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DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL TO ASSESS THE EFFICACY OF INTRAVENOUS GAMMAGLOBULIN FOR THE MANAGEMENT OF CHRONIC FATIGUE SYNDROME IN ADOLESCENTS

KATHERINE S. ROWE

Department of Paediatrics, The University of Melbourne Royal Children's Hospital, Melbourne, Victoria, Australia

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Summary A double blind randomized controlled trial was conducted in 71 adolescents aged 11-18 years. Inclusion in the trial required fulfilment of the diagnostic criteria, (Fukuda et al., 1994). Three infusions of 1 gm/kg (max 1 litre of 6 gm/100 ml in 10% w/v maltose solution) were given one month apart. The dummy solution was a 10% w/v maltose solution with 1% albumin of equivalent volume for weight. Efficacy was assessed by difference in a mean functional score including school attendance, school work, social activity and physical activity, between baseline, three months and six months after the final infusion. There was a significant mean functional improvement at the six month follow-up of 70 adolescents with Chronic Fatigue Syndrome of average duration 18 months. There was also a significant improvement for both groups from the beginning of the trial to the six month post infusion follow-up. Adverse effects were common with both solutions but not predictive of response. Neither solution could be identified by recipients. © 1997 Elsevier Science Ltd.

Introduction

CFS is a condition of unknown aetiology, characterized by extreme fatigue exacerbated by minimal physical activity. In addition, symptoms such as difficulty with concentration, headache and sleep disturbance are common (Holmes et al., 1988; Fukuda et al., 1994; Lloyd et al., 1988). Depression may occur but it is not known whether it is more common than in other young people with chronic illness. The onset usually follows a defined illness, (eg., sinusitis, influenza-like illness, gastroenteritis, or glandular fever-like illness). Disordered cell-mediated immunity is common in adult patients with CFS, (Barker et al., 1994; Lloyd et al., 1989; Murdoch, 1988; and Tirelli et al., 1994) and may be pivotal in the pathogenesis of the syndrome (Lloyd, 1994; Lloyd et al., 1992; Wakefield & Lloyd, 1987). No effective therapy is known, although recently, therapy with an antiviral immunomodulating drug Poly(I)·Poly($C_{12}U$) appears promising (Strayer et al., 1994).

In adolescents, the illness is associated with significant disruption to school and social life that may extend for several years. As there have been no long term studies of outcome

Correspondence to: Dr Katherine Rowe, Department of Paediatrics, Royal Children's Hospital, Flemington Road, Parkville, Victoria Australia 3052.

or intervention, the duration of illness is not known. Management usually involves expensive rehabilitation programmes, Visiting Teacher Services and other support services (Rowe et al., 1993, 1996), so a treatment that may decrease the morbidity would be significant.

High dose intravenous immunoglobulin therapy (2 gm/kg) has been shown in a double-blind, placebo-controlled trial, to be effective in producing clinical remission and immunological improvement in adult patients with CFS (Lloyd et al., 1990). In this study, three months after the third monthly infusion, 10 of 23 (43%) responded with a substantial reduction in symptoms and recommencement of work, compared with 3 of 26 (12%) placebo recipients. A second study (Peterson et al., 1990), did not observe any significant difference between the two groups treated with 1 gm/kg intravenously every 30 days for six months or an equivalent volume of placebo. Twenty-eight patients completed the study. The dosage regimen (2 g IgG/kg/month) used by Lloyd et al. (1990), was identical to that used in immunoregulatory treatment of other immunological disorders including idiopathic thrombocytopenic purpura (ITP) (Imbach et al., 1981; Dwyer, 1987; Berkman et al., 1990). Immunoglobulin in a dose of 800 mg/kg has been shown to be of similar benefit in the treatment of patients with ITP (Blanchette et al., 1994).

A preliminary study of intravenous immunoglobulin therapy in 10 children with CFS was completed at a major tertiary referral hospital, the Royal Children's Hospital, Melbourne, Australia. In this open study, the diagnosis of CFS was made by careful exclusion of other causes of chronic fatigue, including psychiatric evaluation of the family where appropriate. The children and the parents were asked to report independently the benefit gained (if any) from the immunoglobulin infusion(s). A dose of 400 mg/kg of Intragam (Commonwealth Serum Laboratories, Melbourne) was given by continuous infusion over four to six hours on an outpatient basis. The patients received a single infusion, after which they were followed at regular weekly intervals. Seven of the children experienced significant reduction in their symptomatology and improvement in their functional capacity as evidenced by both self-report and parent report. This improvement lasted from four to six weeks, at which time some symptoms returned and function deteriorated. Immunoglobulin was again administered, with further gain in function. The only adverse effect, noted in all subjects, was an exacerbation of the fatigue, myalgia, headaches, etc., occurring 12–24 h after the infusion and lasting for up to 10 days. It was not known whether this was related to having an infusion or due to the gammaglobulin *per se*.

