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PROJECT REPORT

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PROJECT REPORT

TITLE

Intravenous Immune globulin vs Plasma exchange in Guillain Barre' Syndrome – a 5 year retrospective study (1995-2000)

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CERTIFICATE

I, Dr.Ashalatha.R hereby declare that I have done this project under report and the conclusions are my own.

Signature .....

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Forwarded. She has carried out the project under report.

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Dr.Ashalatha.R

CONTENTS

INTRODUCTION

Guillian Barre' Syndrome, an inflammatory demyelinating polyradiculoneuropathy, is one of the causes of areflexic quadriparesis. Artificial ventilation becomes mandatory in about 20% of patients. Although functional recovery is the rule. 15% of the pts have residual deficits. Hence specific therapies have been tried in addition to the various supportive management.

Plasma exchange as well as intravenous immune globulin has been tried in various studies. Both are indicated in patients with major deficits and who are still in the first weeks of the illness.

Although both are found to be equally effective, immunoglobulin has important practical advantages, as it is freely available, can be administered without delay, it is safe and well tolerated and there is no risk of disease transmission. On the contrary, PLEX is difficult to perform especially in children and elderly, is contra-indicated in pts with cardiovascular instability and is accompanied by many untoward side effects like hypotension, cardiac dysrrhythmias, acute pulmonary oedema, hypoalbuminemia, dyselectrolytemia, thrombocytopenia etc.

REVIEW OF LITERATURE

GBS is a non-seasonal illness that affects persons of all ages. With the decline of acute anterior poliomyelitis, GBS is the most common acute paralytic disease in Western countries. The annual incidence is 1.8 per 100,000 population. Incidence rate increase with age from 0.8 in those younger than 18 years to 3.2 for those 60 years and older

Approximately 2/3 of patients report a preceding event, most frequently an upper respiratory or gastrointestinal infection, surgery or immunization, 1-4 weeks before the onset of neurological symptoms.. The agent responsible for the prodromal illness frequently remains unidentified. Specific infections linked to GBS include CMV, EBV, VZV, HAV, HDV and Mycoplasma. The most common identified bacterial organisms linked to GBS and particularly its axonal forms is Campylobacter jejuni, a gram-negative rod that is a frequent cause of bacterial enteritis world wide. Evidence of C. jejuni infection from stool cultures or serological tests was found in 26% of patients with GBS admitted to hospitals in the United Kingdom, compared with 2% of case controls [1]. Retrospective studies from the United States, Holland, Germany and Australia report serological evidence of recent C. jejuni infection ranging from 17-39% of patients with GBS.C. jejuni may play an even greater role in Northern China where infection rates of 76% in patients with AMAN & 42% in patients with AIDP were found [2].

Epidemiological data suggested a slight increase in cases of GBS following the 1976 A/ New Jersey influenza vaccine, although no excess risk of developing GBS was seen with subsequent influenza vaccines. Other vaccines, drugs including Streptokinase, Suramin, Gangliosides & Heroin and Hymenoptera stings have been associated in a few cases. Several cases have occurred in immunocompromised hosts with Hodgkin's lymphoma or in pharmacologically immunosuppressed patients with solid organ and bone marrow transplantation.

Patients may initially present with paraesthesias, other sensory symptoms with weakness or weakness alone . The fairly symmetrical weakness of the lower limb ascends proximally over hours to several days to involve arm,facial and pharyngeal muscles and in severe cases respiratory muscles. Less often, weakness may begin in proximal and cranial nerve innervated muscles. Its severity varies from mild involvement, in which patients are still capable of walking unassisted, to quadriplegia. Hyporeflexia or areflexia occurs by 1-4 weeks into the illness; if it continues longer, the condition is termed either sub acute inflammatory demyelinating polyradiculoneuropathy ie if progression continues for 9-10 weeks or CIDP if there is chronic progression or multiple relapses. Cranial Nerve involvement ranges from 45-75% in different series. The proportion of patients developing respiratory failure & requiring assisted ventilation seems to increase with age and ranges from 12% in epidemiological

series to 23 % in hospital based series. Autonomic dysfunction of various degrees has been reported in 65% of patients [3]

