RESEARCH ARTICLE

Predictors of Missed Research Appointments in a Randomized Placebo-Controlled Trial

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Abstract

Background: The primary aim of this study was to determine predictors of missed research appointments in a prospective randomized placebo injection-controlled trial with evaluations 1 to 3 and 5 to 8 months after enrollment.

Methods: This study represents a secondary use of data from 104 patients that were enrolled in a prospective randomized controlled trial of dexamethasone versus lidocaine (placebo) injection for various diagnoses. Patients were enrolled between June 2003 and February 2008. Sixty-three patients (61%) had lateral epicondylosis, 17 patients (16%) had trapeziometacarpal arthrosis, and 24 patients (23%) had de Quervain syndrome. Each patient completed a set of questionnaires at time of enrollment. Bivariable and multivariable analyses were used to determine factors associated with missed research appointments.

Results: Fourteen patients (13%) did not return for the first follow-up and 33 patients (32%) did not return for the second follow-up. The best multivariable logistic regression model for missing the first research visit explained 35% of the variability and included younger age, belief that health can be controlled, and no college education. The best model for missing the second research visit explained 17% of the variability and included greater pain intensity, less personal responsibility for health, and diagnosis (trapeziometacarpal arthrosis and de Quervain syndrome).

Conclusions: Younger patients with no college education, who believe their health can be controlled, are more likely to miss a research appointment when enrolled in a randomized placebo injection-controlled trial.

Key words: De Quervain syndrome, Lateral epicondylosis, Loss to follow-up, Missed research appointments, Randomized placebo-controlled trial, Trapeziometacarpal arthrosis

Introduction

Missed research appointments ("loss to follow-up") are a common problem in prospective trials. Loss of patients may bias the results (attrition bias) if completers are different from non-completers, particularly if more patients are lost from one cohort than another (1-4). Patients that don't keep a research appointment might be dissatisfied and unwilling to return (3, 5, 6). On the other hand, one might argue that patients with ongoing problems are more likely to return (3).

Some suggest not to enroll patients who are unlikely to return for follow-up (e.g., psychiatric problems, no fixed address, likely to move within study period, lower socioeconomic status, and substance abuse problems) in order to minimize study drop out (4). Although this improves the internal validity, it compromises the external validity of the study (the sample should be representative of the target population) (7).

A better understanding of the factors associated with failure to keep important research appointments might influence future study design and the interpretation of studies with high drop out rates. This study addressed the null hypothesis that there are no factors associated with missed research appointments in a prospective double-blinded randomized placebo injection-controlled trial with evaluations between one and three and five and

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Table 1. Bivariable Analysis of Missing First Research Appointment

	First Research Appointment						n=104	
	Completed (n=90)			Missed (n=14)				
Parameter	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Correlation**	***P* value**
Age (years)	50	10	26-73	44	11	24-67	NS	0.053
Education (years)	15	2.9	8-24	14	3.3	8-20	NS	0.17
DASH	30	16	1.7-77	27	12	3.3-44	NS	0.72
Pain	4.8	2.1	0.6-9.7	6.1	2.3	1.6-8.7	0.21	**0.031**
IHLC	24	4.7	6-34	21	6.4	8-30	NS	0.17
CHLC	17	5.3	6-34	12	5.0	6-23	0.28	**0.0039**
PHLC	17	6.2	6-36	14	7.9	6-36	NS	0.062
CES-D (n = 76)	10	12	0-52	9.5	10	0-32	NS	0.86
PCS (n = 76)	21	8.7	13-49	26	10	13-43	NS	0.19
EPQ-R psychoticism (n = 82)	6.1	4.3	1-26	6.3	4.1	1-14	NS	0.70
EPQ-R extraversion (n = 82)	13	5.5	0-22	16	3.6	9-21	NS	0.12
EPQ-R neuroticism (n = 82)	11	6.3	0-24	10	4.6	2-19	NS	0.98
EPQ-R dishonesty (n = 82)	11	4.5	2-24	12	5.6	3-19	NS	0.28
Parameter	**Number**		**%**	**Number**		**%**	**Correlation**	***P* value**
Gender							NS	0.99
Male	32		35.6	5		35.7		
Female	58		64.4	9		64.3		
Race							NS	0.61
White	81		90.0	11		78.6		
Black	4		4.4	1		7.1		
Hispanic	2		2.2	1		7.1		
Asian / Pacific Islander	3		3.3	1		7.1		
Marital status								**0.023**
Single	16		17.8	7		50.0		
Married / living with partner	60		66.7	5		35.7		
Separated / widowed	14		15.5	2		14.3		
Work status							NS	0.64
Working, full-time or part-time	64		71.1	11		78.6		
Homemaker	5		5.6	0		0.0		
Retired	4		4.4	1		7.1		
Unemployed	9		10.0	2		14.3		
Other / unknown	8		8.9	0		0.0		
Degree of education							NS	0.082
No high school diploma	4		4.4	2		14.2		
High school diploma	22		24.5	6		42.9		
College education	64		71.1	6		42.9		
Diagnosis							NS	0.31
Trapeziometacarpal arthrosis	14		15.5	3		21.4		
De Quervain's tendosynovitis	23		25.6	1		7.2		
Lateral elbow pain	53		58.9	10		71.4		
Injection							NS	0.65
Placebo	38		42.2	5		35.7		
Cortisone	52		57.8	9		64.3		

