Managing nocturnal leg cramps — calf-stretching exercises and cessation of quinine treatment: a factorial randomised controlled trial

Richard J Coppin, Dorothy M Wicke and Paul S Little

ABSTRACT

Background

Quinine is a common treatment for nocturnal leg cramps but has potential side effects. An uncontrolled study suggested that calf-stretching exercises could prevent nocturnal leg cramps (night cramps) but these findings have never been confirmed.

Aim

To assess the effect of calf-stretching exercises and cessation of quinine treatment for patients with night cramps taking quinine.

Design of study

Randomised controlled trial.

Setting

Twenty-eight general practices in southern England.

Method

One hundred and ninety-one patients prescribed quinine for night cramps were randomised to one of four groups defined by two 'advice' factors: undertake exercises and stop quinine. After 6 weeks they were advised that they could take quinine and undertake the exercises freely. Documentation of cramp at 12 weeks was achieved in 181 (95%) patients. Main outcome measures were: symptom burden score, and frequency of night cramps and quinine usage.

Results

At 12 weeks there was no significant difference in number of cramps in the previous 4 weeks (exercise = 1.95, 95% confidence interval [CI] = -3.01 to 6.90; quinine cessation = 3.45, 95% CI = -1.52 to 8.41) nor symptom burden or severity of cramps. However, after 12 weeks 26.5% (95% CI = 13.3% to 39.7%) more patients who had been advised to stop quinine treatment reported taking no quinine tablets in the previous week (odds ratio [OR] = 3.32, 95% CI = 1.37 to 8.06), whereas advice to do stretching exercises had no effect (OR = 0.73, 95% CI = 0.27 to 1.98).

Conclusions

Calf-stretching exercises are not effective in reducing the frequency or severity of night cramps. Advising those on long-term repeat prescriptions to try stopping quinine temporarily will result in no major problems for patients, and allow a significant number to stop medication.

Keywords

exercise therapy; muscle cramp; nocturnal leg cramps; primary health care; quinine; randomised controlled trials.

INTRODUCTION

Idiopathic nocturnal cramps are painful involuntary muscle spasms that commonly disrupt sleep. More than a third of people aged over 60 years experience them, their prevalence increases with age and they occur most commonly in the leg.[1] Of people experiencing nocturnal leg cramps (night cramps) about a third have consulted a doctor about them.[2]

The cause of night cramps is unclear. Cramps can be caused by electrolyte imbalance such as hyponatraemia, and they are reported in patients on renal dialysis and as an unwanted effect of drugs such as diuretics, nifedipine, salbutamol and terbutaline.[3] It has been suggested that leg cramps may be more common in affluent sedentary societies, where muscle use and stretching is less common.[4]

Interest in the management of night cramps has centred mainly on prophylactic pharmacological treatments, particularly quinine,[5] which most GPs prescribe.[6] Prescribing of quinine is evidence based since it is more effective than placebo in reducing the number of cramps,[7,8] but has potentially serious unwanted effects, including tinnitus,[3] which is more common in those taking it for night cramps.[7] In the US, the Food and Drug Administration has prohibited the over-the-counter sale of quinine because of safety concerns.[9] There is little evidence about its long-term effectiveness. Stepping down

***R J Coppin**, B Med Sci, DRCOG, general practitioner; **D M Wicke**, RN, CHCN-GPN, nurse, The Surgery, Overton, Basingstoke. **P S Little**, MRCP, FRCGP, MD, professor of primary care research, University of Southampton.*

Address for correspondence

Dr Richard Coppin, The Surgery, Station Road, Overton, Basingstoke, Hants RG25 3DZ.
E-mail: overtonsurgery@dial.pipex.com

Submitted: 14 October 2003; **Editor's response:** 24 March 2004; **final acceptance:** 27 July 2004.

treatment has been shown to be feasible in some patients with other chronic diseases, such as asthma[10] and hypertension,[11] but, to our knowledge, there has been no trial assessing the effect of discontinuing repeat prescriptions of quinine.

Immediate relief from cramp may be obtained by passively stretching the affected muscle.[12] The use of regular stretching exercises to prevent night cramp was proposed by Daniell.[13] His small uncontrolled trial of a simple programme of leg muscle stretching exercises, based on a short paper in a publication for runners,[14] is widely cited,[3,4,7,12,15–18] but its conclusions have not been confirmed.