CSF examination & serial electrophysiological studies are needed for confirming the diagnosis of GBS. Other lab studies are of limited value. Mild transient liver enzyme elevation without obvious cause are found in approximately 1/3 rd of patients . Hyponatremia is seen most frequently in ventilated patients because of inappropriate secretion of ADH. Deposition of immune complexes may rarely lead to glomerulonephritis & results in microscopic haematuria & proteinuria. In first week of neurological symptoms, the CSF protein may be normal, it then becomes elevated on subsequent examinations. In approximately 10 5 of cases , the CSF protein may be normal throughout the illness.Abnormalities of electrophysilogical studies are found inapproximately 90% of established cases & reflect an evolving picture of multifocal demyelination associated with secondary axonal degeneration. The most common electrophysiological abnormalities include prolonged distal motor & F wave latencies, absent or impersistent F waves, conduction block, reduction in distal CMAP amplitudes with or without temporal dispersion and slowing of motor conduction velocities [4]). Electro diagnostic studies performed in patients enrolled in the North American GBS study found abnormalities of distal motor latencies & F-wave latencies in approximately one half of patients studied within 30 days of onset. The value of specific serological tests in the diagnosis of GBS is limited. Elevated serum antibodies to Mycoplasma, CMV or

C. Jejuni can pinpoint the preceding infection. Preceding Campylobacter infection has been linked to axonal variants, worse outcome & high titre of anti-GM1, GD-1b & GD1a ganglioside antibodies of the IgG class [5] . Elevated anti GQ 1b ganglioside antibodies are consistently found in Miller Fisher Syndrome.

Among specific therapeutic interventions aimed at mitigating the harmful effects of autoantibodies, plasma exchange & high-dose intravenous immune globulin (IVIG) have been shown to be equally effective.

The selective removal of plasma with return of corpuscless was first carried out early in this century by Fleig and Abel et al[6]. The term plasmapheresis was first coined by Abel & colleagues in 1914. Among the various neurological disorders, therapeutic plasma exchange was first reported to be tried and found useful in Guillain-Barre Syndrome by Brettles et al in 1978 [7]. This was followed by several reports of small & uncontrolled trials as well as by two large, prospective multicentric randomized controlled clinical trials [8-12]. They have definitely proved that plasmapheresis produces significant and substantial benefit in patients suffering from GBS, particularly in those with severe disease and in those who require ventilatory support. TPE improves the clinical condition, hastens the milestones of improvement and reduces the duration of ventilation.

The work of Koshki et al has greatly clarified the pathogenesis of GBS.[13] Activated T lymphocytes and macrophages are principle sources of cytokines including tumor necrosis factor alpha (TNF α), a primary mediator of inflammation. TNF α is known to induce autoimmune tissue damage of the

nervous system [25]. There is also good evidence that TNF α is capable of inducing selective and specific damage to myelin in vitro[26], which may contribute to the eventual degeneration of axons in long standing demyelination. TNF α concentrations were found to be elevated in 57.1% of GBS patients and the level was found to decrease following plasma exchange[27]. In a prospective study of 21 patients with GBS admitted to SCTIMST, Trivandrum, who underwent plasma exchange serum IgG titers to GD1b before, during as well as following plasma exchange were measured by ELISA. In 10 out of 18 patients this antibody was present in high titers prior to plasma exchange and the antibody titers in these 10 patients decreased following PE[28].

Through the use of sensitive compliment consumption techniques antiperipheral nerve myelin antibodies were detected in the first week of active phase of illness and in the subsequent 1-3 weeks, the titre began to decline. Disappearance or very negligible titer correlated with cessation of disease progression and onset of improvement. This antibody has been found to be IgM. Removal of this humoral factor by plasma exchange is the rationale in the treatment of GBS by plasma exchange.

Highly informative analysis performed by the GBS study group[14] of 245 patients demonstrated that TPE is both efficacious and safe in the treatment of GBS. A multivariate analysis of data from that study proved that 4 factors

correlated with the outcome, even though the most important factor was treatment with plasma exchange. They are:

1) Mean amplitude of compound muscle action potential of 20% of normal or less.
2) Older age.
3) Interval from onset of disease to bed bound state of 7 days or less.
4) Progression of disease to respiratory paralysis with need for ventilator support.

