Evaluation of a stroke family care worker: results of a randomised controlled trial

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Abstract

Objective: To examine the effect of contact with a stroke family care worker on the physical, social, and psychological status of stroke patients and their carers.
Design: Randomised controlled trial with broad entry criteria and blinded outcome assessment six months after randomisation.
Setting: A well organised stroke service in an Edinburgh teaching hospital
Subjects: 417 patients with an acute stroke in the previous 30 days randomly allocated to be contacted by a stroke family care worker (210) or to receive standard care (207). The patients represented 67% of all stroke patients assessed at the hospital during the study period.
Main outcome measures: Patient completed Barthel index, Frenchay activities index, general health questionnaire, hospital anxiety and depression scale, social adjustment scale, mental adjustment to stroke scale, and patient satisfaction questionnaire; carer completed Frenchay activities index, general health questionnaire, hospital anxiety and depression scale, social adjustment scale, caregiving hassles scale, and carer satisfaction questionnaire.
Results: The groups were balanced for all important baseline variables. There were no significant differences in physical outcomes in patients or carers, though patients in the treatment group were possibly more helpless, less well adjusted socially, and more depressed, whereas carers in the treatment group were possibly less hassled and anxious. However, both patients and carers in the group contacted by the stroke family care worker expressed significantly greater satisfaction with certain aspects of their care, in particular those related to communication and support.
Conclusions: The introduction of a stroke family care worker improved patients' and their carers' satisfaction with services and may have had some effect on psychological and social outcomes but did not improve measures of patients' physical wellbeing.

Introduction

Stroke has long been recognised as common, frequently fatal, and disabling. In recent years there has been increasing awareness of the psychosocial problems experienced by stroke patients and their carers.[1-3] Though the traditional medical model of care, including hospital based rehabilitation in stroke units, may reduce case fatality and institutionalisation,[4] it often fails to identify or adequately address these psychosocial problems. In 1992 we established a "stroke family care worker." As we were uncertain of the effectiveness of this post and which patients and carers might gain most we evaluated the service in a randomised controlled trial.

Patients and methods

All patients who attended our hospital as an inpatient or outpatient with a diagnosis of recent possible stroke (first and recurrent) were seen and assessed by a stroke physician. Details of patients in whom the diagnosis was confirmed according to World Health Organisation criteria[5] were entered into our stroke register. Patients with subarachnoid haemorrhage were excluded. Baseline data were collected before randomisation and as part of the routine registration of patients in our register.

Because we were uncertain about which patients and carers might gain most from intervention by a stroke family care worker we set broad eligibility criteria. Any patient with a confirmed stroke within the past 30 days could be randomised unless (*a*) they were very likely to die within a few days, (*b*) they lived more than 25 miles (40 km) from the hospital, or (*c*) the stroke occurred on a background of another major illness which was likely to dominate the pattern of care—for example, advanced cancer or renal failure.

Randomisation

Randomisation was balanced in blocks of six within strata defined by age, sex, living alone before the stroke, and stroke severity. Those responsible for randomising patients were unaware of the block size. Stroke severity depended on the prediction by the stroke physician at the time of assessment. Patients with severe strokes were defined as those expected to score >2 on the Oxford handicap scale one year after the stroke. A table with random patient allocation was stored on a personal computer so that nobody concerned in randomising patients could discover to which intervention the next patient would be allocated.

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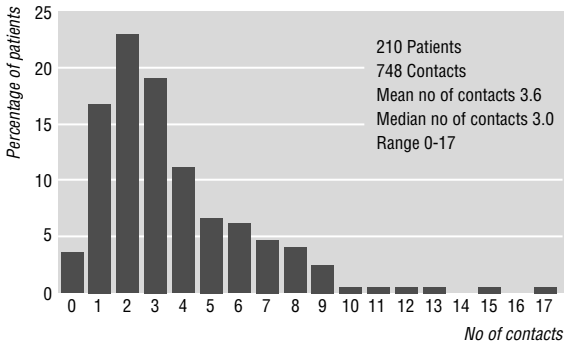

Fig 1 Number of stroke family care worker contacts per patient (or family) in first six months after randomisation. Data include face to face and telephone contacts

Setting and consent

The intervention was tested in the setting of a large teaching hospital with a well organised stroke service. Patients were not required to consent to randomisation but consented to follow up. This approach was approved by our local ethics committee.

Intervention

The stroke family care worker (TS) came from a social work background and had considerable experience in working with voluntary agencies for disabled people. Patients or carers, or both, who were randomised to active intervention were contacted by the stroke family care worker within a week of randomisation. She tried to identify unmet needs and aimed at fulfilling these using any available resources. She would access health services, social services, and voluntary agencies as well as offering some counselling herself. Figure 1 shows the considerable variation in number of contacts she had with patients in the first six months after randomisation. We did not prescribe how many contacts she would have with families; this was left for her to decide and depended on her assessment of their needs. Patients randomised to the control group had no contact with the stroke family care worker for six months, until after our final follow up assessment had been completed.

Follow up

We aimed at following up all patients six months after randomisation. A research psychologist (SO'R), who was blind to the treatment allocation, asked the patients to identify a carer and arrange for him or her to be present at the follow up visit. We followed up only informal carers—that is, spouse or family members—and not, for example, nursing home staff or home helps. Patients and carers were told that we wished to know how they had fared. No reference was made to any assessment of the stroke family care worker.

Follow up comprised several questionnaires aimed at measuring outcome in various domains. The psychologist helped patients complete the Barthel index,[6] Oxford handicap scale,[7] Frenchay activities index,[8] general health questionnaire (30 item),[9] and social adjustment scale[10] during the follow up visit. Meanwhile any carer was asked to complete independently the Frenchay activities index, general health questionnaire, social adjustment scale (on the carer's behalf rather than the patient's), and caregiving hassles scale.[11] Patient and carer were then each left a further questionnaire to return to the psychologist by post. The patient's questionnaire comprised several measures, including the hospital anxiety and depression scale,[12] the mental adjustment to stroke scale,[13] and a patient satisfaction scale.[14] The carer's questionnaire comprised the hospital anxiety and depression scale and a carer satisfaction questionnaire. We modified the mental adjustment to cancer scale[13] for use in stroke patients simply by substituting the word stroke for cancer. In addition, we added further questions to a standard questionnaire to determine the patients' satisfaction[14] with aspects of their care which we thought might be influenced by input from the stroke family care worker. We adjusted the wording of this questionnaire slightly for use with carers (see fig 4).

When patients had cognitive or communication problems which prevented them completing the follow up questionnaires their cognitive status was assessed with the Hodkinson abbreviated mental test[15] and as much information as possible gathered from carers. At the end of the follow up visit the research psychologist guessed which treatment group the patient was in to test the efficacy of our efforts to blind her to the treatment allocation.

Analyses

Results were analysed on an intention to treat basis—that is, the patient or carer was assessed depending on the intervention to which each was randomised even if he or she had no direct contact with the stroke family care worker. Dichotomous variables at baseline and follow up were compared by means of risk ratios with 95% confidence intervals and the χ^2 test. Continuous variables were compared by Student's t test. When comparing outcomes measured on ordinal scales we calculated 95% confidence intervals for the difference between medians.

Results

Between 1 October 1992 and 30 September 1994 we randomised 417 patients, 210 to receive intervention by the stroke family care worker and 207 to receive standard care (controls). The patients represented 67% of all stroke patients assessed at the hospital. The main reason for non-randomisation was that patients lived more than 25 miles (40 km) away. There were few statistically significant differences between randomised and non-randomised patients with respect to baseline variables. Randomised patients were slightly older (mean age 67.8 years v 64.6 years; P = 0.006) and more likely to be living alone (relative risk 1.54; 95% confidence interval 1.14 to 2.08).

There were no substantial or significant differences between patients randomised to the two intervention groups in terms of lesion location, stroke severity, and pre-stroke function as well as those variables shown in figure 2. The mean age of the treatment group was 67.1 years and that of the controls 68.4 years (P = 0.33).

Outcomes

All randomised patients were accounted for at the end of the study. Nineteen (9.0%) patients randomised to the stroke family care worker and 22 (10.6%) controls died before follow up (risk ratio 0.85; 95% confidence interval 0.48 to 1.53). In four survivors in the treatment

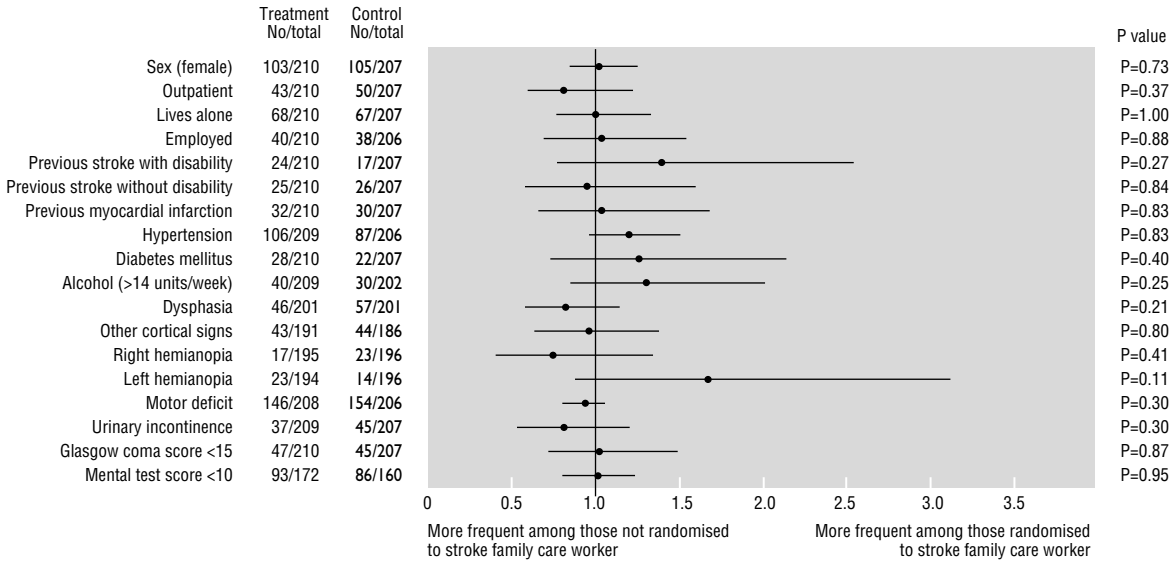

Fig 2 Comparison of baseline characteristics (for dichotomised variables) in patients randomised to treatment and control groups. Points are point estimates of relative risk of characteristic occurring in treatment group compared with control group. Bars are 95% confidence intervals. Denominators vary because some variables were not assessable in a few patientsfor example, hemianopia in unconscious patients

group no further follow up was possible. One patient had emigrated, another had a brain tumour and was too ill to be followed up, and two patients refused.

Of the patients successfully followed up (187 in the treatment group, 185 controls), 29 (15.5%) in the treatment group and 31 (16.8%) controls had cognitive or communication problems which prevented them completing any questionnaire apart from the Barthel index, Oxford handicap scale, and Hodkinson abbreviated mental test score. Of the 158 patients in the treatment group given the second questionnaire, 145 (91.8%) returned them; and of the 154 patients in the control group given the second questionnaire, 147 (95.5%) returned them. On most measures controls tended to have better outcomes, though the difference was significant only for social adjustment and was of borderline significance with respect to helplessness and depression (table 1). Despite this, however, patients in the treatment group were more satisfied with certain aspects of their post-hospital care (fig 3).

We identified 246 carers. Of these, 119 (48.4%) were carers of patients randomised to the stroke family care worker. Six carers in the treatment group and seven in the control group refused follow up and two carers in the control group were not assessable. The remaining 231 (93.9%) carers completed the first questionnaire and 102 (90.3%) in the treatment group and 110 (93.2%) in the control group returned the second questionnaire. Carers of patients in the treatment group tended to have better outcomes than those in the control group. Differences were significant for mood symptoms and of borderline significance for anxiety and hassles (table 2). Carers of patients in the treatment group were also more satisfied with several aspects of their care (fig 4).

Length of hospital stay was slightly shorter in the treatment group than in the control group (mean 34.7 *v* 38.9 days; median 12 *v* 19 days (P = 0.1)). There were no significant differences between the groups in the patients' placement after discharge.

