

RESEARCH

HIGH AND LOW DOSE IVIG THERAPY IN GUILLAIN-BARRE-SYNDROME CHILDREN: A COMPARISON

*P. KARIMZADEH MD¹,
M. GHOFRANI MD²*

1. Pediatric Neurologist, Assistant Professor of Shaheed Beheshti University of Medical Sciences, Child neurology department, Mofid Children's Hospital, Tehran, Iran
2. Pediatric Neurologist, Professor of Shaheed Beheshti University of Medical Sciences, Head of Child neurology department, Mofid Children's Hospital, Tehran, Iran
Corresponding Author:
P. Karimzadeh MD
Tel: +98 21 22227033
Fax: +98 21 22220254
Email: Pkarimzadeh@yahoo.com

Abstract:

Introduction:

Acute inflammatory demyelinating peripheral neuropathy (Guillain-Barre-Syndrome) is by far the most common cause of immune-mediated peripheral nervous system disease in children; with the near disappearance of poliomyelitis, GBS is responsible for the great majority of cases of acute flaccid paralysis. So far, in several controlled studies, corticosteroids, plasmapheresis and IVIG have been utilized in pediatric patients, afflicted with GBS. Regarding IVIG therapy, two methods have been used; the high dose (1 gr/kg/day for 2 days), and the low dose (400mg/kg/day for 5 days). Review of literature shows that a faster rate of recovery can be accomplished in patients who receive total dose of IVIG in 2 days as compared to the dose being given over 5 days.

Materials & Methods:

In this study we have compared these two types of treatment in an investigation, conducted in the Mofid Children Hospital on pediatric patients who had sudden onset of acute flaccid paralysis, and were diagnosed as having GBS. Based on histories, physical examination and electrodiagnosis, subjects were divided in two groups, the high dose IVIG treatment, 1gr/kg/day for 2 days (experimental group), and the low dose IVIG treatment, 400 mg/kg/day for 5 days (control group). Statistical analyses were then carried out using the appropriate software.

Results:

Result of this study showed a faster rate of recovery for patients in the high dose IVIG group; in this group duration of weakness of limbs was shorter and returning of DTR was faster than in controls. In fact, in this type of treatment, the relationship between high dose IVIG therapy and drug side effects was not significant.

Conclusion:

Base upon the finding in the present study, we conclude that the high dose IVIG therapy is superior to low dose, in view of faster duration of recovery and shorter hospital stay.

Also we may infer that shorter hospital stay could be a factor in reducing of more nasocomial infection.

In conclusion, we suggest using high dose IVIG treatment of choice in GBS.

Keywords: Gullian Barre Syndrome-High dose, Low dose IVIG-comparison of two types of treatment

Introduction

The Guillain Barre' syndrome (GBS), a post infectious poly neuropathy, is by far the most common cause of immune- mediated peripheral nerve disease in children; with the near disappearance of poliomyelitis, this is responsible for the majority of cases of acute flaccid, paralysis. (1, 2, 3)

The first cases were recorded in 1859 by Landry, who noted that the disorder produces both motor and sensory symptoms, especially the former, which involves the distal parts of the limbs. Guillain, Barre and Strohl stressed the presence of albuminocytologic dissociation, of CSF in this condition.

GBS consists of four subgroups:

1. Sporadic GBS, the most common, (85% to 90%) (Acute inflammatory demyelinating peripheral neuropathy-AIDP)
2. Acute motor sensory axonal neuropathy (AMSAN)
3. Miller fisher syndrome
4. Chronic inflammatory demyelinating peripheral neuropathy (CIDP)

Characteristically it is symmetric. A prodromal respiratory illness or gastroenteritis occurs in approximately two-third of the patients. Elevation in the CSF protein content is typical, exceeding 45mg/dl in 88% of affected children; CSF cell count is usually normal and the EMG-NCV shows conduction block. (1, 2, 3)

Since GBS is the most common cause of acute flaccid paralysis in children, several large controlled studies have been conducted to determine the most effective therapies in pediatric patients. In clinical practice today, Plasmapheresis, IVIG and corticosteroids are routinely used, of which, IVIG treatment is safer and less traumatic for children. High dose IVIG¹ is another effective means of treating GBS. In this study we have assessed the use of high dose IVIG in the treatment of GBS patients, believing that it can be more effective than low dose IVIG² therapy. (1, 2, 3, 8, 9, 10) this method of treatment shortens the hospital stay and is consequently less expensive for patients (5, 6, 7).

