RESEARCH ARTICLE

INTRAVENOUS IMMUNOGLOBULIN PER SE OR COMBINED WITH INTRAVENOUS METHYLPREDNISOLONE IN CHILDREN WITH GBS; COMPARING THE EFFECTS

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Abstract

Objective

Guillain-Barre syndrome (GBS) is the most common cause of acute neuromuscular paralysis in children, its pathogenesis most probably involving an autoimmune response to Schwann cell or peripheral nerve myelin antigens. Steroid regimes improve demyelinating diseases such as chronic GBS. We assessed the benefit of high dose methylprednisolone (MP) combined with Intravenous immunoglobulin (MP-IVIG) and compared the effects with those of IVIG per se in children with GBS.

Materials& Methods

Thirty-six children, aged between 1-12 years were randomized to receive IV MP 20mg/kg/day combined with IVIG 400 mg/kg/day (MP-IVIG) or IVIG per se at same dose for 5 days. All patients were diagnosed by standard clinical criteria and entered the trial within less than 2 weeks of the onset of neurological symptoms. All patients were too weak to walk. Functional grade (FG) was at 3 or more (able to walk with support).

Results

In the MP-IVIG group, FG improved at least one grade after 5 days of treatment ($P<0.05$), while those who received only IVIG had no significant improvement in their FGs after 5 days of treatment ($P<0.2$). The main outcome result remained significantly in favor of the MP-IVIG treatment group.

There was no significant difference in improvement of one or more FG between the groups, after 4 weeks of treatment (secondary outcome).

The median time required to improve one FG was 12 days in MP-IVIG as compared with 21 days in IVIG per se ($P<0.5$), and the median time required to reach the stage of walking independently (FG=2) was 36 days in MP-IVIG as compared to 43 days in IVIG per se ($P<0.03$).

Conclusion

This study suggests that combined treatment with MP-IVIG in children with GBS does cause rapid improvement in the acute phase, but does not result in any significant difference in the long term outcome.

Keywords: Guillain-Barre Syndrome, 6-Methylprednisolone, IVIG, Children

Introduction

GBS is a demyelinating disease of peripheral nerves which causes flaccid paralysis,

autonomic dysfunction, and minor sensory symptoms (1, 2). Despite modern intensive care and respiratory support, the mortality rate is approximately 5% and the rate for permanent weakness is 20% (3, 4, 5, 6).

Encouraged by the results of treatment with high dose methylprednisolone in adult patients with acute inflammatory demyelinating polyneuropathy (7,8), we undertook a study of this treatment in children with GBS. We aimed at evaluating the effect of treatment with the MP-IVIG combination in children with GBS and to compare its effect with that of IVIG used alone.

The aims of this study were to determine whether there is an improved outcome with MP-IVIG and whether this treatment is safe in GBS patients.

Materials & Methods

Thirty-six children, aged between 1 to 12 years were selected during 18 months, based on recommended clinical criteria, which were progressive motor weakness affecting more than one limb with or without cranial nerve involvement, areflexia, and absence of pleocytosis within 2 weeks of the onset of weakness. They were admitted to the Mofid Pediatric Hospital;

laboratory studies included routine testing of blood, urine, and cerebrospinal fluid, serum IgA measurements. No patients had IgA deficiency. Electromyography was performed after the second week of disease.

The degree of motor function was expressed on a 7-point functional grade (FG) scale as follows: 0, healthy; 1, minor symptoms and signs, fully capable of manual work; 2, able to walk more than 5 meters without any assistance; 3, able to walk more than 5 meters with support; 4, bed or chair bound (unable to walk even with support); 5, assisted ventilation required for at least part of the day; 6, dead.

All patients who were tetraplegic, with involvement of autonomic system and the cranial nerves (IX, X), were admitted to the ICU.

Regardless of their age and sex, all patients were randomly divided into 2 groups, according to the number of patients referred to the emergency section (even & odd); the odd group was treated for 5 days with IVIG in a dose of 400 mg/kg of body weight/day and 20 mg/kg/day of methylprednisolone intravenously (MP-IVIG) for 5 days. The even group received 400 mg/kg/day IVIG per se for 5 days.

The main outcome criterion was improvement by at least one functional grade after 5 days of treatment (Wilcoxon signed ranks test). One of the secondary outcome measures was the time required to improve by at least one functional grade after 4 weeks of treatment (Wilcoxon signed ranks test). The median time required to improve one functional grade and the median time required to the stage of walking independently (FG=2) in both groups were compared using the Wilcoxon two sample test (Mann Whitney test). This study was approved by the medical ethics committee of the institution consent. Written informed consent was obtained from all parents.