On the basis of this preliminary data, a double-blind study of intravenous immunoglobulin therapy in children with CFS was planned, incorporating a placebo control and careful evaluation with monitoring of physical, psychological and immunological parameters.

Patients and methods

A pilot study of eight subjects was conducted, single blind (as the subjects did not know whether they were receiving placebo or not), but not placebo-controlled, to confirm the logistics of the study, and whether the estimate of likely improvement was realistic.

Subsequently, 71 young people (age 11–18 years) who met the criteria for CFS as outlined by (Fukuda et al., 1994) were enrolled in the study. The criteria were: (1) an identifiable

time of onset, and subsequent course marked by chronic persisting or relapsing fatigue of a generalized nature, exacerbated by minor exercise, causing significant disruption of usual daily activities and present for greater than six months; (2) neuropsychiatric dysfunction including impairment of concentration evidenced by difficulty in completing mental tasks which were easily accomplished prior to the onset of the syndrome, and/or new onset of short term memory impairment; (3) persistence or recurrence of at least three of the following symptoms and signs which were present with no other cause found on investigation: myalgia, arthralgia, headaches, sleep disturbance, abdominal pain, dizziness, nausea, pharyngitis, and lymphadenopathy. Subjects were similarly excluded if they were receiving steroid medication, non-steroidal anti-inflammatory drugs, immunomodulatory agents, or were currently receiving, or had received, intravenous immunoglobulin (IgG).

One hundred patients who were referred to the Royal Children's Hospital, Melbourne, were the source of the study group. Fifteen did not meet the entry criteria, or a judgement was made that psychological and family issues were salient in the presenting symptomatology. Fourteen chose not to participate because they did not wish to, had improved, or were improving at such a rate they estimated that they would be functioning well by the end of the trial.

From the pilot study, 7/8 had a greater than 25% mean functional improvement and 50% had >50% mean functional improvement at the six month follow-up. The rate of improvement for those receiving placebo was estimated from the natural history of the illness in 10 young people.

Approximately 35 in each group were required for a power of 0·8 to detect a difference at the 0·05 level of significance (two-tailed), based on a 25% mean functional improvement in 33% of the young people in the placebo group, and 66% in the gammaglobulin group, ie., a 33% difference in improvement rate between the two groups (Bavry, 1987).

Drug formulation

Immunoglobulin for intravenous infusion [Intragam, Commonwealth Serum Laboratories (CSL), Melbourne] was used as the treatment drug. This product is a low pH (4·25) solution, prepared with an immunoglobulin concentration of 6 gm of IgG per dl (6%) in a 10% w/v maltose solution. The immunoglobulin is prepared by CSL under licence from Cutter Laboratories Inc. CA, U.S.A., according to the formulation of Gamimune N. This latter product has general marketing approval in the U.S.A., and an established safety record with adverse effects occurring in less than 2·5% infusions. The reported adverse effects most commonly include constitutional symptoms (fever, headaches, nausea, and malaise) which are dependent on the rate of infusion and hence typically resolve with slowing of the infusion rate. Major allergic (anaphylactoid) reactions such as urticaria, bronchospasm, or hypotension are rare (less than 0·1% of infusions). Screening of blood donors, the Cohn fractionation and heat inactivation procedures used in the preparation of this immunoglobulin product, make the possibility of transmission of Human Immunodeficiency and Hepatitis B virus highly improbable. Hepatitis C has not been reported following the use of Gamimune N.

The placebo solution was 1% albumin in a 10% w/v maltose solution, chosen to appear

identical in appearance to Intragam (very slightly yellow-brown and able to produce a frothy layer when agitated). The solution was prepared by CSL.

Study design

The study was a double-blind, placebo-controlled study. Patients were randomly allocated to receive either immunoglobulin or placebo, in a block randomization design with block sizes of six to ensure approximately equal numbers in each group. The solutions were administered by continuous intravenous infusion, on three occasions at four-weekly intervals. Patients were admitted to hospital as short stay admissions. The volume given was 16·7 ml/kg of body weight (being equivalent to 1 g of immunoglobulin/kg), or an identical volume of placebo solution. Infusions were commenced at a rate of 15 mls/h and increased over one hour to a rate not exceeding 160 ml/h. The infusion rate was slowed if constitutional symptoms appeared. Frusemide (40 mg orally) was administered with infusions greater than 500 ml. The maximum infusion given was one litre, for those subjects of 60 kg or greater. Follow-up interview with a paediatrician who was unaware of the treatment regimen occurred three months and six months after the date of the final infusion for assessment of functional status.