Considering the fact that GBS is today the most common cause of acute flaccid paralysis in children in our country, and in view of the lack of any literature comparing the two types of treatments (high dose vs. low dose IVIG),

this study was conducted to determine which is more effective.

Materials and Methods

Subjects were 50 children presenting with the chief complaint of acute flaccid paralysis, to the pediatric neurology department of the Mofid childrens' hospital; all patients were admitted and appropriate investigations (history, physical examination, laboratory analyses and EMG-NCV) were carried out.

Only children with acute inflammatory demyelinating polyneuropathy were included in our study and those with acute motor-sensory axonal neuropathy, acute motor axonal neuropathy and Miller Fisher syndrome were excluded . Eventually our patients were randomly divided into 1-High dose IVIG treatment or experimental group (25 patients), and 2- Low dose IVIG treatment or control group (25 patients); the children were matched for age, sex, and grade of illness. SPSS and statistical software were used for analysis of data obtained.

Scaling:

To evaluate the severity of illness, 5 grades for GBS were defined:

Grade 1: Force of distal lower extremities 3/5

Force of proximal lower extremities 4/5

DTR of lower extremities decreased

DTR of upper extremities normal

Gag reflex, crying, phonation and swallowing normal

Grade 2: Force of distal lower extremities 3/5

Force of proximal lower extremities 3/5

Force of distal upper extremities 4/5

Force of proximal upper extremities 4/5

DTR of upper and lower extremities decreased (especially in lower E.)

Gag reflex, crying, phonation and swallowing normal

Grade 3: Force of proximal lower extremities 3/5

Force of distal lower extremities 2/5

Force of proximal upper extremities 4/5

Force of distal upper extremities 3/5

DTR of upper extremities decreased

DTR of lower extremities decreased or absent

Gag reflex decreased, crying and phonation weak and swallowing normal

1-High dose IVIG means 1 gr/kg/day for 2 days

2- Low dose IVIG means 400mg/kg/day for 5 days

Grade 4: Complete flaccid paralysis in lower extremities

Force of distal upper extremities below 2/5

Force of proximal upper extremities below 3/5

DTR of upper extremities one plus (+)

DTR of lower extremities absent

Gag reflex decreased, crying weak

Mechanical ventilation needed during hospital stay.

Grade 5: Complete flaccid paralysis in upper and lower extremities (flaccid quadriplegic)

DTR of upper and lower extremities absent

Gag reflex absent

Aphonic

Needs immediate mechanical ventilation

Results:

In the experimental group, the youngest patient was 8 months old and the oldest one 13 years (peak age between 2-5 years old). Among the controls, the youngest patient was 15 months and the oldest 14 years (peak age between 2-5 years old). (Table 1)

Table 1: Frequency of age in experimental and control groups

Age Groups	< 5years	> 5years	Total
High dose	12	13	25
Low dose	13	12	25
Total	25	25	50

P=0.77 NS

In the experimental group, 4 patients were female and 21 were male. In the control group, 5 were female and 19 male. Our study had a 5:1 male: female ratio, whereas other studies this ratio was 3:2 or 3:1 (table2).

Table 2: Frequency of sex in experimental and control groups

Sex Groups	Female	Male	Total
High dose	4	21	25
Low dose	6	19	25
Total	10	40	50

P=0.72 NS

All patients (experimental and control) fell into grades II, III, IV and V

Grade II: In grade II we had 10 patients (3 female and 7 male) in the experimental group and 11 patients (4 female and 7 male) in the control group. Bed /day time in the experimental group was under 5 days in 3 patients, between 5-9 days in 8 patients, and in 3 was 10-15 days. Duration of weakness in this group in lower extremities was 2-5 days in 7 patients and between 5-10 days in 3 patients. For controls, this duration was between 5-10 days in 10 patients and in 1 patient was over 10 days. In all patients in the experimental group, duration of weakness in upper extremities was between 2-5 days and in all the controls this was between 5-10 days. Duration of decreased, or absence of, DTR in lower extremities in the experimental group was 2-5 days in 9 patients, and between 5-10 days in one patient; in control group however this duration was between 5-10 days in one patient and over 10 days in 10 patients. Duration of decreased DTR in upper extremities in the entire experimental group was between 5-10 days, the time being 5-10 days in one patient of the control group and over 10 days in 10. No super imposed infections or drug side effects were observed in grade II.(tables 3-11)

