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Recruitment of Patients to a Glaucoma Drug Trial in a District General Hospital

PALANISWAMY SUNDERRAJ and COLIN S. L. PEIRIS
Southport

Summary
We report the difficulties experienced in identifying and recruiting 21 patients with ocular hypertension or primary open-angle galucoma to participate in a clinical trial of two topical beta-blockers. The case-notes of 374 consecutive patients expected to attend routine glaucoma clinics were reviewed to recruit 21 eligible patients who were willing to undergo the drug trial. Recruitment of patients to prospective drug trials may be complicated by a high proportion of exclusions due to ineligibility and also by refusal of otherwise eligible patients.

Recruitment of eligible subjects who are willing to take part in a clinical trial is one of the major problems encountered in clinical research.[1,2] In spite of several reports from other specialties on the extent of this common problem,[2–8] only limited information is available in the ophthalmic literature.[9] We report the difficulties experienced in identifying and recruiting patients with ocular hypertension (OH) or primary open-angle glaucoma (POAG) to participate in a double-masked, cross-over evaluation of two different beta-blockers.

Patients and methods

The proposed, comparative, evaluation of two topical beta-blockers was to be carried out in the eye department of the District General Hospital, Southport. The study patients, already well controlled on treatment with a topical ocular hypotensive agent, were required to attend the hospital on five occasions over a period of four months with each visit lasting approximately 30 minutes. The study patients were identified and recruited in the following stages:

Stage I

The case-notes of all the patiens attending the weekly glaucoma clinic were reviewed on the preceding day to identify subjects with OH and POAG who fulfilled the following conditions for possible inclusion in the trial—untreated intraocular pressure greater than 21mm HG with or without glaucomatous visual field defect and pathological cupping of the optic disc, open angle of the anterior chamber on gonioscopy and no demonstrable secondary cause of raised intraocular pressure.

Case-notes of the patients so selected were studied in detail and excluded according to the following criteria:

(1) patients younger than 18 years or older than 80 years of age
(2) history or evidence of serious respiratory disorder including bronchial asthma
(3) history or evidence of bradycardia (less than 55 beats per minute), heart block, ischaemic heart disease or cerebro-vascular insufficiency
(4) history or evidence of neuro-psychiatric

Correspondence to: Mr P. Sunderaj, Department of Ophthalmology, Southport and Formby District General Hospital, Southport.

problems including depression and anxiety neurosis
(5) presence of chronic ocular disease like blepharitis, recurrent corneal ulceration or dry eye syndrome
(6) current contact lens wear
(7) history of glaucoma filtration surgery or intraocular surgery
(8) glaucoma controlled with more than one medication
(9) history of intolerance to beta-blocking agents
(10) taking concurrent medications with systemic beta-blockers, beta-antagonists, tri-cyclic anti-depresessants, mono-amino oxidase inhibitors, oral or topical corticosteroids, carbonic anhydrase inhibitors or other drugs which may affect intraocular pressure or interact with topical beta-blockers
(11) pregnant women or nursing mothers
(12) judged by the investigator to be unsuitable for the study

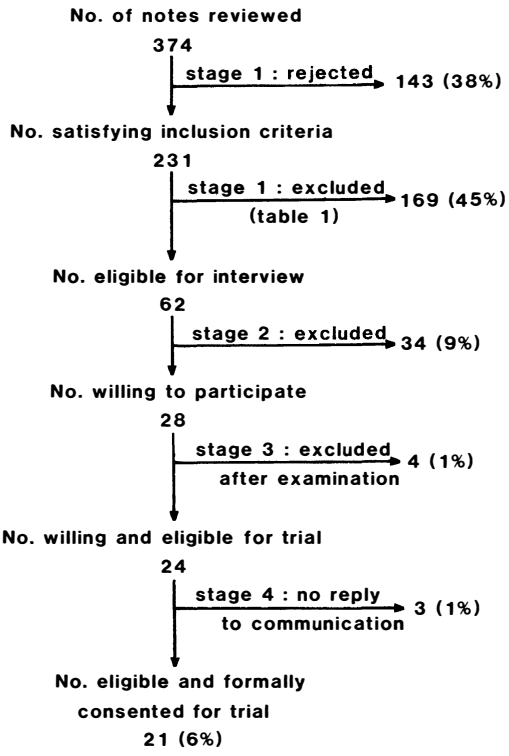

Fig. 1 *Flow-chart summarizing the identification and recruitment of study patients.*

Stage II
The patients who satisfied both the inclusion and exclusion criteria and attended the routine glaucoma clinic review were interviewed. The objectives of the study and the implications of participation were fully explained to each potential subject. Those who were unwilling to participate in the trial or were judged unsuitable were excluded from the study.

Stage III
The remainder of the potential subjects for the study underwent a comprehensive general medical examination including the cardiovascular and respiratory systems to assess their fitness for participation in the trial. A detailed medical history was also obtained. Some patients were excluded from the study at this stage due to medical problems.

Stage IV
All the willing and eligible patients were subsequently contacted to inform them that both the investigators were available for any final clarification required before the potential subjects gave formal consent for participation in the evaluation of two ophthalmic beta-blockers.

This routine is summarised as a flow-chart in Figure 1.

Results

Reveiw of the case-notes of 374 consecutive patients expected to attend the routine glaucoma clinics revealed 231 case-notes of patients with OH or POAG who satisfied the inclusion criteria. The remaining 143 case-notes belonged to patients with suspect glaucoma (16), narrow-angle glaucoma (34), normal tension glaucoma (16), secondary glaucoma (10) and others including post-operative and casualty patients.