All patients received additional information regarding services available such as Visiting Teacher Service, Distance Education (lessons by correspondence), availability of Social Security support and had access to a support group (Rowe et al., 1996).

Informed consent

Ethical approval had been obtained from the Royal Children's Hospital Research Foundation Ethics Committee. Patients and their parents were informed of the aims of the study; the nature of the material being tested; the use of a placebo solution; the potential benefits and risks of the procedures undertaken; the time commitment required and the type and extent of testing required during the trial. Patients and their parents were also informed that they may withdraw from the trial at any time.

Patient monitoring

Paediatrician

At enrolment and at follow-up, the paediatrician, assessed the degree of functional participation during the previous two weeks in four domains for all patients in the trial: (a) attendance at school or work; (b) proportion of school or work attempted; (c) proportion of "normal" physical activities attempted, including sports; and (d) proportion of "normal" social activities attempted. All ratings were compared with estimates of premorbid activities, with 100% indicating premorbid levels of activity and each functional rating was estimated as a proportion to within 5%. The mean was taken of these four ratings. It was important to assess these four domains to provide an overall score because there was considerable variation in how young people preferred to spend their time and energy. For example, some would prefer to do a greater proportion of school work at home rather than attend school, and some preferred to do some physical activity at the expense of school work. For others,

social life occurred outside of school, while others were able to do some school work, meet their social needs and have some physical exercise by attending school. The mean percentage functional score was compared with an overall estimate of functional rating provided by both the subject and a parent. The weekly recording of activities was also used as a check against the validity of the estimate. Parents confirmed the patient's reports and where possible feed-back was obtained from the school or Visiting Teacher regarding school attendance and proportion of school work attempted. Many schools and parents kept diaries to record activities and attendance.

Psychological monitoring

At enrolment and at follow-up, the patient and the parents were required to complete appropriate report forms from the Child Behavior Check-List (Achenbach & Edelbrock, 1983). The patient completed the following self-report measures: Spielberger Self-evaluation-State Trait Anxiety Inventory (Spielberger, 1977), Beck Depression Inventory (Beck et al., 1961), and the 12 item General Health Questionnaire (Goldberg & Williams, 1988). At enrolment these reports were reviewed by the paediatrician. Patients whose responses suggested major psychiatric morbidity were required to attend a formal psychiatric evaluation with their parents. The results of this assessment did not exclude any patient from the trial. Psychiatric intervention was offered if required. The General Health Questionnaire was scored in two ways, the traditional (0, 0, 1, 1) and Likert (0, 1, 2, 3). A score of five or more using the traditional method indicated psychological morbidity.

The subjects were required to complete a Quality of Life Visual analogue scale, and Activities Record at weekly intervals throughout the period of the trial (32 recordings). The Adverse Effects Record was to be completed 14 days after each infusion. Subjects were also asked to state whether, in their opinion, they had received gammaglobulin or placebo after each infusion and at follow-up.

Immunological function

Delayed-type hypersensitivity skin testing (Multitest CMI-Institut Merieux) was measured at baseline, three month follow-up and six month follow-up. The Multitest CMI is a single application apparatus with seven standardized antigens (Tetanus, Diphtheria, Streptococcus (group C), Tuberculin, Candida albicans, Trichophyton mentagrophytes, Proteus mirabilis and glycerine control solution) for intradermal penetration by nine tines on each of the eight heads. Induration at 48 h is measured in mm in two perpendicular diameters and the mean is taken as the score for that antigen. Greater than 2 mm is considered a positive response for each antigen. The sum of the scores provides a total score, no response (0 mm) being anergic and 2–9 mm considered hypoergic for both males and females age 13–16 years (Corriel et al., 1985). In addition, less than three positive antigen scores is also scored as hypoergic (Kniker et al., 1984). There is no increase in sensitization with repeated use (Institut Merieux, 1982).

T-cell subset analysis was performed at baseline, three month follow-up, and six month follow-up. IgG subclass analysis was performed at baseline and six month follow-up. In

addition, a full blood count with differential white cell count, and liver function tests were measured with each infusion and again at follow-up.

Statistical analysis and criteria for efficacy

The two groups were compared using a Chi-square two-tail test of independence and a t-test of differences between proportions at the $p < 0.05$ level of significance was computed. Descriptive and inferential statistics were calculated using Statistical Package for Social Sciences, 1991.

Results

Seventy-one patients were allocated to receive either gammaglobulin or placebo. One female who received placebo was lost to six month follow-up when the family moved interstate in search of work. Thus 70 patients completed the trial, 34 receiving placebo and 36 receiving gammaglobulin. No difference was found at baseline between the placebo and the gammaglobulin groups for age, sex, duration of illness or baseline score (Table 1).