It is advisable to initiate plasmapharesis as soon as possible once the clinical severity dictates it, preferably within the first one week. Patients on assisted walking who are steadily deteriorating under observation, those who have become bed bound and ventilator bound are indicated for plasma exchange. Another significant observation was that patients who received TPE on continuous flow machine fared better than those on intermittent flow machine, who in turn were better than untreated patients. Replacement fluids do not affect the outcome of TPE according to the various study groups. The duration of ventilation was also found to be shortened by TPE in the French study. In fact, they demonstrated a better outcome with TPE as measured by the time to attain independent ambulation. The reason was the difference in the study design – initiation of TPE in the first 2 weeks to illness by them as opposed to anytime

within the first 4 weeks in the North American study. The earlier the initiation of plasmapheresis, the greater its efficacy.[15] Plasma exchange is associated with early relapse or exacerbation in 6-11% of patients with GBS[16-20]. It occurs within 15-30 days of initiation of treatment. Persistence of anti PNM antibodies at least in low titers is responsible for this phenomenon. Hence, the relapse, which occurs only after the stopping of plasma exchange, is an additional evidence of the therapeutic efficacy of plasma exchange. Another mechanism suggested is the rebound phenomenon of heightened antibody production once its serum level falls during PE. Treatment of this phenomenon is by additional plasma exchange. The first report of plasmapheresis from India was by Tharakan et al. [21]. Later there were many other studies showing its beneficial effect in GBS[22-24].

The other preferred modality in the treatment of GBS is intravenous immuneglobulin. The mechanism of action of the same is through supply of idiotypic antibodies, neutralization of auto antibodies and suppression of antibody production. IVIG preparation from normal humans contain low titre antibody against wide spectrum of human proteins and anti idiotypic antibodies. Anti idiotypic antibodies have the potential to bind and neutralize pathogenic antibodies preventing their interaction with auto antigens. It also suppresses pathogenic cytokines like, IL-1, TNF α and IL-1 β. It also forms complexes with C3 fragments and inhibit the uptake of C3b and C4b fragments. The

complications noted with IVIG are very few including headache, chills, myalgia, chest discomfort, nausea, vomiting, skin reactions like urticaria, pruritus, etc. Severe anaphylaxis can occur in patients with deficient IgA. Other complication to be anticipated is hyperviscocity and thromboembolic events especially in bed bound patients, patients with DVT etc. Acute tubular necrosis can occur in patients with preexisting renal dysfunction.

IVIG when compared to plasma exchange has important practical advantages, as it is freely available ,can be administered without delay, it is safe and well tolerated and there is no risk of disease transmission. The relative efficacy of plasma exchange and IVIG for the treatment of GBS has been compared in many studies. In the Dutch study [29] in 150 patients after treatment, strength improved by 1 grade or more in 34% of those treated with plasma exchange as compared with 53% of those treated with IVIG ($p=0.024$). The median time to improvement by I grade was 41 days with plasma exchange and 27 days with IVIG therapy ($p=0.05$). The IVIG group had significantly fewer complications and less need for artificial ventilation. The duration of hospital stay was less by 14 days in the IVIG group. The duration of intubation was also 7 days less in the IVIG group when compared to the PLEX group.

In the SandoGlobulin Study group[30] trial, which compared plasma, exchange, IVIG and combined treatment in 379 patients (121 in the plex group,

130 in the IVIG group and 128 received both plex and IVIG), the outcome measures were same as that of Dutch study. No significant difference in outcome was observed in different groups at 4 weeks and 48 weeks.

In the Canadian study group[31] which again was a smaller trial comprising 44 patients, the outcome measures were comparable to Dutch Study group.

OBJECTIVES

The aim of the present study was to compare the relative efficacy of plasma exchange with intravenous immuneglobulin for the treatment of Guillian Barre' Syndrome.

MATERIALS AND METHODS

Our study group comprised 112 patients with GBS admitted in our hospital during the time period May 1995-March 2000. Only 97 patients could be selected from this group – 6 patients lost follow up, 4 patients did not fall into our study age group and in 5 patients, treatment had to be with held due to major complications. The two groups were comparable with regard to age, sex, and duration between onset of symptoms and start of treatment as well as functional grade at entry.