One hundred and sixty-nine case-notes from the 231 initially identified for inclusion in the study were excluded due to the various causes listed in Table I. A single case-note was occasionally excluded for more than one reason. Forty-two patients were judged unsuitable for the study on the basis of information found in their case-notes (Table I) because of visual impairment (13), poor

Table I *Reasons for excluding case-notes of patients with ocular hypertension/primary open-angle glaucoma**

Reason		*Number of case notes*	*(percentage)*
Multiple anti-glaucoma medication		87	(38)
More than 80 years old		49	(21)
Judged unsuitable for the study		42	(18)
Trabeculectomy		26	(11)
Problems contra-indicating beta-blockers		23	(10)
Respiratory	17		
Cardio-vascular	6		
Neuro-psychiatric	2		
Pre-existing eye disease		11	(5)
On prohibited medication		10	(4)
Others		21	(9)

*a single case-note may have been excluded due to more than one reason

general health (12), lived or worked a long distance away (9) and other reasons (13).

Of the 62 patients who were eligible to proceed to Stage II, four failed to keep the glaucoma clinic appointment. The other patients were interviewed, of whom 13 declined to participate in the study. A further 17 patients (nervous disposition 5, poor general health 5, lived or worked a long distance away 4, difficulty in performing appalantion tonometry 2, other reasons 3) were found unsuitable for the study. The 28 remaining patients were examined in Stage III and of these, four were excluded due to cardiac (one patient) and respiratory (three patients) problems.

The 24 eligible and initially willing patients were subsequently contacted for definite participation in the study. Three patients failed to give formal consent leaving 21 patients for inclusion in the study of two topical beta-blockers.

These 21 patients were recruited from a review of the case-notes of 374 patients expected to attend routine glaucoma clinics, a ratio of 1:18.

Discussion

Identification and recruitment of eligible subjects who are willing to participate in a clinical trial is a major and common problem.[1-9] Several studies from other medical specialties[3-8] have reported progressive loss of patients who were initially identified as potential subjects for inclusion in the clinical trials. The ratio of final participants in the study to those who were initially identified as likely subjects varies from 1:4 in the Scottish breast conservation trial[8] to 1:136 in the Systolic Hypertension in the Edlerly Programme Study.[7] In comparable ophthalmic literature Quick *et al.*[9] reported a ratio of 1:93 (15 patients with OH or POAG were recruited from 1358 potential subjects for participation in a glaucoma drug trial) which is significantly different from the ratio of 1:18 experienced in the present study despite similar inclusion and exclusion criteria.

We identified potential subjects for the glaucoma drug trial by reviewing the case-notes of the patients who were to attend routine glaucoma review clinics unlike Quick *et al.*[9] who used an 'outpatient diagnostic index'.[10] Quick *et al.*[9] rejected 32% of all the case-notes reviewed because these belonged to 'glaucoma suspects', a patient group which was not eligible for participation in the topical beta-blocker trial. These patients comprised only 11% of all the case-notes we reviewed because glaucoma suspects who are normally followed at yearly intervals or more, unlike glaucoma patients who are followed at shorter intervals, are more likely to be encountered in a diagnostic index system than in a regular glaucoma clinic.

The case-notes of 176 (13% of the total) patients identified as potential subjects for the trial using the diagnostic index was not available to Quick *et al.*[9] for the purpose of review. This problem did not arise in our study as all the case-notes except one were traced and kept ready for the routine glaucoma clinic appointment. Thus glaucoma suspects and unavailable case-notes accounted for the loss of 45% of the potential subjects identifed by

Quick *et al.*[9] for possible inclusion in the glaucoma drug trial compared to 11% in our study. We did not compare the frequency of other causes of exclusion of the original case-notes because the previous authors[9] mention only one reason for excluding a case-note.

Twenty-two per cent (13) of the patients we invited personally to participate in our drug trial declined to do so. This was less than the 38% (73 patients out of the 193 invited by letter to participate in the glaucoma drug trial) reported by Quick *et al.*[9] This may be because our study was of shorter duration, required fewer visits to the hospital and involved less of the patient's time. Possibly also, a direct personal approach by the doctor evokes patient confidence and works better than the postal approach in securing the patients' consent to undergo a clinical trial (Villada and Joyce, personal communications).

Twenty-nine per cent (17) of the interviewed patients were found ineligible to proceed to the examination stage in our study compared to the 80% (96 patients out of the 120 interviewed) reported elsewhere.[9] The majority of the exclusions in that study[9] after interview were due to patients on prohibited medication, presence of extensive field loss and cardio-respiratory disease and other reasons which would normally be found recorded in case-notes. It appears that either the case-notes did not contain all the relevant information or whilst unlikely, they were overlooked during the initial review of the case-notes. This may account for the high rate of rejections of potential subjects at this stage of recruitment.[9]

In summary, the progressive loss of potential subjects for participation in a glaucoma drug trial during the various stages of identification and recruitment was significantly more in the previous report[9] than in our study. This was due to multiple factors like the method used to identify potential subjects for inclusion in the trial, availability of the case-notes for the subjects so identified, the design of the trial in terms of duration and number of patient visits required, the approach used in securing the patient's consent to undergo the drug trial and other miscellaneous factors. The impact of these factors on the progressive loss of patients during the organisation of any clinical trial is highly variable not only within the same medical speciality[8,11] but also between different medical specialities. Hence, in our opinion, one should avoid estimating the number of subjects who can be expected finally to undergo a clinical trial by adopting a specific number such as 10^2 or 100^9 to divide the number of potential subjects. This may turn out to be too optimistic or conversely, dampen efforts to conduct trials in smaller District General Hospitals.

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KEY WORDS: Beta-blocker, Identification, Clinical trial, Drug trial, Ocular hypertension, Patients, Primary open-angle glaucoma, Recruitment

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