The mean percentage functional score at baseline (compared with premorbid levels) for the gammaglobulin and placebo groups was 23.9% and 25.9% respectively, 49.9% and 44.6% at three month follow-up, and 64.1% (gammaglobulin group) and 52.1% (placebo group) at the six month follow-up. The differences between the baseline mean functional score and scores at both three months and six months follow up were significant for each group. For the group receiving gammaglobulin there was a significant difference in mean functional score from baseline (mean 23.9, sd 19.6) to six month follow up (mean 64.1, sd 28.2) as determined by a t-test for paired samples, ($t = -8.83$, $p < 0.001$, $df = 35$). For the placebo group the difference between the baseline functional scores (mean 25.9, sd 20.5) and six month follow up (mean 52.1, sd 31.4) was also significant ($t = -5.47$, $p < 0.001$, $df = 33$). These results are graphically illustrated in Figure 1.

The comparison between the two groups for mean functional improvement from baseline to six month follow-up was significant using the t-test for independent samples ($t = -2.12$, $p < 0.04$, df 68). Nine (25%) of the group receiving gammaglobulin returned to full function whereas four (11%) of the placebo group did so. (Figure 2)

When subjects were categorized based on improvement in mean functional score of 25%

Table 1
Baseline Comparison for Age, Sex, Duration of Illness and Baseline Mean Percentage Functional Score for the Two Treatment Groups Showing Means and Standard Deviations (in parenthesis)

	Placebo group (N = 35, M:F = 1:4)	Gammaglobulin group (n = 36, M:F = 1:2.4)
Age years	15.6 (2.0)	15.3 (2.0)
Duration (months)	16.9 (11.4)	19.2 (13.2)
Baseline score	25.9 (20.5)	23.9 (19.7)

Placebo and gammaglobulin groups not significant at the $p < 0.05$ level by univariate two-tailed test.

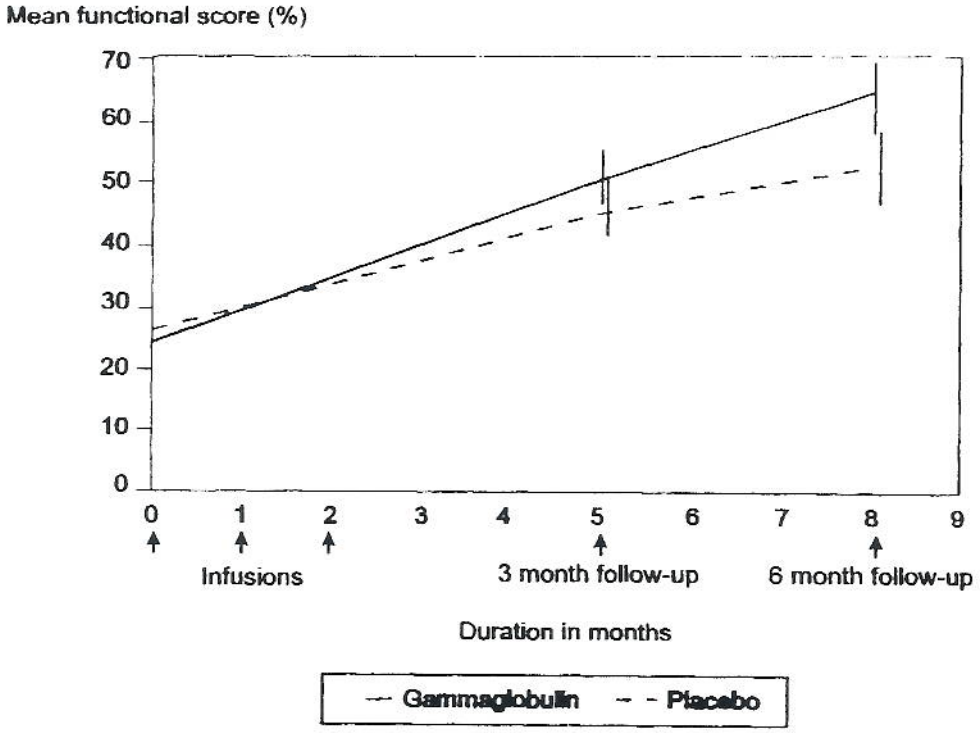


Figure 1. Mean percentage functional score for placebo and gammaglobulin groups from baseline to six months post infusions.

or greater at six month follow up, there was a significant difference between the two treatment groups (χ^2 5.8; df = 1; $p < 0.02$), in favour of the gammaglobulin group, (Table 2).

Subjects were unable to identify whether they had received placebo or gammaglobulin. For those receiving gammaglobulin, 50.1% thought they had had gammaglobulin, 38.4% thought they had received placebo, and 11.5% "did not know". For those receiving placebo, 36.8% thought they had had placebo, 47.4% thought they had received gammaglobulin and 15.8% "did not know".

