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A randomised controlled trial of a psycho-educational intervention to aid recovery in infectious mononucleosis

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Abstract

Objectives: Glandular fever is associated with an approximate fivefold increase in fatigue at 6 months. Reduced levels of fitness and illness beliefs may be important predictors of fatigue following glandular fever. We therefore developed a brief psycho-educational intervention aimed at improving recovery from infectious mononucleosis, and piloted a randomised controlled trial to evaluate the intervention. **Methods:** We performed a randomised-controlled trial in primary health care in Southeast London and Kent. Sixty-nine patients aged between 16 and 45 years who were diagnosed, serologically and clinically, with acute infectious mononucleosis between December 1999 and December 2000 were randomised. The control group received a standardised fact-sheet about infectious mononucleosis, which gave no advice on rehabilitation. Patients who were randomised to the intervention received an individual treatment session, two follow-up telephone calls, and an information booklet. Fatigue score 6 months after the onset of infectious mononucleosis was the main outcome measure. **Results:** Sixty-nine out of 139 patients referred were recruited and randomised. Eighty-seven percent of those recruited completed the Fatigue Questionnaire at 6 months. The intervention was acceptable to all who received it. There were fewer fatigue cases in the intervention group than the control group at 6 months follow-up (odds ratio 0.31, 95% confidence interval 0.09–0.91). **Conclusions:** A brief intervention at the diagnosis of infectious mononucleosis is acceptable, and may help prevent the development of chronic fatigue. Definitive randomised controlled trials are required to test the intervention.

Keywords: Glandular fever; Infectious mononucleosis; Randomised controlled trial; Fatigue; Chronic fatigue syndrome; Prevention

Introduction

Infectious mononucleosis (IM), often referred to as glandular fever, is associated with significant prolonged ill health [1]. The symptom most commonly found to persist after IM is fatigue [2], and at 6 months after onset up to 22% of patients have a chronic fatigue syndrome (CFS) [1]. In a recent review, we found that reduced physical activity following the onset of IM was the single most consistent factor associated with prolonged ill health [2]. In contrast the most common advice patients report being given by their general practitioner was to rest [3]. Rest is unhelpful in chronic lower back pain and in chronic fatigue syndrome there has been a shift of emphasis to more active rehabilitative approach [4,5]. However, little attention has been paid to rehabilitation interventions aimed to reduce the risk of chronic ill health following IM.

A brief psychoeducational intervention that aimed to increase activity has been evaluated in a randomised controlled trial (RCT) in primary care, and found to improve outcomes for patients with chronic fatigue [6]. We aimed to adapt this package to test the hypothesis that in recent onset IM a similar package that offered graded activity and life style management would be more effective than a neutral fact-sheet in reducing fatigue 3, 6 and 12 months later. The aim of the present study was to develop the intervention and pilot a randomised controlled trial in order to demonstrate (a) such research was feasible

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and (b) if feasible to provide preliminary data for a power calculation for a definitive study.

Methods

Design

We performed a randomised controlled trial to compare the active intervention with a control condition. Three local research ethics committees in Southeast London and Kent gave ethical approval.

Recruitment

Potential participants were identified by positive IM serology from three haematology and two virology laboratories, from five general practices and one student health centre. First contact with the patient was made by their GP and only after obtaining their consent were they approached and invited to participate by the researcher. If they agreed to participate they were interviewed in their own home as soon as possible.

Participants

The inclusion criteria were (1) aged between 16 and 45 years; (2) clinical diagnosis of IM; and (3) serological evidence of recent IM either from a heterophile antibody test (Microgen Bioproducts, UK) or by the VCA IgM immunofluorescence assay (Immuno concepts, Sacramento, CA). Patients with IM were not eligible if they had additional physical illnesses, which may be associated with fatigue (such as endocrine disorders). Patients recognised by their general practitioner to have psychotic illnesses (schizophrenia and bipolar disorder) or substance misuse were also excluded, on the basis that these disorders are exclusion criteria from chronic fatigue syndrome. Individuals who had limited literacy skills were also excluded as most of the variables were measured using questionnaires.

Randomisation

Randomisation was performed using random number tables and sealed opaque envelopes. It took place in blocks of random size (2 to 8) to ensure balanced and concealed allocation. The envelope containing trial allocation was extracted sequentially and opened after gaining written informed consent. Envelopes were sufficiently opaque to ensure the contents were unreadable even using strong light (e.g., X-ray boxes). Participants were allocated to receive an illness fact sheet (control) or the intervention. Participants were advised that we were testing the effects on recovery of two types of information and that although there was no proven treatment that could speed recovery, for the majority the illness was not prolonged.

