the control group, with approximately 45% having a Hughes score of 4–5, which was not significantly different between the two groups (p = 0.39).

Because PLEX after IVIG may negate the effect of IVIG, we tried to look at patients who received a second IVIG alone. There was no significant difference between the group of patients who received two courses of IVIG and the control group.

Discussion

Both IVIG and PLEX are widely accepted primary treatment options for GBS patients. However, there is no consensus on how to treat patients who do not respond or who deteriorate after the primary treatment course.

Only a few studies have addressed the value of a second course of treatment in GBS patients. An open label, controlled, single-center study by Haupt et al.[12] compared the

efficacy of selective adsorption extracorporeal elimination (SAE) alone or SAE followed by IVIG. They found better outcomes, with respect to improvement in disability scores, from admission to day 28, a trend toward improvement from nadir to day 28 and a reduction in the duration of the hospital stay. However, the decision to treat with IVIG after SAE was not based on the patient's disability or lack of response after the primary treatment.

In the PLEX/Sandoglobulin GBS trial,[13] patients were randomized into three arms to receive IVIG, PLEX, or both. Randomization to the various arms was irrespective of their disability before initiation of therapy. The authors found no significant difference between the three arms. It is not known whether those patients who had the combined treatment had a poor response after the initial treatment and whether a second course was clinically indicated. Furthermore, the study found improvements in the combined treatment group, although it was not significant. This difference became significant between the IVIG group and the combined group when adjusted to the same prognostic factors.

In another study,[10] four groups of patients with different treatments (IVIG, PLEX, IVIG + PLEX, or neither) were compared to include the cost effectiveness of giving a second course of treatment for poor responders. The study found no significant improvement of giving a second course of treatment, and thus a second treatment was not cost-effective. The authors concluded that patients who were treated with two modalities were clinically worse than those who received only one.

Farcas et al.[9] treated four patients who had poor response to initial treatment with IVIG with a repeated course of IVIG and noted good improvement. This was shown again in a report of three cases by Godoy and Rabinstein.[14]

The optimal dose of IVIG in GBS remains unknown. The total dose of 2 g/kg over 5 days was initially imported from the hematological indications of IVIG. Raphael et al.[15] found that a higher dose of IVIG (2.4 g/kg) was more effective than the lower dose (1.2 g/kg), with a faster recovery rate at the 6-month follow-up. This suggests that the therapeutic effect of IVIG is dose dependent. More recently, Kuitwaard et al.[16] studied the level of Immunoglobulin G (IgG) in the serum of GBS patients before and 2 weeks after treatment with the standard dose of IVIG (2 g/kg). They found a large variation in the IgG level at 2 weeks after treatment. The study group calculated the difference between IgG concentrations before and 2 weeks after treatment (ΔIgG). They found that when ΔIgG was small, the beneficial response was less robust, and this difference persisted even after modifying for different risk factors, including the extent of disability before starting treatment. This study concluded that calculating the ΔIgG levels may be useful, and that some patients may benefit from higher doses of IVIG. Particularly in light of new models for the early prediction of poor prognosis in GBS patients.[17]

In our study, rescue treatment was provided only to patients with poor response after primary treatment. We found improvement in disability scores at 1 month with rescue course of IVIG or PLEX, similar to the observations by Haupt et al.[12] The hospital stay was shorter for those who did not receive second-line treatment. However, most of the patients were expatriates who were repatriated to other hospitals at their countries of origin and were lost to follow up, which likely confounded the duration of hospital stay. The disability score, which was better in the treatment group, became insignificant at 3 and 6 months. Again, because of expatriation, the groups compared at 3 and 6 months were smaller in number, which could explain the obscuration of differences between the two groups.

Our study included patients with a poor prognosis, and 50% of them were axonal type. GBS studies in the Middle East showed the axonal type in the range of 37%–38.8%.[18,19] In addition, in one of the studies, the axonal type was 45% when the patients has a disability score of 3 or more on the Hughes disability scale.[19]

We acknowledge the following limitations of this study. This was a retrospective study, and there were no clear criteria recognized to choose patients who should receive the rescue treatment. Instead, the decision was made by the responsible physician depending on his or her interpretation of the patient's clinical situation. Furthermore, follow-up was limited because most patients were expatriates. Moreover, it was clear that more patients in the control group were lost to follow up, and the increasing disability score at follow up suggests that the less severely patients were the ones lost. In addition, the wide range of ages introduces more variability in the results. Finally, financial issues were sometimes a factor in not giving a second course of treatment to some patients who may have otherwise benefited from the treatment.

Conclusion

The best strategy to be applied for GBS patients who do not respond to the first course of treatment is yet to be determined. Some trials showed benefit or a trend of benefit of a second modality of treatment. Our study showed, that a second course of treatment to carefully selected patients may be beneficial. RCTs should be performed and include only patients who did not respond to first-line treatment to be randomized to either a second-line treatment or supportive management.

Author contribution

A.M.A. contributed to study concept and design, data acquisition, data analysis and interpretation, and performed statistical analysis. P.S. contributed to data acquisition and critical revision of the manuscript for intellectual content. S.S.G. contributed to data acquisition, analysis and interpretation of the data. D.M.K. contributed to data acquisition J.I. scientific guidance and supervision. A.B.A.

critically revised the manuscript for intellectual content and study supervision. S.P.P. collected neurophysiological data. B.K. critically revised the manuscript and he is a major contributor to the writing process.

ORCID iD

Ayman Mahmoud Alboudi https://orcid.org/0000-0003-3091-0868

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