Outcome in relation to duration of symptoms

For illness less than 15 months duration at the commencement of the trial, 9 of 18 (50%) of those receiving placebo had greater than 25% mean functional improvement in the subsequent eight months, compared with 14 of 20 (70%) of those receiving gammaglobulin (ns). For a duration of illness of 15 months or greater, 6 of 16 (37.5%) of those receiving placebo improved compared with 12 of 16 (75%) receiving gammaglobulin ($\chi^2 = 4.7$, df = 1 $p < 0.05$). The regression of baseline functioning on duration of symptoms, however, showed

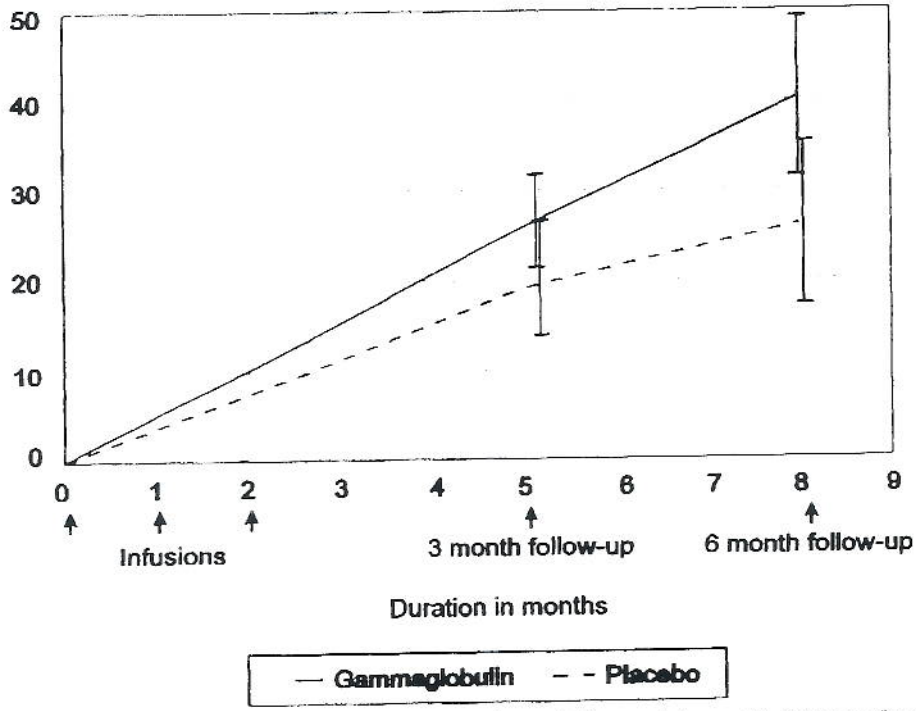


Figure 2. Change in mean functional score between baseline and three and six month follow-up for subjects receiving placebo (n = 34) and gammaglobulin (n = 36) with 95% confidence intervals.

no association (adjusted $R^2 = -0.05$). Moreover, duration of illness did not affect outcome in the gammaglobulin group. The regression of final level of functioning on duration of symptoms for the placebo group also showed no association (adjusted $R^2 = 0.03$, $\beta = 0.65$, se $\beta = 0.47$, $t = 1.38$, $p = 0.17$).

Adverse effects

Reported side effects were common with both solutions, particularly headache, fatigue and weakness, nausea, muscle aches and pains and difficulty concentrating. These effects are summarized in Table 3 and in Figures 3 and 4.

Table 2
Outcome Classified in Terms of > or <25% Mean Functional from Improvement Basline Functioning