Control

The control involved the research worker (BC) giving the patient a fact-sheet on IM. This made no specific recommendations about recovery.

Intervention

The intervention was based on a behavioural model of fear and avoidance. This model suggests that recovery may be delayed due to prolonged rest in the acute or subacute phase of the illness, and this may happen for several reasons. Firstly, some patients continue to experience symptoms, and are afraid of making them worse, so rest in an attempt to control them. Second, patients are sometimes advised to rest by their doctors. Third, a commonly held belief is that it is sensible to rest when symptomatic. Whatever the reason, continued rest may be an unhelpful coping strategy that results in a vicious circle of fatigue and disability.

The intervention aimed to restore physical function by providing the patient with a personalised strategy of graded time-targeted activity and advice about a balanced life-style. This advice was given in a brief face-to-face session administered by BC. An experienced cognitive behavioural therapist (TC) gave training and supervision. All sessions were audiotaped and a random proportion listened to during supervision. A patient booklet specifically designed for the project supported the session. To reinforce advice given, two brief phone calls were made 2 and 4 weeks later.

Assessments

Data were collected in questionnaire format at interview and at postal follow-ups 3, 6 and 12 months later. In addition to baseline questions on demographics, medical history and current illness, the questionnaires contained existing standard psychometric scales. The Fatigue Questionnaire [7] was used to measure the main outcome, fatigue. This 11-item scale assessed the severity of physical and mental fatigue. The questionnaire can either score fatigue as a continuous variable or as a binary outcome with cases having a score of over 3. Additional scales were used to assess psychological health [8], adverse life events [9], emotional and physical functioning [10], and work and social functioning [11].

Sample size

No power calculation was performed for this study, as an explicit aim was to provide such data for a subsequent definitive study. We estimated that we would require

Table 1
Characteristics of intervention and control group at baseline

Variable	Intervention $n=36$	Control $n=33$	Statistic	P
Sociodemographic variables				
Age in years (S.D.)	23.3 (9.4)	22.6 (6.6)	$U=556.5$	.65
Female gender (%)	22 (61.1)	20 (60.6)	$\chi^2=0.00$	.97
Student (%)	17 (47.2)	15 (45.5)	$\chi^2=0.02$	.88
Social class I or II (%)	18 (50.0)	16 (50.0)	$\chi^2=0.00$	1.00
Lives with parents or partner (%)	28 (77.8)	18 (54.5)	$\chi^2=4.18$	.04
Psychosocial variables				
Number of negative life events (S.D.)	1.4 (1.5)	2.3 (2.2)	$U=455.50$	.09
Past history of emotional problems (%)	9 (25.7)	5 (16.1)	$\chi^2=0.90$	.34
GHQ score (S.D.)	16.4 (6.1)	17.2 (6.5)	$U=545.50$	.56
Characteristics of glandular fever				
Given advice to rest (%)	26 (72.2)	22 (68.8)	$\chi^2=0.10$	.75
Days in bed (S.D.)	7.1 (8.2)	6.9 (8.2)	$U=247.00$	.89
Days from onset to seeing a GP (S.D.)	13.7 (18.7)	13.2 (19.8)	$U=497.00$	.43
Fatigue main symptom (%)	20 (55.6)	7 (21.2)	$\chi^2=8.53$	.004
Self report of recovery at interview (%)	9 (25.7)	14 (27.0)	$\chi^2=2.12$	.14
Baseline functional status				
Usually does regular exercise or sport (%)	16 (44.4)	18 (54.5)	$\chi^2=0.70$	.40
SF36 daily activity in last month (S.D.)	12.3 (29.5)	30.3 (38.9)	$U=418.50$	.02

GHQ–12 item General Health Questionnaire; SF36–Medical Outcomes Study Short Form 36.

approximately 50 subjects to determine whether any effect exists worthy of further research. In practice we were able to continue recruiting to gain a final sample of 69.

