Original Article

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The effect of 2 days vs 5 days regime of intravenous immunoglobulins on the outcome of patients suffering from severe guillain barre syndrome

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[1,3]Conception, data acquisition, revision, and approval of the final draft, [6]Designing and drafting of work, [2]Drafting and revision of work
Conception and data acquisition
[3,4]Data analysis and interpretation
[5]Critical revision of intellectual content

Funding Source: None
Conflict of Interest: None

Received: Aug 08, 2020
Accepted: Nov 29, 2020

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ABSTRACT

Objective: To compare the mean time lapse till improvement of functional grades in 2 days regime of IVIG versus 5 days in severe pediatric guillain barre syndrome
Methodology: This randomized clinical trial was conducted in Children Hospital Lahore pediatric neurology department from August 2015 to February 2016 after ethical clearance. There were 64 patients with severe GBS were randomized into Group A which received IVIG 400mg/kg/day over 5 days and Group B which received 1 g/kg/day over 2 days, making 2 g/kg in both groups. The disability grade was done at the start of treatment on daily basis till a decrease in GBS disability grade by grade 1. The data was entered on SPSS 25.
Results: Both study groups were comparable for gender and age of the subject in this study. Out of 64 cases (32 in each group), 65.63%(n=21) in Group-A and 71.88%(n=23) in Group-B, were between 2-10 years of age while 34.37% (n=11) in Group-A and 28.12% (n=9) in Group-B were between 11-15 years. Mean+SD was calculated as 8.69+3.48 and 8.34+3.27 years. The mean time lapse till improvement was significantly less in group B, 18.38±1.79 compared with group A, 22.09±2.16, p value 0.0001 which shows statistically significant improvement in group B regardless of gender and age of subjects.
Conclusion: The mean duration for improvement of functional grades was significantly lower in GBS patients administered 2 days regime of IVIG as compared to5 days.
Keywords: GBS, IVIG.

Cite this article as: *Hafeez M, Saeed T, Aslam Qurat UA, Liaquat I, Tariq A, Javaid MK. The effect of 2 days vs 5 days regime of intravenous immunoglobulins on the outcome of patients suffering from severe guillain barre syndrome. Ann Pak Inst Med Sci. 2020; 16(4):180-184.*

Introduction

"Guillain barre syndrome is an acute, monophasic, symmetrically progressive, peripheral ascending demyelinating polyneuropathy characterized by rapidly evolving symmetrical limb weakness, areflexia, absent or mild sensory signs, and variable autonomic disturbances".[1,2,3] This syndrome affects people of all age groups and is not hereditary. There is also seasonal variation occurring more in spring and summer seasons.[3] Annual incidence of the disease is reported to be 1.65 -1.79 per 100,000 population.[4]

Hallmark of GBS is limb weakness but initial symptoms may include paresthesias, numbness, myalgias, and irritability.[5] The weakness usually starts in the lower limbs and progressively ascends to the upper limbs. This progression is variable and may occur over hours to days or even weeks. The weakness is typically symmetrical. In approximately 50% of cases, there is bulbar involvement which can lead to dysphagia and respiratory insufficiency.

In some cases involvement of autonomic nervous system can cause labile blood pressure, variable heart rate, postural hypotension and even asystole. Though very rare, miller fisher syndrome which is a variant of GBS have extra ocular muscle weakness(ophthalmoplegia) and ataxia. It mainly involves motor system in ascending pattern and there is also variable sensory involvement. There are various types of GBS i.e acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and miller fisher syndrome. Apart from clinical examination, there are various methods to diagnose GBS including electromyography (EMG) and nerve conduction studies (NCS) and cerebrospinal fluid examination (CSF) and MRI of spinal cord. NCS show reduced conduction velocities and focal conduction blocks and variable other patterns according to GBS type. EMG shows evidence of acute denervation of muscle while CSF shows albumin-cytological dissociation with a normal white cell count and negative bacterial culture. Glucose levels remain normal. CSF examination is usually carried out in second week of illness because characteristic CSF findings occur after the first week. Magnetic resonance imaging of spinal cord shows the thickening of cauda equina. Prognosis is generally good and up to 90% achieve complete recovery within 3-12 months.[6] Improvement starts in descending pattern with recovery of bulbar functions at the beginning and resolution of weakness of lower limb in the end. Approximately 5-10% of patients have permanent disability.[7] Poor prognostic features include need of ventilatory support, the involvement of cranial nerves and maximum disability at presentation. Relapse can occur in 4% of the cases. 1-10% of patients are left severely disabled and mortality rate in GBS is less than 5%.[8,9,10]Cause of death is mostly due to respiratory failure, cardiac involvement secondary to autonomic instability and ventilator related sepsis.