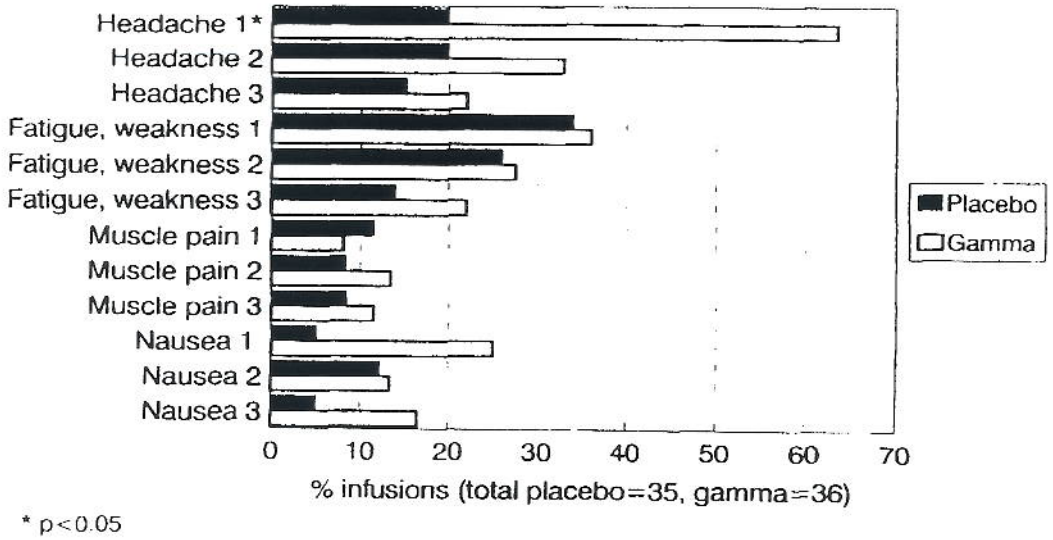
Group	Three month follow-up		Six month follow-up	
	Not improved	Improved	Not improved	Improved
Placebo	24 (68.6%)	11 (31%)	19 (55.9%)	15 (44.1%)
Gammaglobulin	17 (47.2%)	19 (52%)	10 (27.8%)	26 (72.2%)

Chi square 5.8, df = 1, $p < 0.02$ for six month follow-up. Improved = 25% or greater mean functional improvement. Not improved = <25% mean functional improvement.

Table 3.
Proportion (%) of Infusions (gammaglobulin, placebo and total) with Reported Adverse Effects

Symptom	Gammaglobulin (n = 145)	Placebo (n = 98)	Total (n = 243)
Headache	69	58	61
Fatigue	52	46	47
Nausea	54	30	42
Muscle pain	38	39	37
Difficulty concentrating	26	26	25
Abdominal pain	26	14	19
Vomiting	9	4	16
Dizziness	15	6	8
Sore eyes	10	2	5
Swollen glands	13	7	8
Sore joints	4	5	4
Earache	3	6	4
'Sweaty' mild fever	5	1	4
Short of Breath	4	0	3

The symptoms were generally described by the patient as an exacerbation of their CFS. Adverse effects were rated in terms of duration and severity. There was a significant difference in the severity and duration of reported headache ($t = -2.98$, df = 107, $p < 0.01$), duration of fatigue and difficulty with concentration between those receiving placebo and those receiving gammaglobulin. Severe headaches following the first infusion of gammaglobulin occurred in 64% compared with 20% of those receiving placebo (Chi-square = 4.15; df = 1; $p < 0.01$). Headache severity remained constant for the placebo group but decreased



* $p < 0.05$

Figure 3. Percentage of infusions with adverse effects rated as "severe"

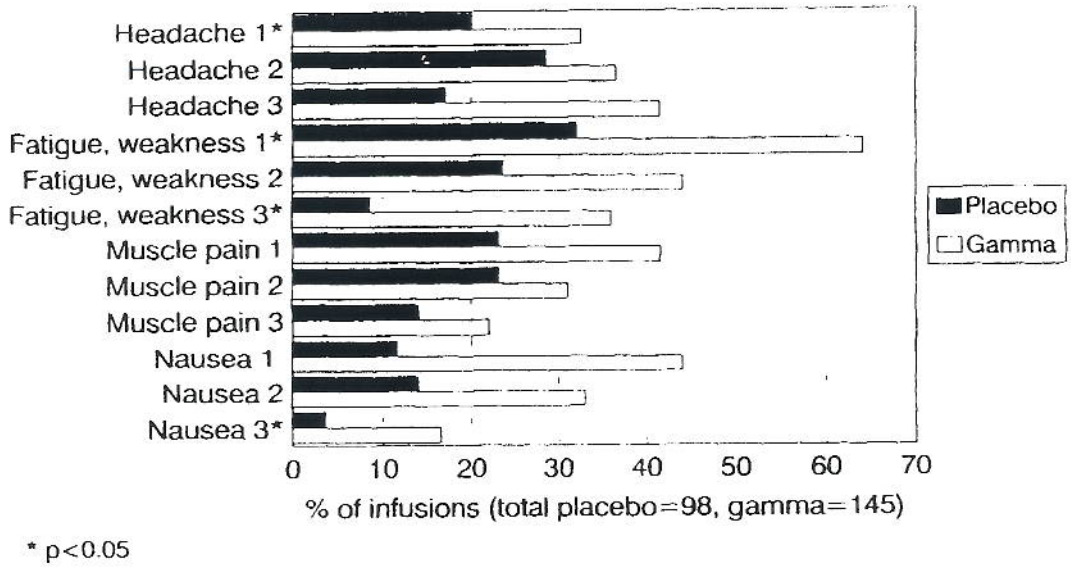


Figure 4. Percentage of infusions with duration of adverse effects greater than three days.

in reported severity for those receiving gammaglobulin by the third infusion. Reduction in the severity of fatigue following the subsequent infusions occurred for both placebo and gammaglobulin groups. However, using discriminant analysis, only 60% of cases could be correctly classified in terms of receiving gammaglobulin or placebo by "severity of headache" and this increased to 71% if only the first infusion was included in the analysis. The addition of other symptom variables did not improve the discrimination. "Severity of headache" and "duration of nausea" were sensitive for predicting clinical improvement but were not specific since 15/16 subjects who minimally improved, also experienced such symptoms. Other symptom variables were not significant in predicting functional outcome.