Grade III: In grade III, we matched 7 patients from the experimental group with 8 controls. In this grade all patients in the experimental and control groups were male. Bed/day time in all patients of the experimental group was 5-9 days, while for the controls, it was between 5-9 days in 3 patients and between 10-15 days in 5. Of 7 patients in the experimental group, 5 patients had normal(or mildly decreased) gag reflex at admission, 2 of the patients this reflex was decreased and after treatment, the reflex became normal, without any need or mechanical ventilation. In 8 patients of the control group, 7 had normal gag reflex at admission, while 1 patient had reduced gag reflex, requiring mechanical ventilation. Duration of weakness in the lower extremities of 6 patients in the experimental group was between 2-5 days, while in one it was 5-10 days. In all of the controls, this duration lasted between 5-10 days. Duration of weakness in the upper extremities in the experimental group was between 2-5 days, being 2-5 days in 2 patients of the control group and between 5-10 days in 6. The

duration of decreased or absence of DTR in lower extremities in the experimental group was between 2-5 days in 5 and 5-10 days in 2 patients; in all in the controls this duration was over 10 days. Decreasing in the upper extremities in all individuals of the experimental group took 5-10 days and in all of the patients in control group was more than 10 days.(Tables 3-11)

Grade IV: 4 patients (3 male, 1 female) of experimental group were matched to 3 of the controls (2 male, 1 female). Bed/day time in one patient of the experimental group was between 5-9 days, while in the controls, this duration was 10-15 days in 2 patients and over 15 days in one. In the experimental group, 4 patients had decreased gag reflex and following treatment, in 3 patients this condition normalized in 2 days, without any need for mechanical ventilation. In 1 patient however, who did need mechanical ventilation this reflex returned in 2-5 days. In 3 of the controls, 2 needed mechanical ventilation, their gag reflex returning in 2-5 days; in the third child, gag reflex returned spontaneously in less than 2 days. The duration of weakness in lower extremities in the experimental group was between 2-5 days in one patient and between 5-10 days in 3 patients, while in the controls, in 2 patients this was between 5-10 days and in one patient was over 10 days. Duration of weakness in the upper extremities in all patients of the experimental group lasted 2-5 days, whereas in 2 of the controls this duration was between 2-5 days in one. Duration of decreased, or absence of, DTR in lower extremities in all 4 patients of the experimental group was between 5-10 days, while it was over 10 days in all the controls of this grade. The duration of decreased, or absence of, DTR in upper extremities in all 4 patients of the experimental group was between 5-10 days, but lasted over 10 days in 3 of the controls. There was no occurrence of either superimposed infections or any drug side effects in any patients of groups II, III, or IV.(tables 3-7)

Grade V: All those classified as GBS grade V, were matched for degree of weakness, age and sex; these included 4 patients of the experimental group and 3 controls, all males. Bed/day time in the experimental group in 3 patients was 5-9 days, while one patient stayed for 14 days. Upon admission, all patients in the experimental and control groups had decreased gag reflex,

for which they were transferred to ICU and connected to mechanical ventilation. Of 4 patients in the experimental group, 2 had gag reflex of four patients in experimental group, two of them had gag reflex after 2 days whereas in other 2 patients, this reflex returned within 2-5 days. Of the 3 controls, in one gag reflex returned in 5 days and in the other two it returned after 7 days. While the duration of weakness in the lower extremities of 4 patients in the experimental group lasted 5-10 days, in the 3 controls of this grade it was over 10 days. Duration of weakness in the upper extremities in all patients of experimental group was between 2-5 days, being between 5-10 days in all controls of this grade. Duration of decreased, or absence of, DTR in the upper extremities in all individuals of the experimental group was 5-10 days, while in the corresponding controls it was over 10 days. Complications related to super imposed infection occurred in 2 individuals of the experimental group, whereas all 3 controls in this grade were affected by this problem. Symptoms of fever were observed in patients suffering from infection, but these were not related to any side effects. No patients complained of headache or vomiting, except for one control, who developed high blood pressure while receiving assisted ventilation, and was treated with Diazoxide. (table 3-11)

Table 3: Frequency of grading in experimental and control groups

Groups \ Grade	Experimental	Control	Total
II , III	17	19	36
IV , V	8	6	14
Total	25	25	50

P=0.75 NS

Discussion

Hospital stay in patients receiving high dose IVIG treatment (experimental group) was shorter than low dose IVIG treatment (controls). The relationship between high dose IVIG therapy and the shorter bed/day time was significant. (Table 4) $P < 0.05$ ($P = 0.0198$). Our findings are similar to those of other studies (4,5).