Blinding

After each of 312 consecutive follow up assessments the research psychologist was asked to guess whether

Table 1 Comparison of outcomes based on completed questionnaires in patients randomised to treatment and control groups

	Treatment			Control			
Measure	**No**	**Median**	**Interquartile range**	**No**	**Median**	**Interquartile range**	**Difference between medians (95% confidence interval)†**
Frenchay activities index	164	37	29-42	164	38	26-45	–1 (–4.0 to 3.0)
General health questionnaire	156	7	2.3-11.8	154	5.5	1-12	–1.5 (–3.0 to 1.0)
Social adjustment scale	164	1.7	1.5-2	160	1.6	1.4-1.8	–0.1 (–0.07 to –0.1)
Hospital depression subscale	128	4.5	3-8	124	3	2-7	–1.5 (–2.0 to 0.0)
Hospital anxiety subscale	128	5	2-8.8	124	5	1.3-7.8	0.0 (–1.0 to 2.0)
Barthel index	187	19	16-20	183	19	15-20	0.0 (–1.0 to 1.0)
Oxford handicap scale	184	3	2-4	184	3	2-4	0.0 (–1.0 to 1.0)
Mental adjustment to stroke scale	113			120			
Fighting spirit—helplessness		60	53-63		57	48-62	–3.0 (–5.0 to 0.0)
Anxious preoccupation		53	48-58		56	48-58	3.0 (–1.3 to 3.0)
Fatalism		54	48-59		54	48-59	0.0 (–5.0 to 0.0)

†Positive value for difference between medians indicates better outcome in treatment group; negative value indicates better outcome in control group.

Table 2 Comparison of outcomes based on completed questionnaires in carers of patients randomised to treatment and control groups

	Treatment			Control			
Measure	**No**	**Median**	**Interquartile range**	**No**	**Median**	**Interquartile range**	**Difference between medians (95% confidence interval)†**
Frenchay activities index	87	47	42-52	84	48	44-50	–1.0 (–2.4 to 2.0)
General health questionnaire	94	4	0-11	92	7.5	1-13	3.5 (0.7 to 7.0)
Social adjustment scale	112	1.7	1.4-2	116	1.7	1.5-2	0.0 (–0.01 to 0.10)
Caregiving hassles scale	70	4	1-13	69	8	1-21	4.0 (0.0 to 9.0)
Hospital depression subscale	89	4	1-7	96	4.5	1-7	0.5 (–1.0 to 2.0)
Hospital anxiety subscale	89	7	3-10	96	7.5	4.3-11	0.5 (0.0 to 3.0)

† Positive value for difference between medians indicates better outcome in treatment group; negative value indicates better outcome in control group.

the patient had been randomised to be seen by the stroke family care worker or not. She guessed correctly in 183 (58.7%) cases, which was more than should have occurred by chance alone (P = 0.002), indicating that she was unblinded to some extent. However, the size of any observer bias resulting from this degree of unblinding in a follow up assessment based mainly on self report questionnaires was probably small. This is especially so with respect to the carer questionnaires, which were not completed in the presence of the psychologist.

Discussion

Our stroke family care worker and other similar posts were set up with the expectation that they would help patients and their families. However, there is very little evidence from previous randomised trials on which to base this assumption.[16-20] Most of these trials included few patients and were thus prone to type II error, and no systematic review of these trials has been published. We aimed at overcoming this problem by conducting a large trial with greater statistical power and at least partially blinded outcome measurement.

Though we successfully randomised reasonably large numbers of patients, we found few statistically significant differences in outcome between the treatment and control groups. Clearly, it is possible that some bias may have been introduced by patients or carers failing to complete a questionnaire. Theoretically, failure to complete all questions may have been related to the treatment allocation. However, the most common explanations for missing data were patients' cognitive and communication problems and simple omissions—for example, as a result of turning two pages over at once. Similar numbers in each treatment group encountered these sorts of difficulties. Thus significant bias seems unlikely.

The most convincing evidence of benefit of the stroke family care worker was in improving both patients' and carers' satisfaction in respect of various aspects of communication. Intriguingly, patients in the treatment group tended to be more helpless, less well adjusted socially, and possibly more depressed. We

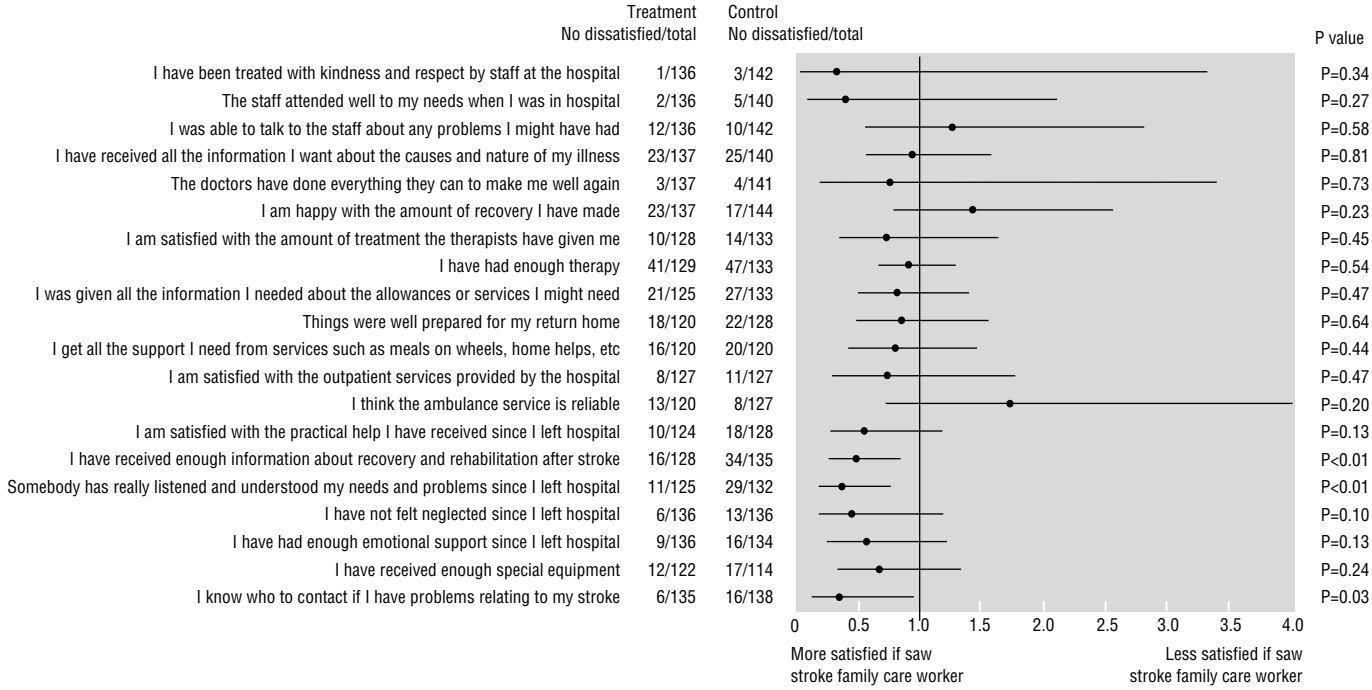

Fig 3 Comparison of responses to individual questions in patient satisfaction questionnaire in treatment and control groups. Points are point estimates of relative risk of patients expressing satisfaction in treatment group compared with control group. Bars are 95% confidence intervals. Difference is significant where confidence interval does not overlap vertical line (relative risk 1.0). Denominators vary because responses were missing in some questionnaires

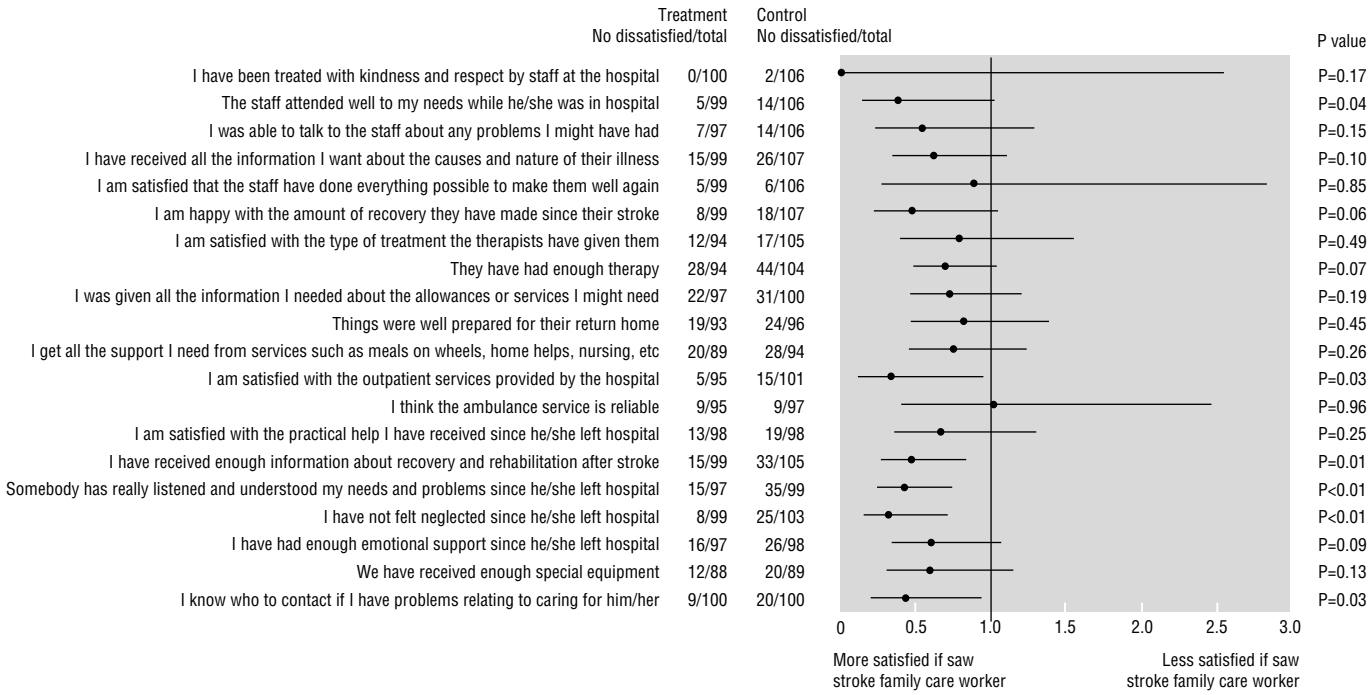

Fig 4 Comparison of responses to individual questions in carer satisfaction questionnaire in treatment and control groups. Points are point estimates of relative risk of patients expressing satisfaction in treatment group compared with control group. Bars are 95% confidence intervals. Difference significant where confidence interval does not overlap vertical line (relative risk 1.0). Denominators vary because responses were missing in some questionnaires

could postulate that intervention by the stroke family care worker, by providing support rather than improving patients' coping skills, induced a passive response to their illness which led to depression and poor social adjustment. Also there was an encouraging trend for carers in the treatment group to be less hassled and to have fewer mood symptoms, especially anxiety, than those in the control group. These moderate effects may, if real, accurately reflect the effectiveness of our stroke family care worker. There are, however, several possible explanations.

Firstly, the post was set up in the context of a well organised stroke service with excellent social work support, and many potential problems for patients and carers were already predicted and averted or managed by the hospital based team. The post might have had a greater effect in a less well organised service. Secondly, we were concerned that follow up at six months might be too early to show the real benefits of the post. Patients and carers may still be adjusting to the stroke and major problems may not yet have developed. At this stage many will still be receiving conventional input from hospital and primary care. Thirdly, we may have used measures of outcome which either were not measuring outcomes which might be influenced by our intervention or were insufficiently sensitive to any differences due to the intervention. Fourthly, our trial was pragmatic and included 67% of stroke patients. Possibly a subgroup of patients did benefit from the input of the stroke family care worker. Fifthly, the stroke family care worker responded to families' needs and wishes and may therefore sometimes have provided too little input to affect outcome.

Though our trial results may be of limited generalisability because we evaluated only a single worker, they suggest that any gain was mainly in satisfaction with aspects of communication and support after hospital discharge, certainly in the setting of a well organised stroke service. Future studies should examine these outcomes as well as psychological ones. Whether purchasers will be willing to fund interventions such as this will depend on the value that they and patients place on such outcomes. Perhaps we need to establish how important patients and their carers regard such outcomes before making any judgments. Pound *et al* identified being "cared for" and "cared about" as of value to patients, and they regarded them as important advantages of hospital admission after stroke.[21] We are currently planning a systematic review of previous and ongoing trials of similar interventions which may go some way in establishing whether stroke family care workers from different backgrounds—that is, working with different intensities for greater durations in different settings—might be more effective.

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Key messages

- A stroke family care worker in the context of a well organised hospital based stroke service has no definite beneficial effect on the physical, social, or psychological outcome of patients or their carers
- A stroke family care worker may reduce carers' hassles and anxiety but render patients more helpless, less well socially adjusted, and more depressed
- A stroke family care worker may improve patients' and their carers' satisfaction with those aspects of stroke services relating to communication and support
- Purchasers of health care need to decide the value they and their patients place on satisfaction with health care

trial was funded by the Scottish Office Home and Health Department.

Conflict of interest: Continued funding of the stroke family care worker relied on the outcome of this trial. As a result of the outcome the post has been terminated.