Eligibility Criteria

- Patient should fulfill the criteria for acute GBS.
- Should enter the study within 2 weeks of the onset of disease.
- Should not have received any form of treatment from outside (especially immunosuppressants).
- Should not be able to walk independently for 10 m/more.
- Age <4 yrs excluded.
- No history of GBS in the past.
- No history of severe allergic reaction to properly matched blood products.
- Patient should not have known selective IgA deficiency.
- Pregnancy is a contraindication.
- Severe concurrent medical disease is a relative contraindication.
- Patients who lost follow up after 6 months were excluded.
- Nerve conduction study, CSF study and Urine porphobilinoge for all patients.

TREATMENT RECEIVED

PLASMA EXCHANGE

100 ml of plasma/ kg body weight in approximately 5 sessions within 7-14 days.

Replacement fluid is 5% albumin/saline.

INTRAVENOUS IMMUNE GLOBULIN

0.4 g/kg/day - 5 days

ASSESSMENT OF MOTOR FUNCITON

(at entry and during follow up)

HUGHE'S 7 – point scale

0 - healthy.

1 – minor symptoms and signs – fully capable of manual work.

2 – able to walk > 10 m without assistance.

3 – able to walk > 10 m with a walker / support.

4 – bed ridden or chair – bound.

5 – requiring assisted ventilation.

6 – dead.

FOLLOW UP SCHEDULE.

- Functional score (as mentioned above) & MRC power score was assessed – 6 muscle groups on either side + trunk + neck + respiratory status was assessed

  - 3 times a week during first 2 weeks.
  - Once a week in the next 2 weeks.
  - At 3 months.
  - 6 months.
  - 1 year.

OUTCOME MEASURES

Improvement by one/more grade on the functional scale 4 weeks after completion of the treatment.

The secondary outcome measures were the time required to improve by at least one functional grade & the time required for the patient to regain the capacity for independent locomotion.

STATISTICAL ANALYSIS

The mean value between the two treatment groups were compared using the Chi-square test.

The outcome which was assessed by grades were compared by a non-parametric test – Mann – Whitney U test.

A p value of < 0.05 was considered significant, a confidence interval of 95% was also calculated for each variable associated with outcome.

OBSERVATIONS

ENMG1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	AX+ A+D	78	80.4	80.4	80.4
	Dem	19	19.6	19.6	100.0
	Total	97	100.0	100.0	

Comparison of means between treatment groups

Group Statistics

	ID	N	Mean	Std. Deviation	Std. Error Mean
fnc status-entry	1	48	4.35	.48	6.98E-02
	2	49	4.16	.55	7.90E-02
AGE	1	48	35.17	16.19	2.34
	2	49	33.76	20.28	2.90
DURN	1	48	6.75	4.21	.61
	2	49	8.14	4.55	.65
improv by 1 grade	1	48	37.52	33.98	4.90
	2	49	29.39	30.96	4.42
independent	1	48	136.29	79.02	11.41
	2	49	108.51	70.38	10.05
hosp stay	1	48	26.10	18.33	2.65
	2	46	16.78	12.56	1.85
Ventilator days	1	22	20.59	13.62	
	2	17	17.71	7.36	

1- PLEX gr
2 - IVIG gr

Treatment groups

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	plasma	48	49.5	49.5	49.5
	IVIG	49	50.5	50.5	100.0
	Total	97	100.0	100.0	

SEX

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	61	62.9	62.9	62.9
	female	36	37.1	37.1	100.0
	Total	97	100.0	100.0	

Fnc status-entry

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3	4	4.1	4.1	4.1
	4	64	66.0	66.0	70.1
	5	29	29.9	29.9	100.0
	Total	97	100.0	100.0	

ENMG

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Axonal	64	66.0	66.0	66.0
	Demyelin	19	19.6	19.6	85.6
	A+D	14	14.4	14.4	100.0
	Total	97	100.0	100.0	

✓ Comparison of baseline parameters between groups based on ENMG findings

Parameter		No. of pts.	Mean	S.D	t statistic	P Value	95% Confidence Interval	
							Lower limit	Upper limit
Fnc status at entry	D	78	4.17	0.49	3.673	< .001	-0.72	-0.21
	A	19	4.63	0.50				
Age	D	78	35.44	18.72	1.073	0.286	-4.27	14.30
	A	19	30.42	16.22				
Duration	D	78	7.60	4.09	0.670	0.504	-1.49	3.01
	A	19	6.84	5.68				
Improvement by gr 1	D	78	28.03	23.84	3.486	0.001	-43.16	11.84
	A	19	55.53	50.86				
Independent ambulation	D	78	108.32	61.47	3.943	<0.001	-106.98	-35.33
	A	19	179.47	100.46				
Hospital stay	D	75	18.31	12.59	-4.122	<0.001	-23.72	-8.29
	A	19	34.32	22.75				
Ventilator-days	D	75	16.50	8.95	-2.344	0.025	-15.85	-1.15
	A	19	25.00	13.58				

D - demyel.
A - Axonal.