Treatment involves both supportive and specific measures. Supportive measures include monitoring of vitals in the form of respiratory rate, oxygen saturation, heart rate and blood pressure. Bed-side spirometry can also be helpful in monitoring of respiratory muscle involvement in older children. Frequent change of posture, bowel and bladder care, nutritional support, treatment of neuropathic pain and prevention of deep venous thrombosis (DVT) also has a pivotal role in management of these patients. Treatment of secondary bacterial infections is important. Gabapentin is used for pain. DVT is avoided by physiotherapy and leg stockings. Specific treatment options include IVIG and plasmapheresis, both are effective but plasmapheresis is an invasive procedure and associated with some complications. IVIG is preferred and is the treatment of choice in pediatric GBS.[11, 12]Results with steroids are not uniformly good. Immunosuppressive drugs and plasmapheresis are used if IVIG is ineffective or relapse occurs.

The available data regarding the treatment options for children with severe GBS varies and contradicts. In literature review, we found two international studies regarding dose and duration of IVIG. One study comparing results of two groups in Toronto (Canada) and anakara(Turkey)shows that faster improvement occurred in patients who were given IVIG over 2 days as compared to 5 days.[13]In another study done in Germany including two groups, one being treated for 2days while other for 5 days showed that there is no significant difference in recovery.[14]However in both studies cumulative dose of IVIG remained same.

In routine use, IVIG is given 2 g/kg equally divided over 5 days but appropriate treatment protocol is yet to be determined.[15]Cochrane review also says that dose-ranging studies are still needed.[16]No study has been done in last 5 years regarding dose regimen of IVIG in GBS and literature in local studies is also not available. In developing countries with limited sources, the two days regimen will lead to better outcomes by reducing the hospital burden in the form of less ICU stay, early weaning off from ventilator and total stay in hospital as well. If 2 days regime is better or no significant difference is found then we can prefer the 2 days regime in our population which can be cost effective and reduce hospital stay burden.

Methodology

After approval from ethical review board, this randomized controlled trial was conducted at indoor of Neurology department of children hospital Lahore, for a period of 6 months, from August 2015 to February 2016.

Patients between age group of 4-15 years, including both genders, suffering from severe GBS and presenting within 5 days of onset of symptoms were enrolled in the study. Diagnosis of severe GBS was made on the basis of history, clinical examination and electrophysiological studies. Severe GBS was labeled as disability grade 4 and above according to Hughes Scoring system for functional grading scale of GBS. Stool examination is done for

isolation of polio virus according to WHO acute flaccid paralysis surveillance program. Patients having co-morbidity, meningitis, pneumonia and previously treated/relapse of GBS were excluded from this study. Sample size of sixty four patients (32 in each group) was

calculated by open epi version 3.01 with confidence level of 95% and power of test was 80% and taking mean time lapse till improvement 17.4±4.35(2 days regime) and 20.8±5.2 (5 days regime)[13]. Written informed consent was taken from parents/guardians for enrollment in the study. Consecutive non- probability sampling was used and patients were randomized into group A or B by lottery method. The first group (A) was given IVIG for 5 days at the dose of 400 mg/kg/day, while second group (B) was given for 2 days at the dose of 1g/kg/day. The disability grade was done at the start of treatment on daily basis till decrease in GBS disability grade by grade 1. Time lapse in days till improvement was taken as primary end point in the study. The data was documented on a specially designed Performa

All data collected was analyzed by SPSS version 25. Quantitative variables like age and time lapse till improvement were presented by mean and standard deviation. Qualitative variables such as gender were given presentation in the form of frequency and percentage. Student t- test was applied on quantitative variable which is time lapse till improvement in disability grade to compare both groups. P-value $\leq$ 0.05 was taken as statistically significant.

Results

In our study, 64 patients who fulfilled the inclusion criteria were registered for comparison of the mean time lapse till improvement of functional grades in 2 days versus 5 days regimen of IVIG in severe pediatric GBS.

There were 34 male patients and 30 female patients participated in this trial. Among them, 44 patients were of age group 4-10 years and 20 were of age group 11-15 years. There was no statistically significant difference between two groups regarding age and gender of the subjects. (Table I)

Mean time lapse till improvement was calculated as 22.09±2.16 days in Group A and 18.38±1.79 days in Group B. The p value was calculated as 0.0001 showing a significant difference. (Table II)

In our study among 44 patients that were in age group 4-10 years, 21 were in group A and 23 were in group B. Mean time lapse in group B 18.48 ± 1.83 was significantly shorter than group A 22.14±2.08, p-value 0.0001 (Table II)

We stratified data for age and gender of the subjects. We observed that two days regime performed better than 5 days regime regardless of age or gender of the subjects.