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Commentary: No consent means not treating the patient with respect

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It is presumably often difficult for researchers to commit themselves wholeheartedly to the notion that before consent (or refusal) is obtained for research it is necessary that the person concerned should be given the fullest information about the project for which his or her agreement is wanted. The concerns expressed by the researchers—not least the possibility of biasing results—are intelligible. However, they are also insufficient to justify deviation from the general rule.

Researchers in many topics face the same problems about possibly influencing results and seek to minimise the possible impact this may have. Many kinds of research—clinical and non-clinical—must and do tackle similar problems while still turning out high quality work. However, this and the other rationales cited by Dennis *et al* disguise a deeper problem. The researchers claim they did not think that failure to provide the fullest possible information would harm their patients. Though this is probably true in a physical sense, it omits to consider the underlying rationale for providing full information—namely, that good research should not only be scientifically sound but it must also at all times respect the subject. Any failure to offer this respect is in itself a harm, even if its consequences are not physical. Indeed, it could plausibly be argued that omitting any substantial factor in the research protocol is enough to render the research unethical, no matter how important the postulated outcome. This is particularly true given that no researcher can know in advance that his or her results will be important.

Everyone starting a project believes that there is value in knowing the answer to the question being asked. But it is only when the answer is found that the truth or falsehood of that assumption can be known. Thus there is an inbuilt intellectual bias in any project which presumes that the answer is important enough to ignore a fundamental tenet of research method and respect for people.

We must also accept that had people been asked and then regretted their decision this would be unfortunate. It is difficult, however, to see how this differs from other projects. Moreover, that the person in question was rendered vulnerable by the nature of the condition argues for more rather than less information. There are always concerns about including in studies people whose condition is precarious. That this research was not directly physical does not remove those concerns or minimise obligations. In addition, I am puzzled by the argument that, as patients and their families would be included, it was "unclear" who might give consent. The answer is clear: anyone who is to be studied must be given the fullest possible information.

We can agree that the conclusions of the study are of considerable interest and that no physical harm was done to patients whose agreement to participate was based on partial rather than full information. It is, however, also dangerous to believe that this is enough. Nor are possible feelings of disappointment on the part of those who might not have agreed to randomisation different from findings in other research settings.

In sum, the arguments against providing full information are frankly unconvincing, however well intentioned. If certain research cannot be undertaken to the maximum standards of scientific inquiry the question is not how much information can be withheld, it is whether the research should be done in the first place. Otherwise we embark on a slippery slope away from one of our most fundamental ethical principles. In the long run the critical issue is not the consequential one; what matters is that people have not been treated with enough respect.

Commentary: Why we didn't ask patients for their consent

Martin Dennis

In our trial we asked patients to consent to follow up but not to consent to randomisation itself. There were several reasons for adopting this approach, which was approved by our local ethics committee. Firstly, we did not expect our intervention to be harmful, though whether this expectation was fulfilled must be judged from our results. Secondly, patients and their carers could refuse to see our stroke family care worker or follow up psychologist whenever they wished. Thus half the patients and their carers were asked to consent to the intervention and all were asked to consent to follow up after randomisation. Thirdly, we were concerned that if we tried to obtain informed consent this might bias our results. For instance, if we made patients and their families aware of the help they might receive from the stroke family care worker and then randomised them to the control group this might have had a detrimental effect on their morale. This could have led to a false positive result simply by having an adverse effect on the controls.

In addition, as our patients and their carers were not aware that they were in a randomised trial to assess our stroke family care worker and that our follow up was attempting to assess her effectiveness, they were in effect partially blinded. We might imagine that loyalty to the care worker might have biased their responses had they known the precise purpose of our follow up. Fourthly, our approach allowed patients or carers to decide to see the stroke family care worker when it was relevant to them. Some patients might not consent to randomisation shortly after their stroke, when they are unlikely to foresee the possible psychosocial impact of the stroke on them and their families. They might then regret the decision not to be randomised when the potential benefits of the intervention become more evident. Lastly, as our intervention was applied to patients and their families it was unclear who might most appropriately give consent.

Increasingly, purchasers and providers of health care are looking for evidence from methodologically sound randomised controlled trials and systematic reviews to guide their practice. In a trial whose outcome measures reflect the feelings or opinions of the subjects a detailed knowledge of the trial and its exact purpose are likely to influence or bias responses. Thus responses may reflect either a control subject's disappointment or dissatisfaction with not receiving a potentially beneficial treatment or a treated patient's appreciation or loyalty to those providing the treatment. Those who review such studies will be unable to judge whether this source of bias might account for any difference in outcomes between treated and control groups. Thus no studies would be regarded as methodologically watertight. Is it ethical to randomise patients into trials which because of an inherent methodological weakness cannot provide a definite answer to the main question?

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Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study

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Abstract

Objectives: (*a*) To assess the impact of HIV status (HIV negative, HIV positive, AIDS) on the outcome of patients admitted to intensive care units for diseases unrelated to HIV; (*b*) to decide whether a positive test result for HIV should be a criterion for excluding patients from intensive care for diseases unrelated to HIV.

Design: A prospective double blind study of all admissions over six months. HIV status was determined in all patients by enzyme linked immunosorbent assay (ELISA), immunofluorescence assay, western blotting, and flow cytometry. The ethics committee considered the clinical implications of the study important enough to waive patients' right to informed consent. Staff and patients were blinded to HIV results. On discharge patients could be advised of their HIV status if they wished.

Setting: A 16 bed surgical intensive care unit.

Subjects: All 267 men and 135 women admitted to the unit during the study period.

Interventions: None.

Main outcome measures: APACHE II score (acute physiological, age, and chronic health evaluation), organ failure, septic shock, durations of intensive care unit and hospital stay, and intensive care unit and hospital mortality.

Results: No patient had AIDS. 52 patients were tested positive for HIV and 350 patients were tested negative. The two groups were similar in sex distribution but differed significantly in age, incidence of organ failure (37 (71%) *v* 171 (49%) patients), and incidence of septic shock (20 (38%) *v* 54 (15%)). After adjustment for age there were no differences in intensive care unit or hospital mortality or in the durations of stay in the intensive care unit or hospital.

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Conclusions: Morbidity was higher in HIV positive patients but there was no difference in mortality. In this patient population a positive HIV test result should not be a criterion for excluding a patient from intensive care.

Introduction

Extensive data are available on the outcome of patients with AIDS admitted to intensive care units.[1 2] The survival rate of these patients has greatly improved over the past 15 years, and refusal to provide intensive care to these patients on the basis of medical futility is therefore deemed unjust.[1] In Africa the pattern of HIV disease is different from that in the developed world, more patients manifesting early HIV disease and fewer progressing to AIDS.[3] This pattern is reflected in our intensive care unit, where most patients are admitted with diseases unrelated to their HIV status. To our knowledge the outcome of patients with HIV infection admitted to intensive care for other reasons has not been described. Our clinical impression was that their outcome was poor.

Limited resources and the high cost of intensive care have compelled clinicians to rationalise the allocation of resources.[1] For example, in our unit it is policy not to admit patients with incurable malignant disease, end stage liver disease, and patients with multiple organ failure who are deemed non-salvageable. The lack of objective data made it unclear whether patients with HIV infection should be treated similarly. To allow rationalisation of the admissions policy with respect to these patients we conducted a prospective study to determine the prevalence of HIV infection among patients admitted to the unit and assess the impact of HIV status (HIV positive, HIV negative, AIDS) on outcome.

The study embraced a major ethical dilemma. On the one hand, the clinician has an obligation of non-maleficence—that is, patients must not be harmed by the actions of the doctor. On the other hand, the doctor has an obligation to society to ensure that available resources are appropriated fairly, based on objective evidence. Though the basic ethical tenets of patient autonomy, justice, beneficence, and non-maleficence[4] are useful, they are only the starting points for ethical decision making.

Subjects and methods

The study was conducted in the 16 bed surgical intensive care unit at King Edward VIII Hospital, a large teaching hospital in Durban. All patients admitted to the unit over six months (September 1993 to February 1994) were included. There were no exclusions. Informed consent was not sought. The study protocol was approved by the ethics committee of the University of Natal.

A screening enzyme immunoassay for HIV (Abbott HIV-1/HIV-2 third generation plus kit; Abbott Laboratories, Chicago) was performed on all patients at admission. Positive results were confirmed by the department of virology using an immunofluorescence assay (SEROFLUOR; Virion, Switzerland) and western blotting (HIV western blot 1/2; Diagnostic Biotechnology, Singapore). Patients with positive results in the confirmatory tests were considered HIV positive. The department of haematology was informed of these results and requested a specimen of blood for flow cytometry from three patients, one of whom was HIV positive. Staff were thereby blinded to which patients were HIV positive. Flow cytometry was performed on whole blood samples from all HIV positive patients with Coulter's Q-prep method (commercially produced antibodies from the Coulter Corporation, Miami). Samples were analysed on an Epics Profile II Coulter flow cytometer.

In addition to the intensive care unit staff, patients also were blinded to the results of the HIV tests. The protocol permitted disclosure of HIV status to staff in two instances: (*a*) if a staff member sustained a needlestick injury—when the injured staff member, the consultant in charge of the patient, and the matron in charge would be informed of the result; (*b*) if a patient required haemodialysis—when the nurse undertaking haemodialysis and the consultant in charge would be informed of the result.

On discharge all patients were advised that they had been tested for HIV and of the reason for testing and given the option of knowing the result. Post-test counselling was offered to patients when HIV results were disclosed. Results of HIV testing were made available to the research team only after the patient had been discharged and all other data had been collated. On conclusion of the study results of HIV testing were permanently removed from laboratory records.

Three groups of patients were defined. HIV positive and HIV negative patients were identified by HIV testing; patients with AIDS were identified by Centers for Disease Control criteria.[5] The following data were recorded in all patients: demographic details; admission diagnosis and referring discipline; APACHE II score (acute physiological, age, and chronic health evaluation) in the first 24 hours after admission[6]; incidence of organ failure as defined by Knaus *et al*[7]; incidence of sepsis and septic shock as defined by the American College of Chest Physicians and the Society of Critical Care Medicine[8]; incidence of nosocomial sepsis as defined by our intensive care unit protocol; durations of intensive care unit and hospital stay (duration of hospital stay did not include intensive care unit stay); intensive care unit and hospital mortality (hospital mortality did not include intensive care unit mortality).

Admission to the unit and treatment offered were not influenced by HIV status. All patients were treated according to standard intensive care unit protocols.

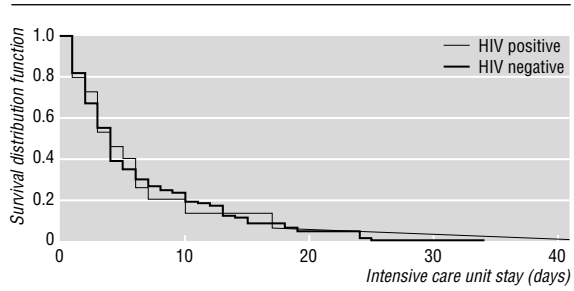

Fig 1 Survival distribution function versus duration of stay in intensive care unit

Table 1 Age and sex distribution of HIV negative and HIV positive patients

	HIV negative (n=350)	HIV positive (n=52)
No (%) male	228 (65)	39 (75)
No (%) female	122 (35)	13 (25)
Mean age in years (SD)	33 (18)	28 (9)*

*P=0.0018.

Table 2 Interdisciplinary distribution of patients

Discipline	No (%) HIV negative	No (%) HIV positive	Overall % HIV positive in discipline
Trauma	188 (54)	30 (57)	14
Obstetrics and gynaecology	40 (11)	8 (15)	17
Paediatrics	30 (9)	2 (4)	6
Vascular surgery	27 (8)	3 (6)	10
General surgery	24 (7)	4 (8)	14
Internal medicine	17 (5)	3 (6)	15
Ear, nose, and throat/maxillofacial	11 (3)	0	0
Orthopaedic surgery	9 (3)	2 (4)	18
Urology	4 (1)	0	0
Total	350 (100)	52 (100)	13

Statistics

HIV positive and HIV negative patients were compared by Student's t test and the χ^2 test for continuous and discrete variables respectively. A probability value of less than 0.05 was considered significant. Associations between HIV status and outcome variables were adjusted for differences in age and analysed by logistic regression. Kaplan-Meier estimates were used to compute the survival distribution function estimates within the HIV positive and HIV negative groups (non-survivors) and the equality of the distributions tested by the Wilcoxon rank sum test. Age was added as a covariate.

Results

No patient had AIDS. The rest of the data therefore refer to HIV positive and HIV negative patients only. Of the 402 patients admitted to the unit during the six months, 52 (13%) tested positive for HIV. Though the male to female distribution in the two groups was similar, they differed significantly in age ($P < 0.002$; table 1).