Results

Baseline characteristics are shown in table 1, and no significant difference was seen between the groups. In the MP-IVIG group, 8 of 18 patients (47%) improved by one FG after 5 days ($P<0.05$), while in the IVIG per se group, just 4 of 18 patients were seen to have made the same recovery ($P<0.2$). The main outcome result remained significantly different in favor of the MP-IVIG treatment group.

In the MP-IVIG group, 13 of 17 patients improved by one or more FG after 4 weeks ($P=0.001$), as compared with 13 of 18 patients with IVIG per se ($P=0.001$). There was no significant difference between the groups.

The median time required to improve one FG was 12 days in the MP-IVIG group, as compared with 21 days in the IVIG per se group ($P<0.5$), and the medium time required to reach the stage of walking independently (FG=2) was 36 days in the MP-IVIG group as compared to 43 days in the IVIG per se group ($P<0.03$).

Table 2 shows the mortality rate and residual disability after 6 months of follow up.

Discussion

The study showed significant improvement of one FG in patients whose received high dose IV Methylprednisolone combined with IVIG after 5 days of treatment.

In this study, we evaluated whether treatment with high dose IVMP and IVIG is more effective than IVIG per se

in children with GBS and whether the former treatment is safe in patients.

The analysis of results revealed not only that the MP-IVIG treatment was safe but also that it was significantly more effective than IVIG per se. In our trial, more patients in the MP-IVIG treatment group reached the main outcome measure of an improvement, by one grade on the FG scale, at 5 days. There was no difference between the two groups at 4 weeks. In the Dutch Guillain-Barre study group, 19 of 25 patients (76%) who received MP-IVIG improved by one or more FG after 4 weeks, as compared with 39 of 74 patients (53%) treated with IVIG per se (P=0.04). They did not compare FG after 5 days (7).

Intravenous MP per se was compared with a placebo in the London trial, and there was no significant difference

Table1: Patient characteristics, according to treatment group

Baseline characteristics	MP-IVIG	IVIG
Number of patients	18	18
Age (mean , yr)	5.6±2.8	4.9±2.8
Duration of disease ≤ 7 days at entry (%)	72	72
FG at entry (%)		
3 (ambulant with support)	3	3
4 (bedridden)	13	14
5 (artificial respiration)	2	1
History of viral infection (%)	72	77.7
CSF Protein ≥ 40 mg (%)	77.7	83
Cranial nerve involvement	22.2	27.7
Requires assisted ventilation (% of patients)	11.1	5.5
Length of requires ICU (mean , day)	4	4

MP = methylprednisolone; IVIG = Intravenous immunoglobulin.

Table 2: Comparison of both groups after 6 months

	MP-IVIG	IVIG
Number of patients	18	18
Motor disability *	2	4
Mortality rate	1	-

* Foot drop

in any outcome variable between patients treated with IVMP and those given the placebo (8).

In our study, the median time to recover to independent locomotion was 36 days for the MP-IVIG treatment group and 43 days for the IVIG treatment group (P< 0.03).

In the Dutch GBS study group, the median time to recover to independent locomotion was 27 days for the MP-IVIG treatment group and 55 days for the IVIG treatment group (P=0.1) (7).

In the London trial, median time to walk unaided was 38 days in IVMP per se patients and 50 days in the placebo patients (8).

In the Dutch GBS study group, the median time until improvement by one FG was 20 days for the MP-IVIG treatment group and 27 days for the IVIG treatment group (P= 0.04) (7). However, in our study, the median time required to improve one FG was 12 days in the MP-IVIG treatment group and 21 days in the IVIG per se group (P <0.5).

In this study, 3 patients had transient hypertension due to high dose MP, and one patient less than 2 years old developed moon face.

In the MP-IVIG treatment group, one patient with persistent hypotension died in an early phase of disease on the second day after started medications were started.

Six months after medications were started for GBS, foot drop was seen in 2 patients (11%) in the MP-IVIG treatment group and in 4 patients (22%) in the IVIG per se treatment group. If the dead patient is included, the difference between the two groups was non-significant.

The main conclusion of the study was that high dose MP combined with IVIG speeds recovery but does not lead to a better outcome, though, and is recommended in children severely affected with GBS. It seems that combination therapy may have a synergistic effect used in the acute phase of GBS in decreasing the immunologic process.

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