✓ Comparison of functional status ranks between 2 treatment groups

Treatment Group	Number	Mean Rank	Mann Whitney	P Value
PLEX	48	52.97	98.50	0.097
IVIG	49	45.11		

✓ **Between EMG groups**

	Number	Mean Rank	Mann Whitney	P Value
EMG1	78	44.89	420.50	<0.001
EMG2	19	65.87		

Comparison of means based on EMG status

Group Statistics

	ENMG1	N	Mean	Std. Deviation	Std. Error Mean
fnc status-entry	1.00	78	4.17	.49	5.60E-02
	2.00	19	4.63	.50	.11
AGE	1.00	78	35.44	18.72	2.12
	2.00	19	30.42	16.22	3.72
DURN	1.00	78	7.60	4.09	.46
	2.00	19	6.84	5.68	1.30
improv by 1 grade	1.00	78	28.03	23.84	2.70
	2.00	19	55.53	50.86	11.67
independent	1.00	78	108.32	61.47	6.96
	2.00	19	179.47	100.46	23.05
hosp stay	1.00	75	18.31	12.59	1.45
	2.00	19	34.32	22.75	5.22
Ventilator days	1	75	16.50	8.95	
	2	19	25.0	13.58	

Comparison of outcome between treatment groups

Parameter	PLEX -1 IVIG-2	No. of pts	Mean	S.D	t value	P Value	95% Confidence Interval	
							Lower limit	Upper limit
Fnc status at entry	1	48	4.35	0.48	1.808	0.074	-2.30	56.93
	2	49	4.16	0.55				
Age	1	48	35.17	16.19	0.378	0.706	-6	8.82
	2	49	33.76	20.28				
Duration	1	48	6.75	4.21	-1.563	0.121	-3.16	0.38
	2	49	8.14	4.55				
No of days for improve by gr 1	1	48	37.52	33.98	1.233	0.221	-4.97	21.23
	2	49	29.39	30.96				
Independent ambuln	1	48	136.29	79.02	1.829	0.070	-2.37	57.93
	2	49	108.51	70.38				
Hospital stay	1	48	26.10	18.33	2.864	0.005	2.86	15.78
	2	49	16.78	12.56				
Ventilation -days	1	22	20.59	13.62	0.787	0.436	-4.54	10.31
	2	17	17.71	7.36				

	PLEX	IVIG	Total
I Gr 1 improv < 28 days	27(56.3%)	37(75.5%)	64
II Gr 1 improv > 28 days	21(43.8%)	12(24.5%)	33
	48	49	97

Chi-square value-4.007
P=<0.05

RESULTS

Of the total 97 patients evaluated with respect to eligibility there were 48 patients (49.5%) in PLEX group & 49 patients (50.5%) in IVIG group. There were 61 males (62.9%) & 36 females (37.1%) among them. The mean age of the study population was 35.17 in the PLEX group & 33.76 in the IVIG group. The duration of the illness before instituting treatment was also comparable in the 2 study population- mean was 6.75 days in the PLEX group & 8.14 in the IVIG group (p value- 0.121). So also the functional status ranks at entry was a mean of 52.97 in PLEX group & 45.11 in the other group which was again comparable (p=0.097)

Primary outcome

In the PLEX group, 27 patients (56.3%) improved by 1/more functional grades within 4 weeks (28days) as compared with 37 patients (75.5%) in the IVIG group, the difference being 19.2% ($p<0.05$)