Cell mediated immunity, as measured by the multitest CMI (Merieux), was abnormal in 52% of subjects at baseline (Table 4). There was a significant difference between the total score at baseline and six months follow up for the placebo group (8·6mm [n=33] compared with 5mm [n=22], $t=2\cdot05$; df 55; $p<0\cdot05$,) with decreased skin test reactivity at the six month follow-up. There was a similar but non significant trend for the group receiving

Table 4
Frequencies (%) of Subjects with Reduced Skin Test Responses at Baseline using CMI-multitest

	Males (n=18)	Females n=45)	Total (n=63)
Hypoergy reduced (2–9mm)	5 (28%)	13 (29%)	18 (29%)
Hypoergy reduced number of reponses (one or two positive scores only)	2 (11%)		2 (3%)
Anergy (no response)	1 (6%)	12 (27%)	13 (21%)
Total	8 (44%)	25 (56%)	33 (52%)

gammaglobulin. There was no significant difference at baseline, or follow-up between the placebo and gammaglobulin group for total score. There were no significant abnormalities in IgG subclasses compared with laboratory age matched norms.

An Activities Record was completed once per week for the preceding day. Activities records were used to confirm the level of return to physical activity as reported by patient and parent. For example, for one 15 year old boy, there was a gradual reduction in the time spent sleeping from 16 hours per day to an average of eight hours between weeks 1 and 11. The amount of time spent in sedentary activity such as writing or reading, increased from zero to nine hours by week 15. Vigorous activity also commenced during week six (between the second and third infusion).

There were significant improvement in the scores for the Beck, Spielberger and General Health Questionnaires from baseline to six month follow up reflecting, an overall functional improvement (Table 5). Using traditional scoring of the General Health Questionnaire to indicate significant psychological morbidity, 49% scored five or greater at baseline and 29% at follow-up. Five patients accepted the offer of psychiatric intervention, three from the placebo group and two from the gammaglobulin group. An average of four visits per patient occurred. Two patients (one from each group) were treated for moderate depression and the other consultations were mainly directed towards strategies for managing anxiety.

Discussion

This study demonstrated a significant difference in functional outcomes between the group receiving gammaglobulin and the group receiving placebo at the six month post infusion follow-up. A 25% mean functional improvement was considered clinically significant as it encompassed physical activity, school attendance, school work and social activity. This study also demonstrated a greater improvement rate in the placebo group than in the adult studies (Lloyd et al., 1990).

The two trials using gammaglobulin in adults with CFS (Lloyd et al., 1990, and Peterson et al., 1990) have yielded conflicting results. In the Lloyd study, 49 subjects were involved, while in the Peterson study only 28 were involved. For improvement rates similar to those of Lloyd et al. (1990), the power to detect a difference with 28 subjects is 0·48 (Bavry, 1987). The results from the Peterson study may therefore be subject to type II error due to sample size. Differences in characteristics of intravenous gammaglobulin may also account for different outcome effects (Imbach, 1991; World Health Organization, 1983).

Table 5

Change in Scores from Baseline to Six Month Follow-up for the Psychological Measures (Beck et al., 1961; Spielberger, 1977; and General Health Questionnaire) (n = 64)

	Scale range	Baseline Mean	SD	se	Range	Six month follow-up Mean	SD	se	Range	t value (df)	Sig (p value)
Beck	0–70	13·7	8·0	1·05	1–38	7·5	7	1·48	0–27	3·23 (83)	0·002
Spielberger	0–120	46·5	24·4	3·9	0–98	28·3	25·0	5·9	0–72	2·63 (56)	0·01
GHQ	0–36	16·0	6·7	0·86	4–29	10·0	6·6	1·19	0–26	4·06 (89)	0·000

Even though reported adverse effects were common, they were not predictive of the treatment used or the functional outcome. Severe headache and nausea, particularly during the first infusion were sensitive but not specific for either solution or outcome. Similarly, the side effects were not constant with each gammaglobulin infusion, which would be expected if they were dose-related or rate-related effects. Subjects were not able to predict which solution they received either at the time, or at review. The symptoms experienced were similar to those occasionally reported with infusions of intravenous gammaglobulin used in the treatment of idiopathic thrombocytopaenic purpura and attributed to immune complex formation (Schiavotto et al., 1993).

