ORIGINAL ARTICLE

A Successful Strategy for Recruiting Elderly Patients with Mild Hyperparathyroidism into a Randomized Controlled Trial

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Abstract

Objective: Effective strategies that improve the inclusion of older persons in clinical trials are needed to better characterize and treat chronic conditions that affect elderly patients. Especially challenging is the recruitment of the elderly into treatment trials for chronic conditions with vague symptoms, as is the case for primary hyperparathyroidism. The incidence of primary hyperparathyroidism increases with age, and the disease may present with symptoms that are difficult to objectively measure but contribute to decline of function and quality of life. Understanding the optimal treatment of primary hyperparathyroidism necessitates inclusion of greater numbers of older persons in treatment trials. As a part of our study of asymptomatic hyperparathyroidism, we also devised a strategy to recruit and retain older persons in a randomized surgical trial for primary hyperparathyroidism.

Design: Individuals greater than 60 years of age who did not meet established criteria for surgical intervention for primary hyperparathyroidism were offered the opportunity to participate in a clinical study evaluating the benefits of immediate minimally invasive parathyroidectomy (MIP) *vs* medical observation.

Intervention: Strategies to encourage participation and compliance included compensation for incidental expenses of lodging, meals, and travel for clinic visits related to the study as well as regular interaction with an experienced study coordinator.

Measurements: Study participation included formal neurocognitive evaluations, functional magnetic resonance brain imaging, functional performance batteries, and sleep studies over a 6-month period.

Results: Thirty-five individuals ranging in age from 61 to 79 years were screened for participation. Nine individuals were ineligible, and 14 of eligible individuals consented to participate in the study. Among the 12 eligible individuals who declined to participate, the most common reason identified was distance to study center.

Conclusion: We report an effective strategy to recruit a substantial proportion of eligible elderly individuals as subjects in a study of treatment strategies for a medical condition with few overt symptoms.

Keywords: Hyperparathyroidism, recruitment, elderly, parathyroid.

INTRODUCTION

Recruiting elderly patients into clinical trials has historically been difficult. A strong inverse relationship has been observed between the fraction of a given group that enrolls in trials and age.[1,2] In fact, the lack of participation of elderly subjects in clinical trials is of significant concern to investigators since this compromises the ability to minimize bias and generalize findings. As the population ages, the importance of having older subjects in trials becomes more acute, especially since a large percentage of studies involve illnesses that affect the geriatric population disproportionately. Hence, the inclusion of elderly patients in clinical trials is critical. The reasons for nonparticipation by elderly individuals vary widely. Reasons identified include difficulty in understanding the objectives of the study, subjective feeling that one is too unwell to participate, difficulty in travelling to the study center, and mistrust of the medical profession.[3]

When overt symptoms are not present, recruitment of elderly subjects can be even more challenging. For example, attempts to enroll geriatric subjects in a study evaluating the effectiveness of a medication review clinic yielded an enrollment of only 2% (48 of 2,505) of eligible individuals.[4]

Similarly, the recruitment of older subjects for a trial evaluating the effectiveness of the influenza vaccine led to participation of only 15% (912 of 6,058) of eligible people.[5] Hence, the study of conditions in which symptoms are not overtly lifestyle altering or a benefit is not obvious is quite challenging.

Three consensus conferences have convened to provide specific recommendations for the appropriate timing of surgical intervention for primary hyperparathyroidism. The surgical criteria established included age and degree of elevated serum calcium, reduced creatinine clearance, elevated urine calcium excretion, and decreased bone mineral density.[6-8] However, significant controversy still exists with regard to patients who do not meet the minimum surgical criteria suggested by the guidelines but who may benefit from early surgical intervention to treat their more subtle symptoms. A challenge in defining that group has been in the area of trial recruitment. Hence, the goal of this study was to devise a strategy to recruit and retain elderly subjects in a study to evaluate the effects of observation *vs* surgical intervention for mild asymptomatic primary hyperparathyroidism.

METHODS

Individuals older than 60 years who had asymptomatic primary hyperparathyroidism that did not meet the criteria for surgical intervention defined by the US. National Institutes of Health in 2001 (Table 1) were offered the opportunity to participate in a clinical study evaluating the benefits of surgery *vs* observation.[7] The majority of patients were referred to the study by other physicians while a minority were self-referrals. Pamphlets describing the study were available to individuals in the Multidisciplinary Endocrine Center clinic area of the institution. The study coordinator, who was a senior research nurse with more than 20 years of clinical trial experience, discussed the details of the study with potential participants. This discussion included details of possible treatments, risks and potential benefits of treatments, the tests required, and duration of the study. The battery of tests required included neurocognitive evaluations, functional magnetic resonance brain imaging assessments, functional performance batteries, and sleep studies, performed at trial enrollment and then six weeks and 6 months following intervention. For the surgical group, the intervention was parathyroidectomy and for the medical observation group it was a telephone interview of cognitive status. Since primary hyperparathyroidism is nonacute, with the efficacy of immediate parathyroidectomy for mild disease not yet definitively established, patients were informed that there was no substantial risk to medical observation.