eight months after enrollment.

Materials and Methods

This study represents a secondary use of data from a prospective double-blind randomized controlled trial comparing arm-specific disability after a single injection of dexamethasone and lidocaine versus a single injection of placebo (lidocaine only) for lateral elbow pain, trapeziometacarpal (TMC) arthrosis, and de Quervain syndrome (8, 9). Secondary use of the data was approved

Table 2. Multivariable Logistic Regression Analysis of Missing First Research Appointment			n = 104	
Predictor	***P* value**	**Odds ratio**	**95% CI for Odds Ratio**	
			Lower	**Upper**
Age	0.018	0.92	0.85	1.0
CHLC	0.0034	0.79	0.68	0.93
No high school diploma	0.015	18	1.7	187
High school diploma	0.045	4.3	1.0	18
N = Number; CI = Confidence Interval; CHLC = Chance Health Locus of Control scale.				

by our Human Research Committee.

One hundred and seven patients were enrolled between June 2003 and February 2008. Each patient completed a Visual Analogue Scale (VAS) for pain, the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, and the general Multidimensional Health Locus of Control (MHLC) scale to measure patients' health-related beliefs (10, 11). The subscales of the MHLC measure Internal Health Locus of Control (IHLC), Powerful Others Health Locus of Control (PHLC), and Chance of Health Locus of Control (CHLC). The Eysenck Personality Questionnaire (EPQ-R; a measure of personality traits) was administered until the lateral elbow pain study was complete and then it was discontinued (12). After enrollment of the first 28 patients, the protocol was amended to include the Center for Epidemiologic Studies – Depression Scale (CES-D) and the Pain Catastrophizing Scale (PCS) (13-15). Patients were asked to return between one and three months and between five and eight months after the injection to complete additional measurements. A research assistant not involved in patient care tried to contact patients by phone (a maximum of three times) if they did not return for a research appointment, to schedule an appointment or ask them to complete the questionnaires via mail.

Three patients were excluded because enrollment data was unavailable, in one case the patient did not return the questionnaires and in the other two cases the data was misplaced. One hundred and four patients were left for analysis: 63 patients (61%) had lateral elbow pain, 17 (16%) had TMC arthrosis, and 24 (23%) had de Quervain syndrome.

Statistical analysis

A post-hoc power analysis showed that the 104 available patients would provide 81% power to detect factors with an odds ratio of 2.3 for missing the first research visit (two-tailed alpha = 0.05, beta = 0.19).

Non-parametric tests were used to assess relationships between variables since the data was not normally distributed. Missing answers and missing or invalid questionnaires were addressed with mean imputation. The Mann-Whitney U test was used to evaluate a dichotomous variable and a continuous variable. An approximate effect size (r value) was calculated from the z value that is reported with the Mann-Whitney U test. The Chi-square test was performed to assess the difference between two categorical variables. Relationships between continuous variables were determined with Spearman correlations. Variables with a significance level of $P<0.10$ in the bivariable analysis, with the exception of the EPQ-R, CES-D, and PCS questionnaires, were included in a multivariable logistic regression analysis using the stepwise backward method. A separate multivariable regression was also performed for patients that completed the EPQ-R questionnaire. Before performing a regression analysis, categorical variables with three or more categories were transformed into dichotomous dummy variables. A *P*-value of 0.05 was considered significant.

Results

Despite three phone attempts to contact patients by a research assistant, 14 patients (13%) missed the first research visit and 33 patients (32%) missed the second research visit. Four patients (all with lateral elbow pain) that missed the first research visit did return for the second research visit.