Analysis

Analysis was undertaken using the Statistical Package for the Social Sciences (SPSS version 8) and STATA. In the analysis, imbalances in randomisation with respect to baseline variables were determined using appropriate univariate tests. The protocol specified that fatigue caseness measured at 6 months by the Fatigue Questionnaire [7], was used as the primary outcome. The outcome was expressed as a percentage of those who met the criteria for fatigue (scoring 4 or more using bimodal scoring) at 6 months, in the two groups. We used outcome at 6 months, as this is the duration of fatigue necessary for a diagnosis of chronic fatigue. Odds ratios were generated, and corrected for baseline differences. We used a completer analysis, where only those with full data at 6 months were included in the analysis, and last observation carried forward, where missing values at 6 months were replaced by the fatigue score at three months (if available) or at baseline. Secondly, we used additional information on recovery status, which acted as a proxy for fatigue caseness; this was obtained over the telephone for patients who had declined to answer the Fatigue Questionnaire.

A secondary analysis, which had greater statistical power, used fatigue as a continuous outcome. We used *t* tests to compare outcome between the two groups. We used multiple regression to model fatigue at each endpoint (3, 6 and 12 months), using treatment group as the dependent variable and entering baseline fatigue score as a covariate. We again used last observation carried forward analysis to deal with missing data. Finally, we compared outcome at 6 months on a number of secondary variables: included self-reported recovery; "handicap" and "degree of improvement"; Social and Work Adjustment Scale; SF36; GP visits and sickness absence. "Handicap" and "degree of improvement" were ordered categorical outcome measured on a seven-point scale (e.g., "how much better are you now?" with answers from *very much better* to *very much worse*). For binary outcomes, chi-square tests were used. For ordered categorical outcomes the nptrend command from STATA was used to give a test for trend. For continuous outcomes either *t* tests of Mann–Whitney *U* test were used.

Results

Of the 139 primary care patients that were initially thought to be eligible to participate we were unable to contact 53, mainly because of incorrect contact details. Eighty-six patient were invited into the study and 69 of these entered the study. Nine declined and six did not meet the inclusion criteria (mainly as they had not experienced clinical IM). A further two did not participate, as they were unable to attend the interview.

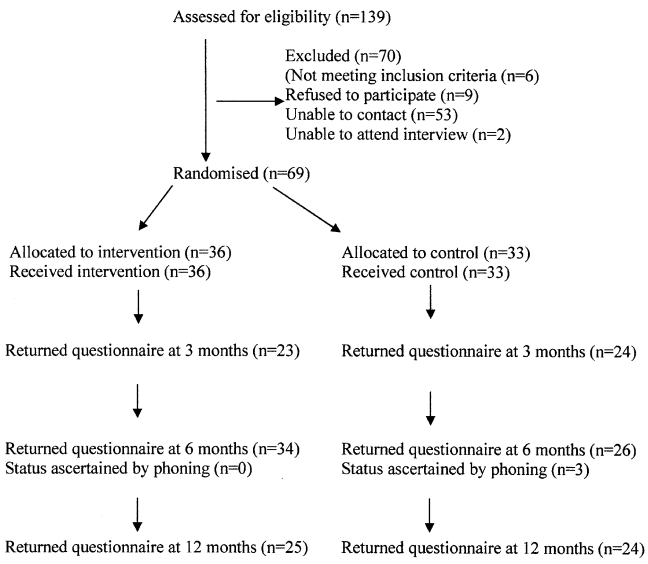

Fig. 1. Consort diagram showing the flow of participants through each stage of the trial.

Table 2
Fatigue cases at baseline and follow-ups

Method used	Fatigue cases in intervention group (%)	Fatigue cases in control group (%)	OR (95% CI)	OR corrected for baseline fatigue, SF36 and self-report of "recovery" (95% CI)
Baseline	30/36 (83.3)	27/33 (81.8)	1.4 (0.4–5.0)	NA
Completers at 3 months	11/23 (47.8)	10/24 (41.7)	1.3 (0.4–4.1)	1.7 (0.4–7.8)
Completers at 6 months	9/34 (26.5)	14/26 (53.8)	0.3 (0.1–0.9)*	0.3 (0.1–0.9)**
LOCF[a] at 6 months	12/36 (33.3)	16/33 (48.5)	0.5 (0.2–1.4)	0.6 (0.2–1.7)
Completers at 12 months	8/25 (32.0)	10/24 (41.7)	0.7 (0.2–2.3)	0.4 (0.1–1.5)
LOCF at 12 months	11/36 (30.6)	16/33 (48.5)	0.5 (0.2–1.3)	0.3 (0.1–1.4)

CI = Confidence intervals, OR = Odds ratio, SF 36 = Short form Medical Outcome Survey.
[a] Includes self-report of recovery ($n = 3$).
* $P = .03$.
** $P = .05$.