Disturbances in cell mediated immunity as measured by the multitest CMI were noted in more than 50% of subjects and did not improve over the course of the trial. Normative data obtained by Corriel et al. (1985), from 448 healthy children age 7-16 years, showed none was anergic and less that 5% were hypoergic. Although the group receiving placebo decreased in measured skin reactivity during the course of the trial, it is likely to be a spurious result as there was no difference between the gammaglobulin group and the placebo group at baseline or follow up, nor for the gammaglobulin group during the trial. There was no relationship between clinical improvement and improvement in cell mediated immunity as measured by the multitest CMI. Wilson et al. (1994) also noted minimal change in cell mediated immunity a mean of 3.2 years after treatment trials, some of which involved gammaglobulin.

The study showed that the improvement rate for the gammaglobulin group was not affected by the duration of illness at the commencement of the trial. There was also no association between duration of illness and baseline functioning at the commencement of the trial. With a natural improvement rate one would expect a negative association between functional score and duration of illness. The placebo group did improve significantly over the course of the trial but the regression of average functional score at the conclusion of the trial on duration of illness at the commencement of the trial did not show any association for the placebo group. These data suggest that although there was a natural improvement rate during the trial, the lack of association between functioning and illness duration at the commencement may be due to one of three things: (1) the selection of subjects — i.e., those who were not improving irrespective of illness duration may be more likely to be selected; (2) the fact that many of these young people experienced long delays before diagnosis and experienced prolonged absences from school which added to their distress; or (3) an interplay of other psychological issues (Krener & Adelman, 1988). Lack of recognition of the illness, and the associated uncertainty that this engenders, can contribute to reduced functioning (Woodward et al., 1995). Similarly, a lack of a management plan could also contribute. As all subjects received the same additional support during the trial (Rowe et al., 1994), the difference in outcome for those who received gammaglobulin remains significant.

Over the course of the trial, there was an overall improvement in the scores for the General Health Questionnaire, depression (Beck et al., 1961) and anxiety (Spielberger, 1977) scales that was consistent with the observed overall improvement. There is a significant overlap between chronic illness and depression (Heiligenstein & Jacobsen, 1988) and with CFS and depression in adults (Blakely et al., 1991; Thase, 1991). Therefore, a more

detailed analysis of the responses compared with other young people with chronic illness is warranted, in view of the item content recording somatic complaints.

The overall improvement rate in this group has contrasted with the reported improvement rate of 6% at three years in adults with CFS by Wilson et al. (1994). This rate may be an underestimation as the follow-up sample was not complete with fewer younger adults than expected. A follow up of clinic patients from the Royal Children's Hospital, (50% of whom were involved in the clinical trial), an average of 4.3 years (range 1.5 8.5 years: sd 1·9) after onset of illness indicated that 40% (26 of 64) considered they were "cured" and were "back to normal" (Rowe et al., 1994). Further follow-up is planned to ascertain if this improvement is sustained.

Results

The male to female ratio was 1:3, and the mean duration of illness was 18 months (s.d. 12.3, range 6 60 months). There was no significant difference between the two groups on the basis of age, sex, socioeconomic status, duration of illness or functional score at baseline.

There was a significant difference between the baseline functional score and six month follow up for both groups, and between the mean functional outcomes ($t = -2.12$, $p < 0.04$, df 68) at six months. The difference between the two treatment groups was also significant when the outcomes were categorized in terms of average functional improvement of greater than 25%. (Chi-square = 5.8, df 1, $p < 0.02$). Side effects with both infusions were common, but severe headache and initial exacerbation of symptoms were more common in the gammaglobulin group.

Conclusions

There was a significant mean functional difference at the six month follow up of 70 adolescents with CFS of average duration 18 months, following a double-blind, randomized, placebo-controlled trial of intravenous gammaglobulin (1 gm/kg) given on three occasions one month apart. There was also a significant improvement for both groups from the beginning of the trial to the six month post-infusions follow-up. Adverse effects were common with both solutions but not predictive of response. Neither solution could be identified by recipients.

Summary

This study demonstrated a significant mean functional difference at the six month follow up of 70 young people who completed a double-blind randomized placebo-controlled trial of intravenous gammaglobulin (1 gm/kg) given on three occasions one month apart. There was also significant improvement in functioning for both groups from commencement of the trial to six month post-infusion follow-up. Adverse effects were common with both solutions but not predictive of response. The young people could not identify which solution they received. The improvement in the gammaglobulin group was not affected by the duration of illness prior to the trial. There was no improvement in delayed type hypersensitivity skin testing (CMI Multitest) ie., reactivity with improved clinical response.

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