Most patients in both groups were admitted after trauma (table 2). HIV infection was more common in patients referred from orthopaedic surgery and obstetrics and gynaecology. There was no significant difference in intensive care unit or hospital mortality or in the duration of intensive care unit or hospital stay (tables 3 and 4). Intensive care unit mortality in HIV negative patients was 24% (84/350) compared with 29% (15/52) in HIV positive patients (odds ratio 1.45; 95% confidence interval 0.75 to 2.80); hospital mortality was 6% (16/247) and 3% (1/37) in the two groups respectively. There was no significant difference in survival distribution between the groups (mean survival time 7.3 (SE 2.6) days in the HIV positive group, 6.9 (0.78) days in the HIV negative group; $P = 0.88$) (fig 1). Information regarding hospital mortality and duration of hospital stay could not be retrieved for 19 HIV negative patients. There was no significant difference in mean APACHE II score between HIV negative and HIV positive patients (scores 9 and 8 respectively).

Organ failure was more prevalent in HIV positive patients. Significant differences were found when cardiac, respiratory, and haematological system failures were compared (table 5). Though there was no difference in the incidence of severe sepsis and nosocomial sepsis, septic shock was significantly more common in HIV positive patients (table 6).

It was not possible to perform flow cytometry on all HIV positive patients. This was because either the patient died soon after admission or the request for testing came after the patient was discharged from the unit and could not be reached. Compared with normal values there were significant differences in T4 count, T4:T8 ratio, and B4 count (table 7). The T4:T8 ratio was reversed and B4 count reduced in HIV positive patients.

Accidental disclosure of HIV status occurred in one instance as a result of a laboratory error. The researcher who became aware of the result did not divulge it to other staff and did not participate in management decisions regarding the patient. Data for this patient were collated by another member of the team, who was unaware of the result. As permitted by the protocol, the HIV status of five other patients became

Table 3 Comparison of mortality between HIV negative and HIV positive patients

	No (%) HIV negative	No (%) HIV positive	P value	Odds ratio	Age adjusted odds ratio (95% confidence interval)
Intensive care unit	84/350 (24)	15/52 (29)	0.558	1.28	1.45 (0.75 to 2.80)
Hospital	16/247 (6)	1/37 (3)	0.308	0.16	†

†Data on hospital mortality for HIV negative patients were available for only 247 patients, therefore maximum likelihood ratios could not be calculated.

Table 4 Mean and median (range) number of days' stay in intensive care unit and hospital for HIV positive and HIV negative patients

	HIV negative		HIV positive		
	Mean	Median	Mean	Median	P value
Intensive care unit	6	4 (1-44)	7	5 (1-41)	0.1
Hospital	10	7 (1-50)	8	6 (2-42)	0.08

Data were available for only 247 HIV negative patients.

Table 5 Comparison of total and individual organ failures between HIV negative and HIV positive patients

	No (%) HIV negative (n=350)	No (%) HIV positive (n=52)	P value	Odds ratio	Age adjusted odds ratio (95% confidence interval)
Total	171 (49)	37 (71)	< 0.003	2.58	2.87 (1.51 to 5.46)
Cardiac	84 (24)	21 (40)	< 0.014	2.11	2.38 (1.28 to 4.42)
Respiratory	150 (43)	33 (63)	< 0.005	2.32	2.60 (1.41 to 4.78)
Haematological	31 (9)	11 (21)	< 0.007	2.76	3.22 (1.47 to 7.09)
Renal	47 (13)	9 (17)	0.45	1.35	1.75 (0.78 to 3.92)
Neurological	19 (5)	5 (10)	0.23	1.85	1.72 (0.61 to 4.85)

Table 6 Incidence of sepsis in HIV negative and HIV positive patients

	No (%) HIV negative (n=350)	No (%) HIV positive (n=52)	P value	Odds ratio	Age adjusted odds ratio (95% confidence interval)
Septic shock	54 (15)	20 (38)	<0.001	3.43	3.64 (1.91 to 6.89)
Severe sepsis	71 (20)	9 (17)	0.62	0.82	0.84 (0.39 to 1.81)
Nosocomial sepsis	83 (24)	13 (25)	0.84	1.07	1.16 (0.59 to 2.31)

Table 7 Flow cytometry results in HIV positive patients. Cell counts are means (SE)

	Cell count ($\times 10^6$/l)		
	HIV positive patients (n=24)	Normal	P value
T3	949 (86)	800-2800	> 0.05
T4	425 (41)	550-1955	0.011
T8	549 (74)	250-1200	> 0.05
T4:T8 ratio	1.2 (0.2)	⩾2.0	< 0.001
B4	186 (18)	245-850	0.001
NKH-1	170 (24)	25-360	> 0.05

known to relevant staff members before patient discharge. One case involved a needlestick injury to a staff member, and the remaining disclosures were in preparation for haemodialysis. In all instances management decisions and collation of patient data were by other, blinded researchers. Of all 402 patients tested, only three wished to be informed of their HIV status. No patient objected to having been included in the study without prior informed consent.

Discussion

Mortality is the best measure of outcome of patients treated in an intensive care unit. Markers of morbidity may be subjective and are therefore less reliable end points. In this study there was no difference in intensive care unit or hospital mortality between HIV positive and HIV negative patients when results were adjusted for age (table 3).

HIV positive patients were more prone to septic shock and organ failure, and we were therefore surprised that the duration of hospital stay and mortality were not increased. This finding is unlikely to have been the result of observer error because, except for one inadvertent disclosure, HIV results were not available until all other data were collated. Abnormalities in flow cytometry results may have been an important factor. HIV positive patients had low T4 counts whereas T8 counts were comparatively high. As a consequence the T4:T8 ratio was reduced but the total (T3) was not affected. The B4 count was also low. All these features are consistent with the latent phase of HIV infection.[9] Though the behaviour of these cell populations predicts clinical progression of HIV disease to AIDS,[10] to our knowledge its impact on intensive care unit patients admitted for non-HIV related disease has not been described. Conceivably the immune response to major trauma and sepsis is altered. The observation by Munoz *et al* that HIV negative patients with sepsis and impaired macrophage responsiveness are more prone to subsequent sepsis[11] lends credence.

Immunological mechanisms have been postulated to play a major part in the pathogenesis of septic shock and multiple organ failure.[12 13] The immune response is complex and paradoxical, pro-inflammatory and anti-inflammatory responses occurring simultaneously and both being mediated by cytokines.[14] This has prompted the use of new drugs which alter the immune response in sepsis.[15 16] We therefore postulate that, though HIV positive patients have disturbances in immune function which make them more susceptible to septic shock and multiple organ failure, the inflammatory response is also altered such that there is no increase in mortality.

The patients in this study were young, predominantly male, and admitted primarily after trauma or surgery. That no patient had AIDS concurs with Gilks's observation that the pattern of HIV infection in Africa differs from that in the developed world.[3] Non-HIV disease is far more prevalent in Africa, with rapid progression from seroconversion to HIV to death from an AIDS defining condition.[3] Data relating to outcome in patients with AIDS cannot therefore be extrapolated to our patients. This emphasises the importance of describing the outcome in patients admitted to intensive care with non-HIV related disease.

Issue of informed consent

Decisions on initiating and terminating care for critically ill patients are difficult.[17] The unique nature of the AIDS epidemic in Africa,[3] the tremendous costs associated with advanced life support,[1] as well as the particular ethical considerations in patients with HIV infection[18] are compelling reasons for these decisions to be based on sound ethical principles and objective evidence of disease outcome. In view of the lack of clinical information in our patient population the acquisition of objective data was imperative. A major ethical dilemma arose when the decision was made not to seek informed consent. This was thought to be essential, as patients who were likely to be at risk for HIV infection would also be inclined to refuse the study, which would seriously limit its value.

There were two consequences of the study. Firstly, patients were denied the option of being excluded and, secondly, they were at risk of having their HIV status disclosed. The first consideration was evaluated in terms of the potential benefit of the study to society as a whole. The consensus of the research team and the ethics committee was that the clinical implications of the study were enough to warrant denying patients the right of refusal. With respect to the second consequence, every effort was made in the design and execution of the study to ensure that indiscriminate disclosure of HIV results did not occur. To our knowledge HIV results were not disclosed except for study purposes and, furthermore, patient care was not influenced by HIV status.

There was no reason to suspect that the racial background of our patients would have any bearing on their outcome. Race as a demographic variable is considered only rarely in South Africa.[19] Our main criterion for denying patients admission to intensive care is futility. This study showed no significant difference in mortality between HIV positive and HIV negative patients. Though the incidence rates of septic shock and organ failure were higher, this did not influence mortality or duration of stay. We therefore conclude that in our patient population HIV status cannot be used as a criterion for denying patients admission to the intensive care unit. Our observations regarding septic shock and organ failure require further evaluation.

Part of this study was presented at the 12th annual critical care congress of the South African Critical Care Society (1995) and at the eighth European congress of intensive care medicine. We thank Mrs Q A Karim, Dr S S A Karim, Professor H M Coovadia, Dr E M Barker, Professor D J Pudifin, Professor A N Smith, Professor J Lipman, and the ethics committee for advice

Key messages

- HIV positive patients admitted to intensive care for diseases unrelated to their HIV status have a similar mortality and duration of stay when compared with HIV seronegative patients
- The incidence of septic shock and multiple organ dysfunction is higher in HIV seropositive patients and needs further investigation
- HIV status cannot be used to deny critically ill patients admission to intensive care
- The HIV and AIDS epidemic raises unique ethical considerations that must be carefully addressed during clinical studies

and Miss E Gouws for statistical analysis. We also thank Mr T Doorasamy, technicians in the department of virology, Mr H Benimadho, Mr N Bhimsan, and Mr R Loykisoonlal for technical help and Mrs A Pillay for secretarial work.

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Conflict of interest: None.

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Commentary: Failing to seek patients' consent to research is always wrong

Rajendra Kale

Doing research without the patient's consent is unethical in any part of the world because it violates the fundamental right of the patient to autonomy and self determination. Bhagwanjee *et al* violated that right because they feared that seeking consent of patients might jeopardise the scientific rigour of their study. They feared that patients at risk of HIV infection would be inclined to refuse the study, so limiting its value.

On what evidence did they base those fears? A separate study designed to find out the willingness of patients admitted to their unit to consent to HIV testing should have been their first step. Such a study might well have shown that their fears were unfounded and that a significant number of patients would have agreed to give informed consent. This would have allayed their fears and obviated their perceived need to do a study without consent. That such a result was likely is suggested by the findings of the "consent after the event" exercise that the authors carried out. The results of that exercise are difficult to interpret but if true suggest that most patients did not object to being forced into the study. They might well have consented to the study beforehand.

Were these patients at all aware of their right to informed consent before being included in research? The study was done in a large and busy hospital in South Africa that mainly looks after non-white, poor patients under developing country conditions—a legacy of apartheid. The question of informed consent is not uppermost in the minds of patients and their relatives who attend surgical emergencies in hospitals in third world countries. This places even greater responsibility on the researchers to make sure that their patients know their rights.

How many of the patients were white? The possibility that different ethical standards might still prevail in South Africa for patients of different races needs to be discussed. I wonder if such a study would have been done or even considered in a hospital serving a predominantly white population in South Africa.

The arguments that medical resources are limited and that the findings of the study would help to utilise resources better are valid—but only in justifying the

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need for the study. They are not enough to permit a study without informed consent.

Such a study would not have been allowed in Britain and other developed countries. But can ethical standards vary from one country to another? Ethical relativism argues that they can and do. But I think that doing research without consent is unethical everywhere. This is possibly more so in a developing county, where patients are likely to be ignorant of their rights.

The *BMJ* was wrong to accept this paper, with or without a commentary. Refusing to publish would not have amounted to ethical imperialism, and any fears that one group was imposing its ethical norms on others are unfounded.

Commentary: Why we did not seek informed consent before testing patients for HIV

Satish Bhagwanjee, David J J Muckart, Prakash M Jeena, Prushini Moodley

We agree completely with the Nuremberg code and the Helsinki declaration that informed consent is an essential prerequisite for medical research. However, we believe that there may be extraordinary circumstances when this right may be waived. We identify four crucial requirements that must be fulfilled before research without informed consent may be permitted.

Requirements that must be satisfied before research without consent

1. It is impossible to obtain informed consent

Eighty five per cent of admissions to our unit are emergency cases. These patients cannot give informed consent because they are critically ill. A second option is to obtain consent from a relative. In our study this would have resulted in two possible scenarios. Firstly, if the patient survived he or she could choose to be informed about the result of HIV testing and maintain the right to limited disclosure. But if the patient died the relative would have the right to know the result. This would be a serious breach of patient autonomy. Furthermore, such disclosure of results obtained in the course of research when there was no risk of infection to the relative would represent an unacceptable breach of patient confidentiality.[1] It was therefore not appropriate to seek consent from relatives. The third option was to obtain consent on discharge. This would have excluded all patients who died, which would have profoundly limited the value of the study.