Some patients returned, but did not complete the questionnaires. This was likely our fault (research assistant failed to have them complete the questionnaires), and was therefore not counted as missing a visit. Three patients returned about one month after the injection, but didn't complete the questionnaires. Five saw the surgeon a second time but didn't complete questionnaires.

Numbers analyzed

Mean imputations were performed for the following missing or incomplete measures: one DASH questionnaire, four VAS pain ratings, three MHLC questionnaires, two CES-D questionnaires, one PCS questionnaire, and three EPQ-R questionnaires. After the mean imputations, CES-D and PCS scores were available for a subgroup of 76 patients and EPQ-R scores were available for all 63 lateral elbow pain patients, and for six patients with TMC arthrosis, and 13 patients with de Quervain syndrome.

Predictors of missing the first research appointment

In bivariable analysis, missing the first research appointment was significantly associated with single status (vs. living with partner/married), greater pain intensity, and lower CHLC. Associations that met the criterion for entry into the regression analysis ($P<0.10$) included younger age, lower PHLC, and no college education (Table 1). The best logistic regression model for missing the first research appointment included

Table 3. Bivariable Analysis of Missing Second Research Appointment **n = 104**

	Second Research Appointment							
	Completed (n=71)			Missed (n=33)				
Parameter	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Correlation**	**P value**
Age (years)	50	9.7	32-73	47	12	24-72	NS	0.20
Education (years)	15	3.0	8-24	15	2.9	8-20	NS	0.55
DASH	28	17	1.7-76	33	13	3.3-62	0.20	**0.041**
Pain	4.7	2.1	0.6-9.0	5.7	2.2	1.2-9.7	0.19	**0.0496**
IHLC	24	5.0	6-34	22	4.6	13-29	0.25	**0.010**
CHLC	16	5.3	6-34	16	5.8	6-26	NS	0.63
PHLC	17	6.3	6-36	17	6.8	6-36	NS	0.96
CES-D (n = 76)	9.8	11	0-51	11	12	0-52	NS	0.78
PCS (n = 76)	21	9.0	13-49	23	9.1	13-43	NS	0.36
EPQ-R psychoticism (n = 82)	5.5	3.5	1-17	7.7	5.6	1-26	0.21	**0.036**
EPQ-R extraversion (n = 82)	14	5.4	2-22	13	5.4	0-21	NS	0.60
EPQ-R neuroticism (n = 82)	10	6.1	0-24	12	5.9	0-22	NS	0.19
EPQ-R dishonesty (n = 82)	11	4.7	2-24	10	4.5	3-19	NS	0.48
Parameter	**Number**		**%**	**Number**		**%**		
Gender							NS	0.91
Male	25		35.2	12		36.4		
Female	46		64.8	21		63.6		
Race							NS	0.34
White	63		88.8	29		87.9		
Black	2		2.8	3		9.1		
Hispanic	3		4.2	0		0.0		
Asian / Pacific Islander	3		4.2	1		3.0		
Marital status							NS	0.17
Single	12		16.9	11		33.3		
Married / living with partner	47		66.2	18		54.6		
Separated / widowed	12		16.9	4		12.1		
Work status							NS	0.94
Working, full time or part time	51		71.8	24		72.7		
Homemaker	4		5.6	1		3.0		
Retired	3		4.2	2		6.1		
Unemployed	7		9.9	4		12.1		
Other / unknown	6		8.5	2		6.1		
Degree of education							NS	0.60
No high school diploma	3		4.2	3		9.1		
High school diploma	19		26.8	9		27.3		
College education	49		69.0	21		63.6		
Diagnosis							NS	0.092
Trapeziometacarpal arthrosis	9		12.7	8		24.2		
De Quervain's tendosynovitis	14		19.7	10		30.3		
Lateral elbow pain	48		67.6	15		45.5		
Injection							NS	0.48
Placebo	31		43.7	21		36.4		
Cortisone	40		56.3	21		63.6		

younger age, lower CHLC, and no college education, and explained 35% of the variability (Table 2).

Predictors of missing the second research appointment

In bivariable analysis, missing the second research appointment was significantly associated with higher DASH score, greater pain intensity, and lower IHLC. In the subgroups with EPQ-R, higher EPQ-R psychoticism score was a factor. The association between missing the second research appointment and lateral elbow pain (vs.

