Older people included in a venous thrombo-embolism clinical trial: a patients’ viewpoint

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Abstract

Background and objectives: despite the numerous publications debating ethical rules of clinical research, older patients’ opinions are rarely taken into account. We report on the feelings and memories related by older patients included in a randomised controlled trial.

Design and settings: a closed-questionnaire was submitted to patients, aged ≥65 years, who had been included in the randomised trial ‘PREPIC’. PREPIC was a multicentre, open trial performed in France, that included 400 patients over 42 months. The aim of PREPIC was to evaluate the benefits and risks of prophylactic filter placement in patients with proximal deep-vein thrombosis who were considered to be at risk for pulmonary embolism.

Results: 104 patients (mean age: 74 years) were interviewed. At the time the trial was proposed to them, 45% of patients felt surprised or shocked and 30% feared incurring additional risks. While 85% of patients did not remember the trial methods (including the randomisation), most older patients (77%) not only judged that they received clear medical information but also well remembered (95%) the aim of the study and the treatment they received (67%). Finally, most older patients not only did not regret their participation (91%), but would also recommend their close relations to participate in a clinical trial (62%).

Conclusions: this study demonstrates that medical scientific information can be understood and remembered by older people.

Keywords: clinical trial, elderly patients, informed consent, patient autonomy, ethics, questionnaire

Introduction

In order to protect and respect the rights of patients, as well as the voluntary nature of their participation in research studies, international ethical codes have been established [1]. Despite the numerous publications – more than 3000 since 1989 [2] – debating this matter, the opinions of older people involved in clinical research are rarely reported in the literature. Our study reports on the feelings and memories of older patients included in a randomised controlled trial.

Methods

Trial concerned in the present study
A closed-questionnaire was submitted to the patients who had been included in the randomised controlled trial ‘PREPIC’. PREPIC was a multicentre, randomised, open trial performed in 44 centres in France, that included 400 patients over a period of 42 months [3]. Its aim was to evaluate benefits and risks of prophylactic filter placement in addition to anticoagulant therapy, in adult
patients with proximal deep-vein thrombosis. The trial had been approved by the local ethical committees. After the diagnosis of an acute proximal venous thrombosis by venography, all patients included underwent baseline ventilation-perfusion scanning within 48 h of enrolment. Pulmonary angiography was performed if the ventilation-perfusion scan was not available or if it was abnormal. All eligible patients received complete oral and written information about the trial. This information was explained by a physician, with particular emphasis on the pathology of thrombo-embolism, and on the methods, aims, benefits and risks of the trial. Before the inclusion, a written informed consent form had to be read and signed by the patient, within 48 h of the beginning of heparin treatment. Using a two-by-two factorial design, 400 patients were assigned to receive a vena cava filter (200 patients) or no filter (200 patients) and to receive subcutaneous low-molecular-weight heparin (205 patients) or adjusted-dose intravenous unfractionated heparin (195 patients). If filter placement was necessary, it was undertaken within 24 h of the patient's inclusion. The primary outcome event was the occurrence of a pulmonary embolism at 12 days and over the following 2 years.

Patients concerned in the present study
The study concerned all the patients aged >65 years, who were included into PREPIC in the four main centres, and for whom the first year of follow-up was completed. At the time of inclusion, and during the first year of follow-up, neither the investigators nor the patients were aware that this study would be performed.

Questionnaire
The patients were interviewed by a physician who was not involved in the performance of PREPIC, on the basis of a pre-established questionnaire. The interviews were performed in the patient's home if they agreed, or by phone in the case of refusal or geographic inaccessibility. The questionnaire (Table 1) included 11 items related to three different aspects: (i) feelings and reactions at the time of proposal of the trial; (ii) quality of information about the study and memories of the study; and (iii) feelings at the end of the study.

Statistical analysis
Chi-square and Fisher exact tests were used for the statistical analysis.

Results
A total of 134 patients were eligible for our study. Among them, 30 patients were unable to answer our questionnaire as a result of death (n=12), poor co-operation (n=11) or refusing to be interviewed (n=7). In all, 104 patients (78%) were interviewed (48 males and 56 females). Their mean age was 74 years (range 65–93). A pulmonary embolism had been found in 36% of them and 38% also presented chronic cardiac or pulmonary insufficiency, or cancer. Eighty percent of them were interviewed at home and 20% by phone.

Feelings and reactions of the patient when the trial was proposed
Reactions when the trial was proposed
Among the 104 patients, 47 (45%) felt surprised or shocked when a physician proposed inclusion in a clinical trial. Thirty-nine (38%) declared that such a proposition seemed natural to them. For 22 patients (21%) the time given for reflection and making an appropriate decision was too short, while for 61 (59%) it was considered adequate for reflection. Twenty-one patients (20%) expressed, at the time of interview, difficulty in remembering their feelings about these two questions.