Participants were compared with nonparticipants on age, gender and location (inner city or not) of the general practice that they were registered at. This revealed similarity in age and practice location, but males were less likely to participate (54% vs. 39%). All participants described their ethnicity as white, they were generally young (mean 23.0 years, S.D. = 8.7) and single (87%). Just under half were attending a school or university (46%).

After randomisation, 36 patients received the intervention and 33 the control fact-sheet. The control and the intervention groups were comparable at entry for most characteristics (Table 1). However, the intervention group was more likely to be living with a parent or partner, to report fatigue as the main symptom at interview, and to have lower physical functioning in the month prior to the research interview.

Dropout rates were comparable between the trial groups (see Fig. 1). We received some follow-up data from 34/36 (94%) in the intervention and 30/33 (91%) in the control group. At 6 months 34/36 (94%) in the intervention and 26/33 (79%) in the control group returned complete data on the main outcome. A further three participants in the control group had their health status reported by a parent when we telephoned their home. The follow up rates at 3 and 12 months were less complete (68% and 71%, respectively). There was no association between follow up status and baseline fatigue score at any of the three time-points.

Treatment effects at 3, 6 and 12 months

Fatigue as a dichotomous outcomes is shown in Table 2. There were no differences in groups at 3 months. At 6 months, our primary outcome was fatigue at 6 months and this was explored using two methods (see Table 2). We generated odds ratios and corrected these for baseline fatigue and other clinical factors. The results were statistically significant for the completer analysis, after correcting for baseline imbalances, suggesting that there were fewer cases of fatigue in the treatment group. For the last observation carried forward analyses there was no significant difference between the two groups. At 12 months there remained more cases of fatigue in the control group compared to those in the intervention, but these differences were no longer significant (see Table 2).

A similar pattern of results is shown for fatigue as a continuous variable (see Table 3). No significant differences were seen at 3 months. At 6 months, the results were statistically significant for both the completer analysis and last observation carried forward method. Analysis of covariance controlled for baseline scores for severity of fatigue, physical functioning and self-report of recovery,

Table 3
Fatigue scores at baseline and follow-ups

Method used	Mean score intervention (S.D.)	Mean score control (S.D.)	Mean difference (95% CI)	*t* Test (*P*)	Mean difference corrected for baseline fatigue score, SF36 and whether "recovered" at baseline (95% CI)	*t* Test (*P*)
Baseline	19.7 (4.8)	19.9 (5.7)	−0.2 (−2.7, 2.4)	0.12 (.90)	NA	
Completers at 3 months	15.0 (5.1)	15.5 (6.2)	−0.5 (−3.8, 2.9)	0.30 (.77)	−0.3 (−3.3, 2.7)	0.20 (.84)
Completers at 6 months	12.7 (3.1)	15.6 (5.5)	−2.9 (−5.2, −0.7)	2.62 (.01)	−3.2 (−5.6, −0.9)	2.73 (.009)
LOCF at 6 months	13.0 (3.4)	15.3 (5.3)	−2.3 (−4.4, −0.1)	2.11 (.04)	−2.6 (−4.8, −0.3)	2.28 (.03)
Completers at 12 months	13.4 (3.6)	14.5 (6.1)	−1.1 (−4.0, 1.8)	0.75 (.46)	−0.5 (−3.6, 2.5)	0.35 (.73)
LOCF at 12 months	13.1 (3.6)	14.8 (5.6)	−1.7 (−3.1, 0.6)	1.49 (.14)	−1.6 (−4.2, 0.9)	1.32 (.19)

LOCF = Last observation carried forward, C1 = Confidence intervals, SF 36 = Short form Medical Outcome Survey.