Table 4: Frequency of bed/day time in experimental and control groups

Bed/day times \ Groups	<10days	>10days	Total
Experimental	20	5	25
Control	11	14	25

$X^2 = 5.43$ $df = 1$ $P = 0.0198$

Of 10 patients with decreased gag reflex in the experimental group, 5 needed mechanical ventilation, while in 5 others, this reflex returned with just drug therapy without any need for assisted ventilation (Tables 5,6). Of 7 controls with decreased gag reflex, 6 had to have mechanical ventilation, while only one recovered with just continuation of drug therapy (Tables 5,6).

Table 5: Frequency of need for mechanical ventilation in experimental and control groups

Need of M.V. / Groups	Yes	No	Total
Experimental	5 (30%)	10 (70%)	15 (100%)
Control	6 (78%)	7 (22%)	13 (100%)

Non significant P=0.7

The relationship between time of returning of gag reflex and the type of treatment (high dose /VS/ low dose IVIG) was not statistically significant (P=0.1544) (Table 6)

Table 6: Frequency of gag reflex return in experimental and control groups

Returning of gag R. / Groups	< 5days	>5days	Total
Experimental	10 (100%)	0 (0%)	10 (100%)
Control	5 (72%)	2 (28%)	7 (100%)

Non significant P=0.1544

Duration of weakness of lower extremities was much shorter in patients, were given high dose IVIG therapy. (Table 7) (P<0.0001); this finding corresponds with the results of other studies (4-7).

Table 7: Frequency of duration of weakness in lower extremities in experimental and control groups

Days Groups	< 5days	>5days	Total
Experimental	14	11	25
Control	–	25	25

$X^2=16.76$ $df=1$ $P<0.0001$

Similar results were obtained for the in upper extremities; duration of weakness in arms was remarkably shorter in those patients who received high dose IVIG (Table 8) ($P<0.0001$). These results are in agreement with those obtained in other studies (4,5).

Table 8: Frequency of duration of weakness in upper extremities in experimental and control groups

Time Groups	< 5days	>5days	Total
Experimental	25	–	25
Control	–	25	25

$X^2=35.79$ $df=1$ $P<0.0001$

In patients receiving high dose IVIG therapy, the duration of decreased, or absence of, DTR in both upper and lower extremities was significantly shorter (table 9-10) ($P<0.0001$); findings correlate with studies from other countries (4,5,6).

Table 9: Frequency of decreased, or absence of, DTR in lower extremities in experimental and control groups

Time Groups	< 10days	>10days	Total
Experimental	25	–	25
Control	–	25	25

$X^2=46.08$ $df=1$ $P<0.0001$

Table 10: Frequency of duration of decreased, or absent, DTR in upper extremities in experimental and control groups

Time / Groups	< 10days	>10days	Total
Experimental	25	–	25
Control	1	24	25

X²=42.38 df=1 P<0.0001

-All patients with super imposed infection, (in both the experimental and control groups) had to be transferred to ICU, needing mechanical ventilation. Since no nosocomial infection was found in other patients, the relationship between superimposed infection and the type of treatment (high dose or low dose IVIG) was not significant (Table 11) (6)(P =1)

Table 11: Frequency of drug side effects in experimental and control groups

Drug side effects / Groups	Yes	No	Total
High dose	2 (8%)	23 (92%)	25 (100%)
Low dose	4 (16%)	21 (84%)	25 (100%)

P=1

Fever was seen only in patients suffering from superimposed infections; it was not a side effect of the drugs.

The relationship between fever and the type of treatment (high dose or low dose IVIG therapy) was not significant (Table 11) (P=1); Other studies have not reported any complications and drug side effects(6).

The relationship between the type of treatment (high dose or low dose IVIG therapy) and hypertension (drug side effect) was not significant (Table 11) (6). Five patients of grade V (3 control, 2 experimental), who suffered superimposed infection had to be transferred to ICU, needing mechanical ventilation; the infection, nosocomial in nature, was not observed in the other grades, and the relationship between superimposed infection and the type of treatment was not significant (Table 11).

Conclusion

Based on the findings of the present study, we conclude that in view of shorter duration of recovery and reduced hospital stay, high dose IVIG therapy is superior to the low dose one; apparently the reduction in time of hospital stay prevented further occurrence of cases of nosocomial infections.

Also, duration of weakness in both upper and lower extremities was significantly shorter in the group of patients receiving high dose IVIG therapy. Lastly no association was found between drug side effects and type of treatment. (High dose/Vs/Low dose)

In conclusion we highly recommend high dose IVIG treatment as the treatment of choice in children with GBS syndrome.

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