Behaviour of the investigator
The investigator's attitude, when proposing participation in PREPIC, was judged too insistent by 21 patients (20%). His attitude was considered to be falsely cordial by 2 patients (2%) and dishonest by 2 others. However, it was considered impartial by 91 patients (88%).

Additional risk related to PREPIC participation
Among the 104 patients, 30 (29%) believed they might incur an additional risk if they agreed to participate in PREPIC (details in Table 2). Among the 30 patients who thought that they might incur an additional risk, 23 (77%) felt surprised or shocked when their participation in PREPIC was proposed. No other significant correlation was found in this group of patients.

Reasons for acceptance
The reasons for agreeing to inclusion in PREPIC are presented in Figure 1. The quality of the information given at the time of inclusion was the decisive reason for acceptance by 75%. The other main reasons were advice of close relations (48%), contribution to scientific research (36%), hope for a better follow-up (31%), and the high number of patients already included (28%).

Quality of information about the study and memories of the study
Quality of the information given by the investigator
The information given about PREPIC was felt to be clear and comprehensive by 80 patients (77%), and to be incomplete or unclear by 23%.
Older patients' opinions related to clinical trial

Table 1. Feelings and reactions at the time of the trial proposition and at the end of the study

<table>
<thead>
<tr>
<th>Number</th>
<th>Feelings at the time of the trial proposition</th>
<th>Feelings at the end of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reactions at the time of the trial proposition (answer ‘yes’ or ‘no’). Did you feel surprised?</td>
<td>Did you retrospectively regret your participation to PREPIC?</td>
</tr>
<tr>
<td>2</td>
<td>Behaviour of the investigator (answer ‘yes’ or ‘no’). Did you think that the investigator’s attitude was too insistent?</td>
<td>Did you retrospectively regret your participation to PREPIC?</td>
</tr>
<tr>
<td>3</td>
<td>Additional risk related to PREPIC participation (answer ‘yes’ or ‘no’). Did you feel that you might incur an additional risk by giving your agreement to participate in PREPIC?</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Reasons for acceptance (answer ‘yes’ or ‘no’, and class according to decreasing importance). Did the following reasons contribute to your agreement in participating in the trial?</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Quality of information given by the investigator (Answer ‘yes’ or ‘no’). Did the information given to you about the trial appear clear?</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Quality of information of the study and patient memorization of the study. Did the content of the consent form were considered as correctly memorized if at least two of the following items were spontaneously mentioned, as an answer to the question: ‘What can you remember about the contents of the consent form you read and signed before inclusion in the trial?’</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Memories concerning the methods of PREPIC. The methods of PREPIC were considered to be memorized if at least four of the following items were spontaneously mentioned. Comparative trial of several treatments Random allocation of the treatment Filter placement or not Two different sorts of heparins (‘medicines, injections’) One year of follow-up Deep vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Memories concerning the aim of PREPIC. The aim of the trial was considered to be memorized if the patients were able to resume it to an evaluation of the efficiency of the filter, in addition to heparin, to prevent the occurrence of pulmonary embolism.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Opinions of patients who had the feeling of incurring an additional risk

<table>
<thead>
<tr>
<th>Patients feelings</th>
<th>Additional risk (n=30) (%)</th>
<th>No additional risk (n=74) (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surprised or shocked</td>
<td>23 (77)</td>
<td>24 (32)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Short time for reflection</td>
<td>12 (40)</td>
<td>31 (42)</td>
<td>0.85</td>
</tr>
<tr>
<td>Correct and clear information</td>
<td>27 (90)</td>
<td>53 (72)</td>
<td>0.04</td>
</tr>
<tr>
<td>Study methods forgotten</td>
<td>28 (93)</td>
<td>61 (81)</td>
<td>0.14</td>
</tr>
<tr>
<td>Regret their participation</td>
<td>5 (17)</td>
<td>4 (5)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Quality of the informed consent form

A majority of patients (88%) did not clearly remember either the contents or the aim of informed consent. Moreover, for 5 patients (5%), the signed consent form
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was thought to be a way for the investigator to discharge his/her own responsibility in case of ‘failure of the treatment’. Three patients (3%) did not even remember having signed anything.

Memories concerning the methods of PREPIC

Among the 104 patients, 89 (86%) were unable to remember the methods of PREPIC and to quote four of the items from our pre-established list.