Eligible patients who agreed to participate and provided written informed consent were prospectively randomized into one of two groups: immediate surgical intervention (parathyroidectomy) or medical observation. The surgical group underwent a minimally invasive parathyroidectomy performed by an endocrine surgeon after appropriate preoperative localizing imaging studies. The observation group was closely followed for 6 months and then was offered a minimally invasive parathyroidectomy upon completion of the study. Both groups of patients underwent the battery of tests and routine laboratory and imaging evaluations for primary hyperparathyroidism. The surgical group underwent testing just prior to parathyroidectomy, while the observation group underwent testing immediately following a telephone interview of cognitive status. The telephone interview was meant to serve as the "intervention" for this group. Two subsequent testing batteries were required, 6 weeks and 6 months following study entry.

Several strategies were used to encourage participation and retention in the clinical study (Table 2). While ethical considerations precluded paying patients for study participation, patients were given parking tokens and cafeteria meal tickets to cover expenses incurred as a result of clinic visits for study participation. In the event that tests could not be completed in 1 day, lodging was also provided. Participants were reimbursed for mileage to attempt to mitigate the cost of travel from a distance. Additionally, the

Table 1: Indications for surgery for asymptomatic hyperparathyroidism, from 2002 US national institutes of health consensus conference

1. Markedly elevated serum calcium (≥ 1.0 mg/dL above normal)
2. Creatinine clearance reduced by ≥ 30% *vs* age-matched normal subjects
3. Markedly elevated 24-hour urine calcium (> 400 mg/day)
4. Age < 50 years
5. Substantially reduced bone mass as determined by direct measurement (bone mineral density < 2.5 standard deviations below normal subjects')

Adapted from Bilezikian JP et al.[7]

Table 2: Strategies used to increase participation and retention in study

1. Compensation for expenses for traveling to the study center
2. Provision of lodging, parking, and meals
3. Minimizing the number of trips to study center
4. Direct contacts between study coordinator and participants
5. Frequent telephone contacts between study coordinator and participants
6. Excellent communication and organizational skills of coordinator

study coordinator minimized the number of separate trips that subjects had to make to the medical center by clustering tests within a few days. For example, in the group that underwent surgical intervention, the study-related appointments were made on same days as routine preoperative and postoperative appointments. Finally, the study coordinator had frequent in-person and telephone contact with the study participants. A variety of data was collected during the study, in addition to demographic information. Sources of data included the baseline telephone interview, laboratory evaluation, neurocognitive evaluation, functional MRI results, physical performance evaluation that include walking tolerance tests, a sleep study for seven days, the Epsworth sleepiness scale, the Brief sleep disturbance scale, sleep diary, and follow-up appointments.

RESULTS

Thirty-five individuals ranging in age from 61 to 79 years were screened for participation in the study. Of these, 9 were not eligible for the study, and 14 consented to participate in the trial. Hence, more than half of eligible individuals (14 of 26) consented to participate in the study. Two of the 14 participants withdrew prior to completion of the study; one withdrew owing to concerns about incurring additional nonreimbursed medical expenses in the observation arm, and a second patient in the observation arm was withdrawn owing to noncompliance with data collection.

Of eligible patients approached to participate in the clinical trial, no difference in participation was noted between men (2 of 6 agreed) and women (12 of 29 agreed). Additionally, distance to the study center, comorbidities, and assistance required for travel were not contributory in determining study participation. Among the eleven individuals who declined to participate in the study, reasons provided included distance to the study center (2 individuals), reluctance to be randomized to an observation group (4 individuals), and family related limitations (1 individual). There were no differences identified with regards to enrolled and refusal groups with regards to age (70.5 *vs* 71.4 years), travel distance (80 *vs* 79 miles), number of comorbidities (0 *vs* 0), and need for transportation assistance (3 *vs* 3).

DISCUSSION

We report an effective strategy to recruit a substantial proportion of eligible elderly individuals as subjects in a study of treatment strategies for a medical condition with few overt symptoms, asymptomatic primary hyperparathyroidism. In previous studies that evaluated the impact of parathyroidectomy *vs* observation for asymptomatic primary hyperparathyroidism that did not meet National Institutes of Health criteria for intervention, the enrollment of potentially eligible patients has varied from 19 to 25%.[9,10] In our study, 40% of approached individuals and 58% of eligible individuals consented to participate in the clinical trial. This high participation rate appears to result from several factors, the most critical of which was likely a motivated study coordinator. A single dedicated study coordinator maintained contact with all of the participants in the trial. In addition to being available by phone and e-mail to answer questions or concerns, the coordinator arranged study-related appointments so as to minimize the time and inconvenience incurred by study participants. Participants frequently commented to the principal investigator that they felt that they were being treated exceptionally well. Many commented that the one-on-one attention was motivating, possibly leading to improved retention of subjects. Additionally, unlike most studies at our institution, subjects did not have to incur a monetary penalty for study participation since incidental expenses such as additional lodging, parking, and meals were paid for as part of the trial. Chang et al reported a similar strategy for recruiting elderly patients for a randomized clinical trial of behavioral therapy for chronic heart failure with interactions with the recruiter being critical. Those authors found a strong correlation between the appearance, personality, manner, and gender of the recruiter and patient agreement to participate in the trial.[4]

In conclusion, the strategies we used to increase study participation by geriatric individuals were successful, even in the context of asymptomatic disease, although the sample size in our study was too small for statistical analyses. Further research in this area is needed, but careful consideration of factors such as reducing the distance to the study site by perhaps offering multiple sites so patients have to travel shorter distances, reducing the total number of visits required by grouping tests and procedures into the shortest time frame possible, providing monetary compensation for the out-of-pocket expenses incurred, and having an experienced recruiter with excellent interpersonal skills can increase elderly patients' participation and retention in clinical trials.

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