2. The research is of sufficient importance that patients' right to informed consent may be waived

The problem of HIV and AIDS in South Africa has reached epidemic proportions.[2-4] By the end of l992 over 300 000 people were infected.[5] In 1994 the figure was estimated to be 1.2 million.[6] Seroprevalence in the antenatal clinic at our hospital was 12% in 1992 and 23% in 1996 (A N Smith, personal communication). If the worst case scenario materialises, by 2010 it is estimated that 28-52% of all deaths will be related to HIV infection.[7] The impact of the epidemic on scarce intensive care resources is likely to be profound. Our 2000 bed hospital is served by 25 intensive care beds (16 in the surgical unit). Furthermore, our unit is the primary referral intensive care unit for the province of Kwazulu-Natal. As a consequence of excessive demand and our limited resources one fifth of all patients referred to our unit are denied admission. Hence given the extent of the HIV epidemic it was essential that any decisions regarding allocation of resources should be based on objective data and not subjective impression (the ethical principle of social justice). The study was therefore deemed to be of sufficient importance to waive patients' right to informed consent.

3. There must be unanimous agreement among appropriate individuals and groups that the aforementioned conclusions are valid

The exhaustive procedure followed in verifying the suitability of the protocol shows that we satisfied the third prerequisite—namely, that there must be unanimous agreement among appropriate individuals and groups about the importance of the research and the impracticability of obtaining consent. In order to pre-empt prejudice against HIV positive patients (and therefore prevent breach of two other principles of medical ethics—namely, beneficence and non-maleficence) and in view of the above considerations it was deemed essential that a prospective blinded trial should be conducted. We consulted three clinical departments, two laboratory departments, and two international AIDS experts. The institutional ethics committee appointed a subcommittee comprising Dr E M Barker (bioethicist and principal author of the Medical Association of South Africa guidelines), Professor D J Pudifin (clinician and AIDS expert), and one of us (SB) to investigate the most suitable approach. Eighteen months after initiation and deliberation among the various parties concerned the protocol was finally approved by the ethics committee.

4. Every attempt must be made to protect patients' interests after enrolment

Every effort was made to protect patients after enrolment. Their HIV status was not disclosed to staff members lest disclosure might result in discrimination. Patient care was never influenced by knowledge of HIV status. HIV status of patients was not disclosed to relatives, and the results were used exclusively for the study. On completion of the study patients' HIV test results were permanently removed from the hospital records.

Conclusion

HIV and AIDS raise unique ethical considerations, which are not limited to patient autonomy but encompass the three other principles of medical ethics (beneficence, non-maleficence, and social justice). In adhering to these three principles we breached the first principle. Our decision to embark on this study was not taken lightly. On the contrary, every attempt was made to ensure that the decision was correct in the light of our unique circumstances.

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Commentary: No simple and absolute ethical rule exists for every conceivable situation

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Y K Seedat, *chairman of postgraduate committee*

The obvious ethical problems posed by this study concern (*a*) the fact that all patients admitted to the intensive care unit over a six month period were included in the study without their knowledge or consent, and (*b*) the fact that blood samples obtained from all patients were tested for HIV infection without the consent of the patients, with the information that blood samples had been tested for the infection being given to patients only after the test had been done.

At first sight the decision to override the patients' right to full information, and to give or to refuse consent to inclusion and testing, seemed to all members of the research ethics committee to be so fundamentally at variance with the ethical principles governing research involving patients that it seemed impossible to give ethical approval for the study. However, during lengthy discussions with the investigators several considerations emerged.

Firstly, the information being sought by the investigators was clearly going to be of crucial importance to the community, not only in South Africa or in Africa as a whole but also worldwide. The importance of the study was perceived to be twofold. If it showed that a patient's HIV status significantly worsened his or her chances of a favourable outcome from intensive care—to a degree comparable to the poor prognosis associated with criteria already established for non-acceptance for admission to an intensive care unit—then the clinicians who have to make decisions on allocating the community's scarce intensive care resources would have to include HIV positivity among the criteria for non-acceptance. If, on the other hand, the study showed that HIV positivity per se did not adversely affect a patient's likelihood of a favourable outcome, then the current widespread tendency to include HIV positivity among the criteria for non-acceptance into intensive care facilities would become manifestly unjust. Such information gained from the study would be of life and death importance to the large and increasing numbers of people who are HIV positive.

Secondly, the study entailed no interventions of any sort different from those that are necessary and are carried out in standard intensive care. The blood samples that would be tested for HIV infection would be aliquots of samples taken for other necessary clinical purposes. Apart from the HIV testing, the study did not depart from normal standard of care and consisted essentially of analysis of data that would be recorded even if the study were not undertaken.

Thirdly, apart from the HIV testing, the "injury" that would be done to the patients as a result of not being given the opportunity to consent to or to refuse inclusion in the study was considered to be so small as to be virtually not appreciable and entirely analogous to the "injury" to patients whose hospital records are reviewed for retrospective research projects. Given the importance of the study, the failure to ask patients for permission to analyse data necessarily generated during their clinical care did not seem to be material.

Fourthly, testing the patients' blood for HIV infection without their consent and only informing them afterwards posed an important ethical dilemma. In considering this aspect of the study, the committee took into account several considerations. It agreed that there is no such thing in ethics—and particularly in the increasingly complex field of bioethics—as a simple and absolute ethical rule that must be observed in every conceivable situation. Virtually every ethical dilemma necessarily poses the problem of competing and conflicting ethical obligations. There are no absolutely satisfactory resolutions of ethical dilemmas, and the best that one can hope to achieve is to accord, with justice, preference to those ethical considerations (or "rules") that seem in the particular circumstances to be of preponderant weight.

The committee was also at pains to satisfy itself that the effective performance of the proposed study could not be achieved if any of the subjects were not to have their blood tested for HIV infection. Unless it could be shown, scientifically, that it was absolutely essential to include all admitted patients in the study, the committee would not have considered the proposed testing of blood without consent as ethical.

The committee was also strongly influenced by the fact that the results of the HIV tests would remain strictly confidential to only one investigator and that all potential linkage of the results of the tests to identifiable

individuals was to be destroyed at the end of the study. The situation, as the committee saw it, was analogous to the anonymous and unlinked testing of attenders at antenatal and sexually transmitted disease clinics, for epidemiological purposes. This testing, to be of value, has to include all attenders, and for this reason consent to testing of aliquots of attenders' blood samples taken for other purposes is not obtained. This practice has ethical approval throughout the world, on the basis that the community's need for reliable epidemiological data outweighs by far the almost imperceptible injury done to the patient's autonomy. From a practical point of view, the clinic attender is in the same situation as he or she would have been if HIV testing had not been done at all. Similarly, for the patients in this study the end result was the same as it would have been if their blood samples had never been tested, with the sole difference that, if they so wished, they would be informed of the outcome of the test. Weighing the importance of the study in terms of the welfare of the community against the almost imperceptible injury that would be inflicted on patients, the committee was satisfied that the proposed method of obtaining complete data regarding the patients' HIV status was ethically acceptable.

In the outcome, it seems that the committee's view on the ethics of this study was vindicated by the fact that no patient expressed any objection to the fact that his or her blood had been tested in this fashion. Furthermore, the fact that only two patients elected to be informed of the result of the test is in keeping with the general reluctance of well people to undergo HIV testing and suggests that if inclusion in the study depended on a patient's consent to HIV testing—even if effectively performed anonymously—then it is quite likely that the study would not have produced a reliable outcome.

The University of Natal's ethics committee is a subcommittee of the postgraduate committee.

Randomised, double blind, crossover challenge study of allergenicity of peanut oils in subjects allergic to peanuts

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Abstract

Objective: To determine the in vivo allergenicity of two grades of peanut oil for a large group of subjects with proved allergy to peanuts.

Design: Double blind, crossover food challenge with crude peanut oil and refined peanut oil.

Setting: Dedicated clinical investigation unit in a university hospital.

Subjects: 60 subjects allergic to peanuts; allergy was confirmed by challenge tests.

Outcome measures: Allergic reaction to the tested peanut oils

Results: None of the 60 subjects reacted to the refined oil; six (10%) reacted to the crude oil. Supervised peanut challenge caused considerably less severe reactions than subjects had reported previously.

Conclusions: Crude peanut oil caused allergic reactions in 10% of allergic subjects studied and should continue to be avoided. Refined peanut oil did not pose a risk to any of the subjects. It would be reasonable to recommend a change in labelling to distinguish refined from crude peanut oil.

Introduction

People allergic to peanuts characteristically take great care in avoiding products containing peanut, but many are accidentally exposed to peanut.[1] Most fatal reactions to peanut occur outside the sufferer's home, often during restaurant meals, despite the person's best efforts to ensure the absence of peanuts from the meal.[2-4] Peanut allergy and the potential for fatal reaction to unseen peanut constitute a "sword of Damocles" over people who are allergic to peanut. One great concern has been the widely held belief that reactions can be caused by peanut oil—also known as groundnut or arachis oil—particularly when it is presented as "vegetable oil."

Highly processed oils, including peanut oil, form the vast majority of oils used in the food processing and catering industries and on sale to the general public. The oil is subjected to physical and chemical methods of purification, including degumming, refining, bleaching, and deodorisation. It is then generally referred to as refined peanut oil. Protein has not been detected in unused refined peanut oil.[5 6]

The absence of detectable protein in refined peanut oil means it should have no potential to cause allergic reactions when ingested by people allergic to peanut. If such an oil is used to cook peanuts, however, peanut protein can subsequently be detected in the previously pure oil.[6] Such contamination of an oil is potentially a great hazard to people with peanut allergy when they eat outside their home environment. The reuse of vegetable oils is widespread in British homes, particularly for deep fat frying, and in fast food outlets (for instance, in fish and chip shops). The reuse of a vegetable oil to cook potato chips after it had been used to cook fish is considered to have caused the death of a person allergic to fish.[2]

Clearly, there is potential for reaction to less processed oils, known as cold pressed or crude peanut oils, though the degree to which this occurs has never been established. Crude peanut oils are strongly flavoured and have been shown to contain protein. Hoffman and Collins-Williams showed that one brand of crude peanut oil contained 3.3 μg of allergenic protein per millilitre of oil.[5]

The minimum amount of protein considered necessary to cause a reaction in a double blind, placebo controlled food challenge is between 50 mg and 100

mg.[7 8] To consume 50 mg of peanut protein in crude peanut oil a person would need to drink more than 15 litres of crude peanut oil. It is clearly more practically relevant to evaluate the safety of peanut oil at the volumes that may be used in cooking. The label on an average 25 g packet of potato crisps (for example, Ready Salted, KP Foods, Leicester) states that the crisps contain 9.2 g of fat, which would be derived mostly from the vegetable oil used to fry the crisps.

The issue of the safety of peanut oils for people allergic to peanuts has been studied before but only in small series. Bock and Atkins safely administered up to 30 ml of purified oil to four subjects with confirmed peanut allergy.[1] Taylor *et al* reported that 10 subjects allergic to peanut did not react to peanut oil in glycerin capsules to a maximum dose of 5 ml of oil.[9] On the basis of population statistics and by assuming a true prevalence of reaction to the oil in 5% of sensitive subjects, the study of Taylor *et al* proved to a probability of only 40% that no reaction would be observed.[10] Furthermore, in their study the capsules of oil were swallowed whole, and the oil therefore bypassed the oral mucosa—the most common site of exposure and first symptoms.[11] Therefore there has been uncertainty surrounding the safety of peanut oils for people with peanut allergy.

A food challenge study with a sample size of more than 58 subjects who do not react to the test substance has a 95% probability of showing that a reaction is likely in less than 5% of affected people.[10] We compared the in vivo allergenicity of two peanut oils—crude peanut oil and refined peanut oil—in a double blind, crossover trial with 60 subjects with proved peanut allergy.

Methods

Subject selection

From a group of 215 adult subjects who participated in a questionnaire study of peanut allergy conducted by the University of Southampton,[12] 69 subjects volunteered to participate in this study. All were skin prick tested with peanut (1:10 wt/vol peanut mix, (Runner, Virginia, Spanish) Miles, Indiana) and with each peanut oil. The result was considered positive if the test elicited a weal equal to or greater than the response to 1% histamine (positive control) in the absence of any reaction to saline (negative control). Subjects who had a negative skin prick test result with peanut were offered an open peanut challenge to prove or disprove peanut allergy.[13] Subjects who had positive skin prick results with peanut undertook the oil challenges on the same day in a clinical investigation unit equipped for resuscitation.[14]

Historical reactions and reactions observed during the challenges were defined as mild, moderate, or severe. Mild reactions were pruritus, rhinoconjunctivitis, local urticaria, swollen lips swelling, and erythema. Moderate reactions were facial swelling and pharyngolaryngeal oedema. Reactions that were characterised by dyspnoea, wheeze, cyanosis, or hypotension were considered severe.