Table 4. Multivariable Logistic Regression Analysis of Missing Second Research Appointment				n = 104
Predictor	**P value**	**Odds ratio**	**95% CI for Odds Ratio**	
			Lower	**Upper**
Pain	**0.043**	1.2	1.0	1.5
IHLC	0.050	0.91	0.84	1.0
Diagnosis of lateral elbow pain	0.066	0.43	0.18	1.1
N = Number; CI = Confidence Interval; IHLC = Internal Health Locus of Control scale.				

TMC arthrosis or de Quervain syndrome) also met the criterion for entry into the regression analysis (P<0.10) (Table 3). The best logistic regression model explained 17% of the variability in missing the second research appointment and included greater pain intensity, lower IHLC, and the diagnosis of lateral elbow pain that lowered the probability of missing the appointment (Table 4). The multivariable model for the subgroup with EPQ-R was not statistically significant.

Discussion

We identified predictors of missed research appointments in a randomized placebo injection-controlled trial of patients with lateral epicondylosis, TMC arthrosis, and de Quervain syndrome. Over one third of the variance in missing the first research visit was accounted for by younger age, less education, and less of a sense that health was simply a matter of chance (lower CHLC). The model for missing the second research visit only explained 17% of the variance and included greater pain intensity, less personal control over health (lower IHLC), and diagnosis (TMC arthrosis or de Quervain syndrome).

Shortcomings to consider include that this was a secondary use of data, that our best logistic regression models might be over fitted (retain too many variables), and our inability to assess the extent to which patients' response to treatment affected the attrition rate because we did not have data on treatment outcomes for patients who were lost.

Our results are consistent with previous studies that identified younger patients with less education as more likely to miss research appointments in clinical trials (16-19). Greater pain intensity was also previously associated with attrition in clinical trials (5, 17). Lower IHLC (less of a sense of control over one's health) is a plausible correlate of missed research appointments. We are not sure how to interpret the higher loss to follow-up of TMC arthrosis and de Quervain syndrome patients which did not significantly contribute to the best multivariable model.

There were different predictors for missing the first and second research visits. The association between greater pain intensity and missing the second visit might indicate that patients with a worse treatment outcome were less likely to return, but we cannot study this because we do not have the outcomes of patients that did not return. The fact that we found different predictors, except for greater pain intensity, for missing the first and second research appointment fits our experience. We believe that it is very likely that patients who completely drop out of a research study with two additional research visits after enrollment are different from those who do complete the first visit but not the second visit. Murray et al. tracked all patients and found that non-attenders after total hip replacement had a worse outcome (5). Chung et al. performed a long-term follow-up (average of 17 years) of patients who had capsular arthroplasties done for congenital dislocation of the hip and found that the least cooperative subjects had poor clinical outcome and were dissatisfied (20). Even a small number of lost patients can result in an over-optimistic conclusion of the studied intervention and could be harmful if leading to incorrect treatment recommendations (3).

There was no difference in missed research visits between the placebo and dexamethasone injection group. Significantly higher attrition rates have been found in placebo arms of placebo-controlled trials of second-generation antipsychotics and classical antipsychotics (21).

In the national Beta-Blocker Heart Attack Trial specific methods were used to enhance study compliance including appointment reminders, assistance with transportation, minimal waiting times, newsletters, continuity of care, involvement of family members, and close contact with private physicians (22). Completion rates with these methods were only slightly higher than those of comparable trials (22).

Sprague et al. implemented several strategies, involving exclusion criteria and the consent process, to minimize loss to follow-up in a multicenter, randomized controlled trial in orthopaedic surgery (4). Study staff was trained in communicating and negotiating with patients. Help was offered to clinical sites from the study center to locate patients with overdue visits. Visits were scheduled at times convenient for the patient, reminders for upcoming visits were provided, contact was regularly maintained, and participation demands were reduced for certain patients. Follow-up during the first year was completed by 94% of 440 patients; however, 15.8% of patients excluded from participation were due to "likely problems with maintaining follow-up" which may affect the generalizability of the study results.

Contacting patients and trying to get them to return requires substantial resources. We speculate that the following factors might improve retention of subjects in prospective research: education of research

personnel that younger, less educated patients can be more difficult to retain; organization of research projects so that as many potential methods of contact are used (e.g., email, phone, family members); and inviting and welcoming patients to express their dissatisfaction and providing an easy means to do so. We also found that we need to keep research assistants and coordinators involved in, focused on, and enthusiastic about research, and we need to develop better methods of tracking when patients involved in research return to the office so that questionnaires are completed at the appropriate time points.

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