Memories concerning the aim of PREPIC

Ninety-nine patients (95%) were able to remember PREPIC as research on a filter placed in order to protect against pulmonary embolism.

Memories concerning the allocated treatment

Seventy patients (67%) were able to say what type of heparin they received, and whether a filter was placed or not.

Feelings of the patient at the end of the study

Retrospective regret over participation

Nine patients (9%) expressed regret about having given their consent, whereas for 95 patients (91%) the absence of any regret was clearly asserted. The retrospective regret of these 9 patients did not clearly appear to be related to the occurrence of a complication directly caused by the filter or by heparin. Indeed, among them, a serious adverse event was present in 4 cases, and among the patients who did not regret their participation, a complication was observed in 19 (P=0.11).

Recommendation to close relations

Sixty-five patients (63%) said they would, if asked, recommend participation in a clinical trial to one of their close relations, while 16 patients (15%) said they would not.

Discussion

There are few studies reporting on the feelings and memories of older patients included in randomised controlled trials [4, 5]. This seems surprising, given the fact that they represent one third of all those to whom drugs are prescribed [6] and are an increasing section of the population. The delay of one year between the inclusion in PREPIC and the interview may have affected the answers, due to normal memory lapse [7–9]. However, we estimated that this delay would somehow homogenise the initial impressions, because feelings are often exaggerated at the time of admission to hospital, which is itself a source of stress [9–12].

The concept of clinical research involving older patients seems difficult for the public, and the elderly in particular, to appreciate. In a study performed in the United States, half of the proxies of older patients who had refused to give their consent, argued that advanced age was an important factor in their refusal, or that no research study involving elderly subjects would be acceptable [4]. A recent analysis of the international literature showed that most geriatric clinical studies are conducted without informed consent or approval by ethics committees [5]. Not surprisingly, among our patients 45% felt surprised or shocked when the trial was proposed, 30% feared additional risks, and 85% did not remember the trial methods very well. In the absence of a control group of younger patients, one could argue that this forgetfulness is due to the advanced age of our patients. However, in younger populations, rates of misunderstanding or forgetting information close to 50% have been reported [7, 11]. A recent French study found that a few months after inclusion in a trial, 50% of the 77 patients (mean age 58 years) had not properly understood the aim of the trial, either the concept of randomisation or the nature of the treatments [13].

Fortunately, this ignorance of clinical research seems to be counterbalanced by the quality of information given to our patients. Most of them not only judged that they had received complete and honest medical information (77%), but also clearly remembered the aim of PREPIC (95%) as well as the treatment they received (67%). Ninety-one percent did not regret their participation, and 62% would even recommend participation in clinical research to one of their close relations. Moreover, more than one third of our patients accepted participation in PREPIC in order to contribute to medical scientific knowledge, and found it natural to participate in a trial. However, some particular aspects of the PREPIC trial might have influenced their decision. Firstly, the information was always given by a senior clinician and not by a nurse [14] or a booklet [15]. Secondly, the time for reflection was 48 h and not a few minutes, as in a recent infarct trial [14]. Thirdly, most of our patients did not feel that they suffered from a really ‘life-threatening’ disease, which is known to decrease understanding and retention of information [11].

Legal aspects of the trial (i.e. the notion of prior approval by an ethics committee, the freedom to withdraw consent at any time, and the anonymity of the data analysis) were not well-understood, nor well-remembered, by our patients. Does this mean that older patients feel little-concerned about their rights, or that they may be more receptive to a paternalistic attitude from doctors than concerned about legal aspects? Probably no more than younger patients, as other studies have shown. For example, after a gynaecological trial [7], 40% of patients (mean age of 23 years) stated that they were not aware of the possibility of withdrawing their consent. And in a stroke trial, where 82% of patients (or proxies) stated that informed consent
should always be an obligation for doctors, 86% of them did not know there was a law protecting them [16]. In the same way, only 11% of our patients asked for the advice of a family physician, whereas the advice of their close relations (second reason for acceptance), was reported as a way of ensuring their understanding of the information, rather than as a means of verifying their legal rights. Thus while for physicians the purpose of requiring informed consent was supposed to be to promote the autonomy of the individual in medical decision making [17], for our older patients a confident relationship with the physician was much more of a determinant in their decision.

Conclusion
This study demonstrates that medical scientific information can be understood and remembered by older people, if part of a confident relationship with their physicians. This is also a clear argument for us to insist on the necessity of always submitting clinical trials involving elderly subjects to ethics committees, and also of the need to try to obtain a genuinely informed consent from older people.

Key points
- French clinical medical research has neglected older people in terms of education and trial enrolment.
- With correct information, older people not only understand the need for clinical research but want to participate fully in it.

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References

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