All subjects gave personal and informed written consent. This study was approved by the local hospital ethics subcommittee.

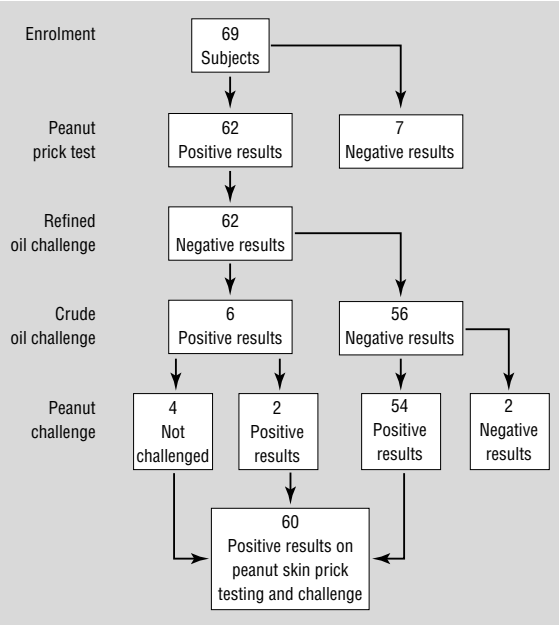

Fig 1 Summary of study results

Double blind challenge protocol

The oils (crude or refined) were tested in random order determined by a member of staff not involved in the evaluation of the subjects. Forty subjects (63%) received the refined oil first. Each oil was administered in increasing doses of 1, 5, and 10 ml disguised with 0.1% peppermint oil or 1% cocoa malt flavouring. Six subjects were offered the oil with bread and one with soya milk. The remaining subjects were given the oil mixed with rice pudding. An interval of 10 to 15 minutes between the doses was allowed for observation of the onset of any symptoms. If a reaction occurred to the first oil at least an hour was allowed to elapse before the second oil was administered.

Peanut challenge

Protein comprises 24.3% of the average weight of a peanut kernel.[15] We found that 100 peanut kernels (roasted and salted, KP Foods, Leicester, bought in the hospital newsagent's shop) weighed 66.35 g. The average protein content of one peanut kernel was therefore $0.6635\ g \times 24.3\% = 161$ mg; 32 peanuts contain 5.16 g of protein.

If the subject reacted to neither oil up to the maximum dose of 10 ml (total dose 16 ml of each oil) a controlled open challenge with peanuts was undertaken. The peanut challenge was performed with increasing doses starting with peanut rubbed on the lip (labial challenge). The dose was increased in steps until a reaction was observed or until the subject had eaten up to an arbitrary total of 32 peanuts without reaction. Subjects were observed for one hour after the completion of the challenge or until one hour after any symptoms had subsided.

Results

Sixty nine subjects were enrolled (54 women). The mean (range) age was 26 years (14-48) years. Figure 1 summarises the study results.

Table 1 Characteristics of nine subjects who proved not to be allergic to peanuts

Case No	Sex	Age (years)	Age at onset (years)	Time since last reaction	Speed of reaction (min)	Diagnosis
Negative peanut skin prick test result						
6	M	44	5-10	> 5 Years	20	Hazel nut allergy
30	F	17	< 0.5	> 5 Years	30	? Outgrown
50	M	46	> 10	1 Month	10	? Psychological
52	M	47	> 10	1 Month	2 days	? Type IV hypersensitivity
53	F	31	5-10	1-5 Years	10	Brazil nut allergy
54	F	34	Unknown	Unknown	Unknown	Never eaten
67	F	23	> 10	1 Month	20	Intolerant; features of chronic fatigue syndrome
Positive peanut skin prick test result						
11	M	24	> 10	1-5 Years	30	? Outgrown
34	F	38	5-10	1-5 Years	30	? Outgrown

Table 2 Reactions to crude oil in six subjects

Case No	Previous reaction	Skin prick test weal size (mm)	Dose of oil (ml)	Reaction
4	Wheeze	9	5	Oral itch
9	Throat tightness	10	5	Oral itch
23	Wheeze	12	1	Wheeze
28	Wheeze	7	10	Oral itch
46	Wheeze	12	5	Throat itch
59	Wheeze	10	5	Lip swelling

Table 3 Results of peanut challenge. Figures are numbers (percentages) of subjects unless stated otherwise

Dose of peanut	Dose of peanut protein (approx)	Reaction*			Not challenged†	Total
		Mild	Moderate	Severe		
On lips		35 (58)	4 (7)	1 (2)	—	40 (67)
Half nut	80 mg	8 (13)	4 (7)	—	—	12 (20)
Four nuts	645 mg	2 (3)	—	—	—	2 (3)
16 Nuts	2.58g	2 (3)	—	—	—	2 (3)
Not challenged†		—	—	—	4 (7)	4 (7)
Total		47 (78)	8 (13)	1 (2)	4 (7)	60 (100)

* See text for definitions of severity of reaction.
† Four subjects who reacted to crude oil were not challenged with peanut.

Table 4 Comparison of severity of reported previous reactions and observed reactions to peanut challenge. Figures are numbers (percentages) of subjects

Previous reaction*	Challenge reaction*			Not challenged†	Total
	Mild	Moderate	Severe		
Mild	3 (5)	2 (3.3)	0	0	5 (8)
Moderate	13 (22)	3 (5)	1 (2)	3 (5)	20 (33)
Severe	31 (52)	3 (5)	0	1 (2)	35 (58)
Total	47 (78)	8 (13)	1 (2)	4 (7)	60 (100)

*See text for definitions of severity of reaction.† Four subjects who reacted to crude oil were not challenged with peanut.

Skin prick tests

Seven subjects (10%) had negative results on skin prick tests with peanut, of whom six also had negative responses to challenge with peanuts. The remaining subject developed symptoms four days after exposure to peanuts and was therefore considered unsuitable for this study (table 1). The 62 remaining subjects (90%) underwent oil challenges.

Challenges

Oil challenges—No subject reacted to refined peanut oil. Six subjects (10%) reacted to crude oil (table 2).

Peanut challenge—Fifty eight peanut challenges were undertaken by subjects who had positive results on skin prick testing with peanut. Four subjects who reacted positively to skin prick testing with peanut did not have peanut challenges because they reacted to challenge with crude oil. Two subjects who had positive results on skin prick testing with peanut had negative results on peanut challenges. Both ate a cumulative dose of 32 peanuts without any reaction (table 1). Fifty six patients with positive results on peanut skin prick test had positive results on challenges to peanut. If we included the four subjects who reacted to crude oil but were not challenged with peanut a positive response to peanut was seen in 60 of 62 subjects positive for skin prick tests (96%) (tables 3 and 4). Twenty nine (48%) had reacted to peanut in the preceding year; only six (10%) had avoided peanuts successfully for more than five years.[1] Table 5 summarises other atopic disorders reported by the subjects with proved peanut allergy.

Discussion

Importance of study's findings

Peanut allergy is the commonest cause of fatal and near fatal allergic reactions to foods in the United States.[3] It is being recognised increasingly in the United Kingdom[12 16] and may affect as many as 1-2% of 4 year old children.[17] The increasing incidence probably reflects increasing consumption of peanuts in a wide range of food products. Heightened public awareness has driven increased medical involvement in the care of affected people who previously have had little access to scientific and medical information. Affected people have rarely had adequate provision and training in the use of rescue treatments such as adrenaline inhalers and injections.

In addition to reporting that they felt ill equipped to treat reactions to peanut themselves, many allergic people have commented that they have greater fear of exposure to the more widespread peanut oil than to peanut itself. Peanut oil is often implicated by those allergic to peanut as a cause of an allergic reaction, particularly in restaurant meals. The absence of antigenic protein in refined peanut oil[5 6] and its presence in such oil after cooking peanuts in the oil[6] suggest that oils may become adulterated with allergenic peanut proteins rather than being intrinsically allergenic themselves.

We believe our results confirm that refined peanut oil is safe for most people who are allergic to peanuts. This finding supports those of previous small studies[1 9] and provides statistically sound data on which to base more confident recommendations to patients, regulatory authorities, and the food and catering industries.

Reactions to crude peanut oil

Six subjects (10%) reacted to crude peanut oil. All these patients had had moderate or severe reactions previously, but only one suffered a comparable reaction to the crude oil. Four of these six had subjective reactions to the crude oil—there were no visible or measurable signs of reaction. These reactions may have been psychologically mediated and the real rate of measurable reaction to crude oil may be 3.3% (2/60) rather than 10% (6/60) of those with peanut allergy. The double blind nature of the challenge minimises the role of psychological reactions, and we have therefore considered the subjective, mild reactions to be real.

The low rate of reaction to crude peanut oil and the generally mild nature of the observed reactions to crude oil provide reassurance to sufferers that the reactions to crude oil are generally considerably less severe than reactions to peanut itself, even in those who normally have severe reactions. This may be a dose effect. Sufferers must continue to avoid the so called "gourmet oils" that are deliberately blended with crude peanut oil to give them a characteristic peanut flavour. Different crude peanut oils may contain different concentrations of peanut protein,[5] so the relative risk of other crude oils may differ from that of the oil we tested in this study.

Table 5 Summary of reported allergies and skin prick test results in 60 adults with proved peanut allergy

	No (%) reporting condition	No (%) with positive result of skin prick test to appropriate allergen
Condition		
Asthma	35 (58)	
Rhinitis	44 (73)	
Allergy		
Eczema	35 (58)	
Soy	3 (5)	32 (53)
Nut allergy (any tree nut, excluding peanut)	34 (56)	50 (83)
Milk	2 (3)	12 (20)
Egg	8 (13)	10 (16)
Grass		49 (81)
House dust mite		42 (70)
Cat*		34 (77)

*44 Subjects tested for sensitisation to cat.

Peanut challenges

There was a striking disparity between the severity of previous reactions and reactions observed during supervised peanut challenge. This is probably due to a combination of two factors. Firstly, the subjects were evaluated when they were otherwise well and were being supervised in a calm, clinical setting with all appropriate precautions taken. Clearly, anxiety that is generated by reactions away from medical help may exacerbate reactions. Also, the controlled dose of peanut that elicited reactions in the challenges was probably much lower than the dose to which subjects are exposed in meals and prepared foods that caused reactions in the community.

Use of refined peanut oil

Our results do not suggest that it is completely safe for all people with peanut allergy to eat in restaurants where refined oils are used. Such oils may come into contact with peanuts and thereby become contaminated.[6] This risk, of course, applies to any oil used in cooking,[2] not just to peanut oil. To minimise the risk to people allergic to peanuts and other foods, it is vital to increase awareness of food allergy among catering and restaurant staff. They must be aware of the risk to people with life threatening reactions to foods of reuse of oils, especially after cooking foods that are known to be allergenic, such as peanuts, tree nuts, fish,[2] and shellfish.

Key messages

- Peanut (groundnut) allergy is the most common cause of deaths related to food allergy. Peanut oil is often suspected of causing reactions to meals in which a more obvious source of peanut cannot be found
- Refined peanut oil is odourless and flavourless and is commonly used in catering. Crude peanut oil, which is known to contain considerable amounts of protein is used only rarely, when a peanut flavour is deliberately required
- In vivo challenges of 60 subjects with proved peanut allergy showed no reaction to refined peanut oil, but six (10%) reacted to the crude peanut oil
- If refined peanut oil is used properly and is not reused after cooking peanuts, it seems to be safe for most people with peanut allergy; crude oil represents a risk
- The confusing use of the term groundnut oil should be stopped, and food labelling should distinguish between refined and crude oils

Labelling

Discontinuation of the use of the term groundnut and clear labelling distinctions between refined and crude oils would simplify many of these issues. Such steps are now justified as a consequence of this study. Refined peanut oil does not seem to pose a risk to most people with peanut allergy.

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Funding: Seed Crushers' and Oil Processors' Association (SCOPA).

Conflict of interest: The research was funded by SCOPA, the trade association for companies who manufacture refined and crude peanut oils.

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A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting

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Abstract

Objectives: To test the evidence for a dose-response with ondansetron for treatment of postoperative nausea and vomiting and to establish whether differences in efficacy between doses are of clinical relevance.
Design: Quantitative systematic review of published randomised controlled trials.
Data sources: Seven trials from 1991 to January 1996 retrieved from a systematic literature search (Medline, reference lists, hand searching of anaesthetic journals, manufacturer's database); no restriction on language.
Main outcome measures: Estimation of efficacy (incidence of complete control of further nausea and vomiting) by using odds ratios and the "number needed to treat" method for early (within 6 hours of administration) and late (within 24 hours) periods.
Results: Four placebo controlled trials with 1043 patients studied intravenous ondansetron 1 mg, 4 mg, or 8 mg. All doses were more efficacious than placebo in preventing further episodes of nausea or vomiting. For combined data, the point estimates for the number needed to treat were between 3.1 (8 mg) and 3.8 (1 mg) for early efficacy and between 4.1 (8 mg) and 4.8 (1 mg) for late efficacy, without significant differences between doses. No difference was found between ondansetron and droperidol in two trials with 129 patients or between ondansetron and metoclopramide in one trial with 80 patients.
Conclusions: Further nausea and vomiting could be prevented with ondansetron compared with placebo in 25% of patients who had nausea or vomiting (number needed to treat, about 4). There was no evidence of a clinically relevant dose-response between 1 mg and 8 mg or a difference between ondansetron and either droperidol or metoclopramide in a limited dataset. A false impression of ondansetron's efficacy may arise because a quarter of all relevant published reports are duplicates, and reporting of study results is uncritical.