Table I: Age and gender distribution of two groups

			Group A	Group B	P Value
Age	4-10 years	44	21 (65.63%)	23 (71.88%)	0.589
	11-15 years	20	11 (34.37)	9 (28.12%)	
Gender	Male	34	16 (50%)	18 (56.25%)	0.616
	Female	30	16 (50%)	14 (43.75%)	

Table II: Mean time elapsed till improvement (n=64)

Time (in days)	Group-A (n=32)		Group-B (n=32)	
	Mean	SD	Mean	SD
	22.09	2.16	18.38	1.79
	P value: 0.0001			

Among 30 female patients, 16 were in group A and 14 were in group B. Mean timelapse in group B 17.93± 1.64 was significantly shorter than group A 22.25± 1.77, P value .0001(Figure 1)

Among 34 male patients 16 were in group A and 18 were in group B. Mean time lapse till one grade improvement in group B 18.72± 1.87 was significantly shorter than group A 21.94±2.54, p value .00002 (Figure 1)

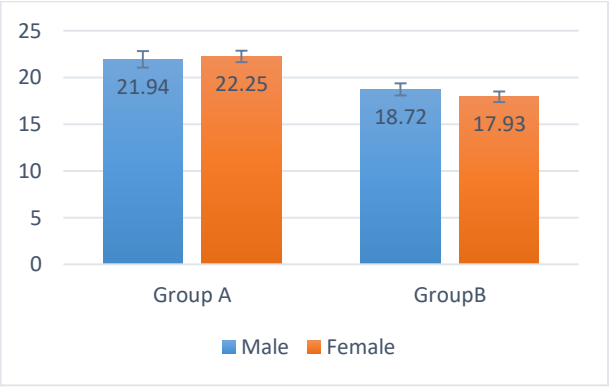

Figure 1. Stratification for gender in each group.

Among 20 patients that were between age 11-15 years, 11 were in group A and 9 were in group B. Mean time lapse in group B 18.11±1.76 was significantly shorter than group A 22.0±2.41, p-value 0.0008(Table III)

Table III: Stratification for age for mean time elapsed till improvement(n=64)

Time (in days)	Group-A (n=32)		Group-B (n=32)		P value
Age:4-10 years	Mean	SD	Mean	SD	0.0001
	22.14	2.08	18.48	1.83	
Age: 11-15 years	22.00	2.41	18.11	1.76	0.0008

Discussion

Guillain-Barre syndrome (GBS) is an autoimmune disorder of peripheral nerves. Exact etiology is still debatable but known causes include post-infectious, post vaccination and autoimmune. Post infectious causes include gastrointestinal infections secondary to campylobacter jejuni and H.pylori while respiratory infections include mycoplasma and viral infections. Vaccination against influenza, rabies and conjugated meningococcal vaccines also resulted in this syndrome in few cases. Recently some association with zika virus infections has also been reported.[17]

Currently, IVIG is the treatment of choice for GBS in pediatric population. IVIG has proven role in GBS but it is an expensive drug and mostly given in severe GBS. In our study we also included all severe cases of GBS. IVIG is commonly given as treatment protocol at total dose of 2g/kg for 5 days but exact dose and duration is yet to be determined. In the past various studies regarding dosage of IVIG were done. Some case studies are available that involve single dose of IVIG.[18]

In literature, there are various studies regarding dose and duration of IVIG in GBS. A combined retrospective study was done in Toronto(Canada) and Ankara (Turkey) comparing 2 days and 5 days regime.[12] Patients from Canada received IVIG 1g/kg/day for 2 days while patients from Turkey received IVIG 400mg/kg/day for 5 days. Results showed faster recovery rate in patients who were given IVIG over 2 days as compared to 5 days, although cumulative dose remained same i.e 2 g/kg. Results from this study showed that mean time lapse till the improvement of functional grades was 17.4 $\pm$ 4.35 days sand 20.8 $\pm$ 5.2 days for 2 and 5 days IVIG treatment groups respectively. These findings are in agreement with our study having a significant difference in 2 groups in the form of improvement of disability grade.

Another study done in Germany comparing the effect of IVIG on GBS in 2 groups i.e 2 days as compared to 5 days treatment. In contrast to our study having patients of severe GBS only, they also included patients having disability grade 2 (unable to walk 5 meter without support) and above."The median time for improvement 1 point on disability score was 5 days in each group."[13]So there was no significant difference in the improvement of functional grades in both groups showing that duration of IVIG do not affect disease course. They also observed that short course of IVIG resulted in early relapses. However this small number of patients suggests low power of the said conclusion.

Side-effects of IVIG reported in our patients were mild although various side effects like liver and renal dysfunction, allergic reactions, aseptic meningitis and proteinuria are reported in adults when it is given in various neurological disorders.[19,20]However in our patient's data no significant side effects observed except fever and mild allergic reactions in few patients.

In accordance with the above studies and our results, the hypothesis **"**there is a difference in mean time lapse till improvement in functional grades in 2 days regime as compared to 5 days regime**"** is justified. However, some other local trials are still required so that our results may be validated. Total dose and duration of IVIG are areas of GBS treatment that still require further studies both at local and international levels which ultimately will benefit pediatric patients in the form of less morbidity. IVIG is an expensive drug and some further trials should be done regarding the total dose to lessen economic burdens on medical facilities in resource-constrained countries.

Conclusion

We concluded that mean time lapse till improvement of functional grades was significantly lower in patients administered 2 days regimen of IVIG as compared to 5 days in severe pediatric GBS. In our setup, it will be cost-effective and reduce hospital burden in the form of less hospital stay but further studies are still required.

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