Secondary outcome

When the number of days needed for independent ambulation was looked into, the mean for the PLEX group was 136.29 and for IVIG group, 108.51 (p=0.070), there was no significant difference between the 2 groups. So also the number of days spends in the hospital were 26.10 in the first group versus 16.78 in the 2nd

group (p-0.005), which was significantly higher in the PLEX group. This may be accounted for by the higher complications and the need for ventilator care in this group. When the number of days of ventilator care was looked into, a mean of 20.59 in the PLEX group & 17.71 in the IVIG group was observed (p-0.436), the difference was not significant between the groups. Another factor, which predicted the outcome to some extent was the type of abnormality in ENMG, the demyelinating group was compared with the axonal type, the axonal group faired poorly in all the parameters i.e. in time taken for improvement by grade I (P=0.001), time taken for independent ambulation (p<0.001), the number of days spend in the hospital (p<0.001) & number of days in ventilator (p=0.025).

Complications

In the plasma exchange group 4 patients were lost for follow up, 4 patients did not fall into the age group criteria, and major complications were observed in 5 patients (profound hypotension in 3 patients which warranted stopping of treatment, 2 patients expired, 1 following a cardiac arrest and the other following acute pulmonary oedema). Minor complications such as correctable hypotension (4 patients), hypoalbuminemia (2 patients), haemolysis with jaundice (1patient) etc were also noted in the plasma exchange group.

In the IVIG group 2 patients were lost for follow up, minor complications like fever, rashes, chills, etc. were noted but treatment could be completed successfully in all these patients. None of the patients who received immune globulin developed any major complications.

DISCUSSION

In this trial we compared the efficacy of treatment with IVIG & PLEX in patients with GBS. The study revealed that immune globin was as effective as PLEX, but that significantly more patients in the immune globulin group reached the main outcome measure of improvement by 1/more grades on the functional scale by 4 weeks. There was a difference of 19.2% in favour of IVIG treatment ($p<0.05$). As is clearly evident from the study, the complications associated with IVIG treatment is also markedly low when compared with the PLEX group. This would again reflect on the number of days spend in the hospital, a mean of 26 days in the PLEX group vs 16 days in the IVIG group ($p=0.005$). The median time until the recovery of independent locomotion was 28 days less in the IVIG group than in the PLEX group ($p=0.070$). In addition, the mean period of intubation was only 4 days less in the IVIG group compared to the PLEX group ($p=0.436$), the difference was not statistically significant. Another observation was that the axonal pattern group showed a poor outcome in both primary as well as secondary outcome measures whatever treatment they have been subjected to.

With regards to the efficacy of the treatment strategies, it is important to note that IVIG is safe & easy to use. PLEX presented practical problems similar to those identified in previous trials. In 15.5% of patients, one or more sessions had to be discontinued for clinical reasons, as compared with 10% in the North American trial, 16% in Dutch group & 18% in the French trial. If we compare

the efficacy of PLEX group, in North American trial, 52% of patients improved by 1 functional grade by 4 weeks, 34% did the same in the Dutch trial & in our study 56% improved by 1 functional grade with in 28 days.

With respect to secondary outcome measures, i.e. the recovery of independent ambulation was not significantly different in the 2 groups as was observed in the North American, French & Dutch trials too.

CONCLUSION

In conclusion, this study revealed that plasma exchange was as effective as immune globulin, but significantly more patients in the immune globulin group showed improvement by 1 or more grades on the functional scale by 4 weeks as compared to plasma exchange group. But recovery with independent ambulation was not significantly different in the two groups. The complication associated with immune globulin treatment was also markedly low when compared to the plasma exchange group.

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PROFORMA

1. Name _____

2. Age (dd/mm/yy) --/--/--

3. Sex _____ (1=male, 2=grade)

4. Body weight _____ (kg)

5. Occupation _____

6. Duration between onset of illness & start of treatment _____

7. Functional status at entry _____

7–point scale

MRG GRADING

UL - Proximal

- distal

LL - proximal

- Distal

Trunk –

Neck -

Respiratory status

Cranial nerve involvement

7. ENMG study

8. LP CSF study

9. Required ventilatory assistance or not

10. Treatment received

11. Functional status during the post treatment period

a) 3 times a week for the initial 2 weeks

i)

ii)

iii)

iv)

v)

vi)

b) Once a week for the next 2 weeks

i)

ii)

c) At discharge (around 4-6 weeks)

d) At 3 months

e) At 6 months

f) At 1 year

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