Introduction

Postoperative nausea and vomiting are unpleasant complications of surgery and anaesthesia. Although much attention has been paid to the prevention of these conditions during the past three decades,[1-5] little information exists on the efficacy of anti-emetic interventions in patients with established postoperative nausea and vomiting.

The first clinical trials in 1991 showed that a single intravenous dose of ondansetron 8 mg was an efficacious anti-emetic compared with placebo in treating postoperative nausea and vomiting.[6 7] Reports of multicentre trials, with data on hundreds of patients and comparing different doses of ondansetron with placebo, concluded that intravenous ondansetron 4 mg was the optimal dose for treating established postoperative nausea and vomiting.[8 9]

We tested the evidence for a dose-response with ondansetron for treatment of postoperative nausea and vomiting and aimed to establish whether differences in efficacy between doses are of clinical relevance.

Methods

Systematic search

We searched Medline (date of search 22 January 1996) back to 1991 for randomised controlled trials that evaluated the effect of ondansetron compared with a control (placebo, no treatment, or another anti-emetic) on established postoperative nausea and vomiting and reported the outcome in dichotomous form. The search was not restricted to the English language and used the combination *(ondansetron and human and (emesis or nausea or vomiting)) not (chemotherapy or cancer).* We identified additional reports from reference lists of retrieved reports and from review articles of postoperative nausea and vomiting and ondansetron and from hand searching locally available anaesthesia journals. We compared our database with the database of published trials provided by the manufacturer of ondansetron. We did not search for unpublished trials or consider abstracts. We did not analyse efficacy data for ondansetron as prophylaxis against postoperative nausea and vomiting.

Scoring and extraction of data

Each report was read by three of the authors independently to assess adequacy of randomisation and blinding and to assess description of withdrawals.[10] These three authors met to agree consensus. Reports

that were described as randomised were given one point, plus a further point if the method of randomisation was described and adequate (such as a table of random numbers). There had been an earlier agreement that trials without randomisation or with an inadequate randomisation method (without concealment of treatment allocation) would be excluded from further analysis. Reports that were described as blinded were given one point, plus a further point if the method of blinding was described and adequate (such as identical ampoules). Reports that described the number of and reasons for withdrawals were given one point. Thus the minimum score of an included randomised controlled trial was 1, the maximum score 5.

When origin of data was unclear in reviewed articles, we wrote to the principal authors for information about duplicate publication.

We took information about patients, dose and route of administration of ondansetron and control treatments, anaesthetics, surgery, incidence of postoperative nausea and vomiting in the studied population before randomisation, and study endpoints from each included report. The endpoint indicating a treatment success that was closest to complete control of postoperative nausea and vomiting (absence of further nausea or vomiting, or of both, after treatment) was extracted in dichotomous form. The incidence of this endpoint was treated as the success rate with ondansetron or control. When success rates were reported at different times after administration of ondansetron, the times nearest to the 6th and the 24th hour were used for extraction of cumulative results. Estimates of efficacy during the two time periods (0 to 6 hours and 0 to 24 hours after administration of the ondansetron) were used as indicators of early and late efficacy, respectively. Post hoc analyses, stratified data analyses (according to sex, for example), different grades of nausea, number of vomiting episodes, or number of patients needing anti-emetic rescue treatment were not considered.

Analyses

The scatter of success rates with ondansetron against success rates with control[11] was used as a graphical means of exploring consistency of ondansetron's efficacy and the homogeneity of the data. On such plots a scatter lying predominantly between the line of equality and the axis of the active intervention (ondansetron) would suggest consistent efficacy with the intervention, and relative homogeneity.

Significance and clinical relevance of ondansetron's efficacy compared with control were evaluated with odds ratios and number needed to treat methods[12] respectively. Calculations were done by combining ondansetron arms for each dose separately, and corresponding control arms. This means that data from patients receiving placebo from studies using several different doses of ondansetron could be included in several analyses. Odds ratios were estimated with 95% confidence intervals with a fixed effect model.[13] A significant improvement of ondansetron over control was assumed when the lower 95% confidence limit of the odds ratio was >1. Point estimates and 95% confidence limits of the number needed to treat were calculated.[14] The number needed to treat indicated how many patients with vomiting and nausea have to be treated with ondansetron to achieve complete control of postoperative nausea and vomiting—that is, to prevent any further nausea or vomiting, or both, in one of them, who would otherwise have had further postoperative nausea and vomiting with control treatment. Absence of a significant difference between different doses of ondansetron was assumed when the 95% confidence intervals of the corresponding odds ratio or number needed to treat overlapped.

Calculations were performed with EXCEL version 5.0 on a Power Macintosh 7100/66.

Results

Trials found

Nine randomised controlled trials were found in eight reports.[6-9 15-18] Results from one multicentre trial with data from 500 patients treated with three different doses of ondansetron compared with placebo[8] were assumed to have been published on two later occasions, in 1993[18] and in 1994 (first study).[9] All contacted authors confirmed that one single dataset had been reported in three publications. Only data from the first publication[8] was analysed for the purpose of this systematic review. Data of an abstract from a scientific meeting,[19] which were identical to the second part of a full paper publication (second study),[9] were not analysed. No other report was excluded from analysis. All trials except two[16 17] were sponsored by the manufacturer of ondansetron.

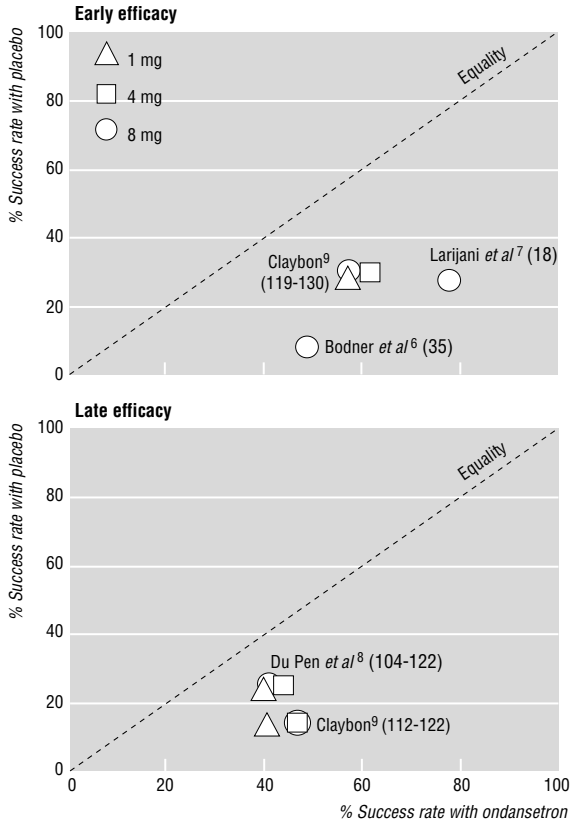

Fig 1 Success rate of ondansetron for treatment of postoperative nausea and vomiting. Each symbol represents one dose of ondansetron compared with placebo in one trial (numbers in parentheses are patients in ondansetron groups). Success rate is the incidence of patients with no further postoperative nausea and vomiting over six hours (early efficacy) and 24 hours (late efficacy)

Table 1 Anti-emetic efficacy of intravenous ondansetron in treatment of established postoperative nausea and vomiting

Comparison (trial)	Success*		Odds ratio (95% CI)	Number needed to treat† (95% CI)
	With ondansetron	With control		
Early anti-emetic efficacy compared with placebo				
Ondansetron 1 mg (Du Pen *et al*[8])	74/130	39/129	3.0 (1.8 to 4.8)	3.8 (2.6 to 6.6)
Ondansetron 4 mg (Du Pen *et al*[8])	73/119	39/129	3.5 (2.1 to 5.8)	3.2 (2.3 to 5.2)
Ondansetron 8 mg (Du Pen *et al*[8])	70/122	39/129	3.0 (1.8 to 5.0)	3.7 (2.6 to 6.5)
Ondansetron 8 mg (Bodner *et al*[6])	17/35	3/36	7.1 (2.5 to 19.8)	2.5 (1.7 to 4.7)
Ondansetron 8 mg (Larijani *et al*[7])	14/18	5/18	7.0 (1.9 to 25.6)	2.0 (1.3 to 4.6)
Ondansetron 8 mg (trials combined)	101/175	47/183	3.8 (2.5 to 5.8)	3.1 (2.4 to 4.5)
Early anti-emetic efficacy compared with intravenous droperidol				
Ondansetron 8 mg×3 *v* droperidol 1.25 mg×3 (Heim *et al*[15])	30/50	34/50	0.7 (0.3 to 1.6)	–12.5 (–3.7 to ∞)
Ondansetron 100 μg/kg *v* droperidol 20 μg/kg (Ummenhofer *et al*[17])	12/16	11/13	0.6 (0.1 to 3.4)	–10.4 (–2.6 to ∞)
Ondansetron *v* droperidol (trials combined)	42/66	45/63	0.7 (0.3 to 1.4)	–12.8 (–4.2 to ∞)
Early anti-emetic efficacy compared with intravenous metoclopramide				
Ondansetron 4 mg *v* metoclopramide 10 mg (Polati *et al*[16])	35/40	30/40	2.3 (0.7 to 6.7)	8.0 (3.4 to ∞)
Late anti-emetic efficacy compared with placebo				
Ondansetron 1 mg (Du Pen *et al*[8])	53/130	19/129	3.6 (2.1 to 6.3)	3.8 (2.7 to 6.4)
Ondansetron 1 mg (Claybon (2nd study)[9])	45/112	28/108	1.9 (1.1 to 3.3)	7.0 (3.8 to 50)
Ondansetron 1 mg (trials combined)	98/242	47/237	2.7 (1.8 to 3.9)	4.8 (3.5 to 7.9)
Ondansetron 4 mg (Du Pen *et al*[8])	56/119	19/129	4.6 (2.7 to 7.9)	3.1 (2.3 to 4.7)
Ondansetron 4 mg (Claybon (2nd study)[9])	49/112	28/108	2.2 (1.3 to 3.8)	5.6 (3.3 to 18.3)
Ondansetron 4 mg (trials combined)	105/231	47/237	3.2 (2.2 to 4.7)	3.9 (3.0 to 5.7)
Ondansetron 8 mg (Du Pen *et al*[8])	57/122	19/129	4.5 (2.6 to 7.8)	3.1 (2.3 to 4.7)
Ondansetron 8 mg (Claybon (2nd study)[9])	43/104	28/108	2.0 (1.1 to 3.5)	6.5 (3.6 to 35)
Ondansetron 8 mg (trials combined)	100/226	47/237	3.1 (2.1 to 4.5)	4.1 (3.1 to 6.2)
Late anti-emetic efficacy compared with intravenous metoclopramide				
Ondansetron 4 mg *v* metoclopramide 10 mg (Polati *et al*[16])	24/40	18/40	1.8 (0.8 to 4.3)	6.7 (2.7 to ∞)

*Complete control of further nausea or vomiting, or both.
†Number needed to treat for success in one patient.
Early and late efficacy = success over 1 to 6 hours and over 24 hours respectively.
∞ = Absence of a significant difference between treatments.
Heterogeneity testing was done when more than two trials were pooled; there was none (P >0.1).

End points and quality score

The remaining seven trials had a median score of 3 (range 2 to 4). The average incidence of postoperative nausea and vomiting before randomisation (before treatment was given) was 36% (22-46%). Four trials compared a single intravenous dose of ondansetron 1 mg, 4 mg, or 8 mg with placebo in 1043 adults (859 females) who complained of nausea or vomited after general anaesthesia.[6-9] In one trial with 100 gynaecology patients intravenous ondansetron 8 mg was compared with intravenous droperidol 1.25 mg; both anti-emetics could be administered up to three times in 24 hours.[15] In one trial 29 vomiting children received either ondansetron 100 μg/kg or droperidol 20 μg/kg intravenously.[17] In one trial with 80 patients undergoing major abdominal surgery intravenous ondansetron 4 mg was compared with intravenous metoclopramide 10 mg.[16]

No recurrence of vomiting was the analysed endpoint in one trial.[7] In all other trials complete control of postoperative nausea and vomiting was the analysed endpoint. Early (short term) efficacy (within 6 hours) of ondansetron was reported on five occasions.[6-17] Late (long term) efficacy (within 24 hours) was reported in two placebo controlled trials[8 9] and one trial with metoclopramide as the control.[16] Data extracted from these reports are available from the worldwide web (http://www.jr2.ox.ac.uk/Bandolier/painres/ondR/ondR.html).