Table 4
Secondary outcome measures at 6 months

Outcome measure	Intervention number or mean	Number responded	Control number or mean	Number responded	Statistic (*P*)
Self-report of recovery (%)	15/23 (65.2)		14/23 (60.9)		$\chi^2 = 0.90$ (.76)
Handicap[a] (S.D.)	2.0 (0.8)	24	2.3 (1.5)	20	$z = 0.04$ (.97)
Better[b] (S.D.)	2.0 (0.7)	24	2.0 (0.9)	20	$z = 0.61$ (.54)
Social and Work Adjustment Scale[a] (S.D.)	2.3 (3.6)	16	4.7 (7.7)	15	$U = 86$ (.29)
SF36-Daily functioning[b] (S.D.)	88.3 (20.7)	24	84.5 (23.7)	19	$U = 214$ (.51)
SF36-Physical functioning[b] (S.D.)	84.3 (29.3)	24	66.2 (42.3)	17	$U = 189$ (.17)
SF36-Emotional functioning[b] (S.D.)	84.6 (28.3)	24	74.3 (32.5)	17	$U = 212$ (.44)
Number of times seen GP since diagnosis of IM (S.D.)	2.9 (2.0)	21	4.8 (4.0)	19	$U = 164$ (.35)
Off-sick at the moment (%)	1/23 (4.3)		3/21 (14.3)		$\chi^2 = 1.31$ (.25)

SF36 = Short form Medical Outcome Survey.
[a] High score = worse.
[b] Low score = worse.

again showed a statistically significant improvement in the intervention group for both methods. At 12 months there were no differences between groups.

Secondary analyses were undertaken to explore other health outcomes, including functionality, self-report of recovery and health care utilisation at 6 months (see Table 4). All results were in the same direction, in that those in the intervention had better outcomes than the controls, but they were not statistically significant. The results of these analyses, though, should be interpreted with caution as fewer participants chose to answer them.

Acceptability of the intervention was evaluated at 6 months. None of the participants who answered reported dissatisfaction (24/24) with the intervention and 78% (18/23) found it to be useful.

Power calculation for a definitive study

As one of the purposes of this paper was to determine the sample size required for a definitive randomised controlled trial of this intervention, we calculated that if 33.3% of the treatment group and 48.5% of the control group had fatigue at 6 months (based on LOCF in Table 2), 177 patients would have to be randomised to each group at 80% power and 95% confidence. If the corresponding figures from the completer analysis were used (26.5% and 53.8%, respectively), we would require 57 patients in each group with the same level of power and confidence.

Discussion

Main findings

In this exploratory study, we were able to develop a brief intervention of advice about rehabilitation for sufferers of IM. The intervention was acceptable, and at 6 months we were able to achieve satisfactory follow up, indicating that a larger multicentre trial of the intervention would be feasible. Our results indicate that for the completer analysis, the main endpoint (fatigue at 6 months) was less frequent in those who received the intervention. This was not the case for our LOCF analysis. However, when fatigue was measured as a continuous variable (affording more statistical power) both completer and LOCF analyses indicated that the intervention group had a better outcome. At 12 months, differences between groups were more modest, and not statistically significant. This partly reflects reduced statistical power due to incomplete follow up. It also might reflect the natural history of IM related fatigue.

Methodological problems

This was a small study, and the estimate of treatment effect was imprecise. The follow-up rates were acceptable, but there were more incomplete data for the control group at 6 months. Unequal follow-up rates may explain the more modest differences between the intervention and control groups when methods are used to take account of missing data. Those who failed to complete questionnaires at follow up had fewer symptoms at baseline, and dropped out of the trial. It is possible that clinical practice in the participating centres was affected by the study, leading to a change in practice among GPs. We do not think such contamination is a major concern as our contact with the patients took place after the GP had made the diagnosis, and most participants were not in regular contact with the GP. Such contamination would have the effect of reducing the observed treatment effect.

The main reason potentially eligible patients were not included was that we were unable to contact them. Of those who were eligible and whom we contacted, the majority agreed to participate. The baseline demographic characteristics of this study were similar to those found in IM populations in a recent surveillance study [12]. Although the treatment was delivered in a standardised fashion, it is impossible to assess whether it is generalisable as only one person delivered it.

This is the second trial to test an intervention aimed at improving recovery in IM; the first (a quasirandomised study)

found in-patients allowed unrestricted activity recovered quicker than those on bedrest [13].

Implications of results

The main finding of this study suggests that a brief intervention of graded activity may help medium- to long-term recovery. If similar findings are found in subsequent larger studies, it could have important clinical and economic implications, in reducing the time lost in long-term sickness and the costs of treating patients with chronic illness. The study also suggests indirectly that unqualified advice to rest because of symptoms of glandular fever may be unhelpful.

In addition to adding to the growing consensus that rest advice is not generally a helpful intervention [14], we suggest that our findings add to the argument that patients should be more involved in their care [15], and are given a guided form of convalescence [16] from this common illness.

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