Efficacy

The success rate scatter, exploring the incidence of treatment success with ondansetron and placebo, suggested homogeneity of data and consistent efficacy (both early and late) of ondansetron compared with placebo, and with no obvious dose-response (fig 1).

Odds ratios showed a significant difference between each of the three doses of ondansetron and placebo for both early and late efficacy, but no difference between ondansetron and droperidol for early efficacy, and none between ondansetron and metoclopramide for both early and late efficacy (table 1). The number needed to treat point estimates for early efficacy with ondansetron compared with placebo were 3.8 for 1 mg, 3.2 for 4 mg, and 3.1 for 8 mg. Over a 24 hour observation period the number needed to treat point estimates were 4.8 for 1 mg, 3.9 for 4 mg, and 4.1 for 8 mg.

The point estimates for the number needed to treat for early efficacy with ondansetron 8 mg were 2.5 (95% confidence interval 1.7 to 4.7) and 2 (1.3 to 4.6) in two small trials with 35 and 18 treated patients respectively,[6 7] compared with 3.7 (2.6 to 6.5) in a large multicentre trial with 122 treated patients.[8]

For all three ondansetron doses, both for early and late observation periods, the 95% confidence intervals of the estimates of efficacy (odds ratio and number needed to treat) overlapped, indicating absence of any significant difference in anti-emetic efficacy between the three doses (table 1).

Discussion

Ondansetron used as treatment for established postoperative nausea and vomiting was effective compared with placebo. About a quarter of treated

patients were prevented from further nausea and vomiting with a dose of 1 mg, 4 mg, or 8 mg. It is difficult to say how well ondansetron performs in this setting relative to other treatments because of the paucity of direct comparisons with other anti-emetics. Nor is it possible to confirm that response rates in men, women, and children will be the same. Most patients (82%) in these trials were women.

There was no significant difference between ondansetron and droperidol when results from the two trials using droperidol were combined. Neither was there a significant difference between ondansetron and metoclopramide in the one trial that investigated this comparison. Indirect comparison of ondansetron with other anti-emetics will be possible by comparing their relative performance against placebo. If these drugs are highly effective in treating established postoperative nausea and vomiting, this would argue against pre-emptive use of anti-emetics.

Postoperative nausea and vomiting seem to have many causes,[5] and it is perhaps naive to think that an anti-emetic, working at one specific receptor, should be universally effective. Given this multiple causation, from patient related factors through to the effects of anaesthesia, surgery, and opioids, preventing further postoperative nausea and vomiting in a quarter of the patients may be the best that can be achieved currently.

Key messages

- Little information exists on the efficacy of anti-emetic interventions in patients with established postoperative nausea and vomiting
- To evaluate the effectiveness of ondansetron in this setting we conducted a quantitative systematic review of all relevant published randomised controlled trials
- Four trials (1043 patients) compared intravenous ondansetron 1 mg, 4 mg, or 8 mg with placebo, two trials (129 patients) compared ondansetron with droperidol, and one trial (80 patients) compared ondansetron with metoclopramide
- All three tested doses of ondansetron were more efficacious than placebo. There was no evidence of a clinically relevant dose-response between 1 mg and 8 mg (number needed to treat to prevent further nausea or vomiting was about 4), or a difference between ondansetron and either droperidol or metoclopramide.
- Stopping further postoperative nausea and vomiting in 25% of the patients may be the best that can be achieved currently

Dose-response

This quantitative analysis did, however, fail to show a significant dose-response for intravenous ondansetron between the 1 mg, 4 mg, and 8 mg tested. Although higher doses had lower point estimates for the number needed to treat, particularly for early efficacy, the differences between doses were not significant, as indicated by an overlap of the 95% confidence intervals of both odds ratio and the number needed to treat. This cannot be dismissed on the grounds of a clinically relevant difference minimised by lack of statistical power, because differences between numbers needed to treat were minor.

This inability to show a dose-response is hard to explain. The bulk (>900/1043 patients) of the data came from two large multicentre trials, and figure 1 shows little graphic evidence of heterogeneity. The two smaller trials[6 7] reported higher early efficacy with ondansetron 8 mg (number needed to treat 2 to 2.5) than the large multicentre trial (3.7).[8] One explanation for the failure to show a dose-response is that the minimum effective dose for treatment of established postoperative nausea and vomiting is less than the lowest dose (1 mg) studied, so that lower doses could be tested.

Clinical messages

Two clinical messages emerge from this analysis. The first is that the number needed to treat for intravenous ondansetron compared with placebo to treat established postoperative nausea and vomiting is about 4. This means that 1 in 4 patients with nausea or vomiting treated with ondansetron will be prevented from further nausea and vomiting, who would otherwise have continued to have nausea or to vomit with placebo. The trials comparing ondansetron with droperidol or metoclopramide showed no difference in efficacy. We do not know if this is the best anti-emetic control that can be achieved.

The second message relates to anti-emetics as prophylaxis rather than as treatment for established postoperative nausea and vomiting. The justification of prophylactic postoperative anti-emetics was queried 35 years ago by Adriani and colleagues.[20] They noted that no more than a quarter of patients in the recovery room vomited in the immediate postanaesthetic period and that most of this vomiting was short lived and subsided spontaneously without anti-emetics. Similar average incidence of postoperative nausea and vomiting has been reported repeatedly, both in large randomised controlled trials[21] and in case series,[22-24] although it may be higher in specific clinical settings, such as paediatric strabismus surgery.[25] In the ondansetron trials analysed here the average incidence of postoperative nausea and vomiting was 36% before starting treatment, suggesting that these trials accurately reflect common clinical practice.

If the incidence is only about 30% and treatment is effective then arguably prophylaxis is unnecessary on grounds of adverse effects and cost. The humanitarian argument is that it is unacceptable to wait and see if a patient is going to vomit or develop nausea before starting a treatment. It is also widely believed that it may be more difficult to treat established postoperative nausea and vomiting than to prevent it,[26] although there is no substantial evidence to support this view. The pivotal answers to resolve the debate will be the relative effectiveness of treatment and prophylaxis of postoperative nausea and vomiting.

We are concerned that data from a large, sponsored, multicentre trial were published three times.[8 9 18] Inclusion of the two duplicates in the analysis would have increased the number of analysed reports by a quarter and doubled the number of

analysed patients. Systematic reviewers are at risk of failing to recognise duplicates of an original report.[27] The danger is that unrecognised duplicates will bias the estimates of an intervention's efficacy. Two duplicates were published in journal supplements,[8 9] and the quality of supplement reports may be lower than reports in the parent journals.[28] Both supplement articles declared that intravenous ondansetron 4 mg was the optimal dose to treat postoperative nausea and vomiting, although there was no good evidence to support this.[8 9] Subsequent uncritical repetitions[26 29] underline the potential influence of such unchallenged assertions.

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Comparison of first degree relatives and spouses of people with chronic tension headache

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Tension headache is known by virtually everyone. Most people have mild and infrequent attacks, but about 3% of the population have frequent attacks—chronic tension headache.[1] Chronic tension headache often affects patients for a major part of their lives, causing considerable personal and socioeconomic expense.[2]

The aetiology of chronic tension headache remains largely unknown. A genetic factor has not previously been suspected, although patients suffering from chronic tension headache commonly report a family history of the condition. We examined the familial occurrence of chronic tension headache in spouses and first degree relatives of probands with chronic tension headache in order to evaluate its possible genetic background.

Patients, methods, and results

We studied 122 consecutive probands meeting the International Headache Society's criteria for chronic tension headache.[3] Probands had a clinical interview and a physical and a neurological examination by neurological residents (junior doctors). Spouses and first degree relatives aged 18 years or above were interviewed by telephone (SØ). The participation rate was 100% among spouses (93/93; some probands were unmarried or divorced) and 95% (377/396) among first degree relatives. The project was approved by the Danish ethics committees.

The risk of familial occurrence was assessed by estimating the population relative risk of the disease in specified groups of relatives.[4] The risk was calculated as the probability that a relative is affected given that the

proband is affected, divided by the probability that a random member of the population is affected. A family aggregation is implied when this risk ratio significantly exceeds 1.

The one year prevalence of chronic tension headache is 3%, 5% among female patients and 2% among male patients.[1] The lifetime prevalence was estimated to be twice that of the one year prevalence. As the prevalence of chronic tension headache depends on age and sex, the value of the denominator was adjusted according to the distribution of age and sex in the group of relatives studied; 95% confidence intervals were calculated by standard methods.

Table 1 shows the risk of chronic tension headache among first degree relatives and spouses. In comparison to the general population, first degree relatives had a significantly increased risk of chronic tension headache, while spouses had no increased risk of chronic tension headache.

Table 1 Risk of chronic tension-type headache among first degree relatives and spouses of probands with chronic tension-type headache, standardised for sex and age

	No of affected first degree relatives		Population relative risk (estimated (O/E) (95% confidence interval))
	Observed (O)	Expected (E)	
Risk in one year period:			
First degree relatives	36	11.31	3.18 (2.26 to 4.31)
Spouses	3	2.43	1.23 (0.26 to 3.49)
Lifetime risk:			
First degree relatives	71	22.61	3.14 (2.50 to 3.86)
Spouses	4	4.85	0.82 (0.23 to 2.68)

Comment

This is the first family study of chronic tension headache. Our main result was that first degree relatives of probands with chronic tension headache had more than three times the risk of chronic tension headache than the general population.

An increased family risk can be caused by genetic or environmental factors. Because probands and spouses in part share their environment but differ in genetic constitution, the risk of chronic tension headache in spouses was used to elucidate the relative role of genetic and environmental factors. As first degree relatives had a significantly increased risk of chronic tension headache and spouses had no increased risk, our results support the importance of genetic factors in chronic tension headache.

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A MEMORABLE PATIENT

An air male delivery

A few days earlier I had arrived to take up my post in an outpatient clinic in a remote part of Gabon, Africa. I was finding the handover period quite stressful. The "good spoken French" that I had described in my curriculum vitae proved not to be quite so good when faced with 40 to 60 Gabonese patients each morning. The French drug names and prescribing habits were a complete mystery to me. I was beginning to wonder if this really was the job I wanted.

One morning a woman arrived in established labour. I couldn't work out what was presenting vaginally, but my colleague immediately diagnosed a transverse lie and ordered an urgent helicopter evacuation to hospital for caesarean section. I remember wondering if perhaps we shouldn't wait and see what happened for a while, but I was new and hesitant to start arguing over urgent cases.

The helicopter seemed tiny, with just myself, the patient, and the pilot on board. We had been flying for ten minutes and the mother was getting restless. I examined her and found what I had feared—a foot in the vagina. She started to push. The body was delivered quickly, and I prayed that the head would follow easily. It did not. As the listless body hung there for what seemed like ages, the situation became increasingly desperate. The mother raised herself to a crouching position, stumbling around the medical bags and the stretcher. The pilot cast anxious glances over his shoulder. What was that manoeuvre used to deliver a head in a breech delivery? Was it applicable to a distressed patient climbing around in the back of a helicopter?

Eventually, I got the mother to settle down, and after a struggle, delivered the baby's head. Afterwards, to colleagues, I described this as a Lovset's manoeuvre of traction and rotation, but the reality was not as slick as I made it sound, and I suspect that the mother's crouching position was what achieved the delivery anyway.

The baby was grey, apnoeic, and completely floppy. I had no doubt that he was dead, but went through the motions of resuscitation to avoid catching the mother's eye. As I intubated him, I reflected wryly that I had left general practice in Cornwall to seek greater stimulation in Africa. My wish had been rapidly and emphatically satisfied.

As the helicopter landed, the baby started to make respiratory efforts and I could hear a healthy heartbeat. He was transferred to hospital and, although he did well, I was convinced that he would be brain damaged. I dreaded the task of recording his ever increasing developmental delay over the coming months and years.

This was not so, however, and as each milestone was reached on time I became increasingly optimistic. I started to shower little gifts on the baby in the form of antiseptic creams and vitamin syrup to encourage the mother to attend for regular follow up. On his first birthday he got most of my son's baby clothes. The mother was clearly perplexed as to why I would want to celebrate his birthday and I was never able to fathom her inscrutable Gabonese mind. She had remained expressionless and, to me at least, emotionless throughout. Did she wonder why on earth we had stuck her in a helicopter to give birth? Or was she grateful that we had helped her to deliver a healthy baby? I will never know.

I saw the child a couple of weeks ago. He is now 2 ½ years old and completely normal. His mother calls him Helico.

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