We therefore compared the effect of advice on the regular use of these exercises with advice on a non-stretching, placebo exercise and the effect of continuing or stopping previously prescribed quinine in a sample of patients with ongoing cramp symptoms and on repeat prescriptions for quinine.

How this fits in

Quinine is commonly used as a treatment for night cramps but there are doubts about its effectiveness and it has potential side effects. In 1979 Daniell reported the effectiveness of regular calf-stretching exercises in preventing night cramps but his findings have never been confirmed by a robust study. This randomised study suggests that calf-stretching exercises have no benefit in night cramps but that a significant number of those on repeat prescriptions for quinine may be able to stop medication without major problems.

METHOD

Setting

We invited practices in a defined area in the south of England to participate in the study. Thirty practices agreed to take part and details of the recruitment of 18 of the practices have been described earlier.[19]

Patients

The practices were asked to carry out a search of their database for patients aged 60 years and over who had been given a repeat prescription of quinine for night cramps in the previous 3 months. This was a workable definition of a population with a chronic condition in which both step-down therapy and an alternative management strategy, such as stretching exercises, might be considered. These patients were invited to participate and those with conditions significantly limiting their ability to undertake the stretching exercises were excluded; for example, severe osteoarthritis; leg pain that might be confused with cramp, such as severe peripheral vascular disease; inability to reliably report on symptoms, such as dementia; and patients who described being previously taught leg exercises aimed at preventing cramp.

Interventions

We trained a nurse from each participating practice. In the first six practices to participate, patients thought to be eligible were sent an information sheet and an invitation to participate in the study. Following a lower than expected response rate we agreed a modification to the recruitment procedure with the ethics committees. In a further 24 practices, patients were invited by letter to express an interest and those responding were then telephoned by the practice nurse, who checked eligibility and sent an information sheet and appointment to those still wishing to participate. Patients then attended an interview at their practice during which the nurse obtained written consent and completed a questionnaire to record baseline data.

Randomisation to the trial took place when the nurse opened a sealed, numbered, opaque envelope containing intervention instructions that had been previously randomised by the research assistant using random number tables. Patients were then shown how to complete a 6-week diary record and given advice to either continue or discontinue taking quinine tablets and to undertake a daily programme of either stretching or placebo exercises for which they received training. The placebo exercise was devised to be of comparable duration and simplicity to the intervention stretching exercise, but was passive and involved negligible stretching of the muscles of the calf and foot (Supplementary Box 1). We sought to minimise intervention contamination by terming the stretching and placebo exercises as ‘standing’ and ‘lying’ exercises, respectively. Patients were told that at the end of 6 weeks they could continue the exercises if they wished and also decide themselves whether or not to continue or resume taking quinine tablets. They were also given an instruction sheet describing the exercise programme and confirming the advice.

One week later the nurse telephoned the patient to check that they were coping with the diary recording. Intervention advice was not repeated. Twelve weeks after the interview, patients were sent a self-completion postal questionnaire. Non-responders were telephoned to record their questionnaire responses. Twelve weeks was considered to be an appropriate interval at which to measure the main outcomes as it captured the considered response of patients to the choice resulting from the intervention advice. To avoid bias, intervention codes from the data sheets were removed prior to data entry and then recombined for analysis.

Validation of self-reported quinine use

We were concerned about validating self-reported quinine use, and in a subgroup of local practices we compared recorded quinine prescriptions with reported quinine usage. A sample of 100 study patients in nine of the study practices was chosen. We asked the practice nurses to record the issue of prescriptions for quinine during the 12 weeks from randomisation. Data were available on 90 patients: eight had moved away or were deceased, and data were missing for two patients. Patients who had been issued with one or more prescriptions of quinine were compared with those who had not.

Time of data collection

The main data collection took place between January 1999 and September 2001 and the validation of self-reported quinine use between November 2002 and March 2003.

Outcome measures

Our main outcome measures were: reported symptom burden and frequency of night cramps (the principal outcome); and quinine usage over the previous 4 weeks. Twelve weeks was considered to be an appropriate interval at which to measure the main outcomes as it captured the considered response of patients to the choice resulting from the intervention advice. The baseline questionnaire recorded cramp symptoms according to frequency over the previous 4 weeks and severity on a four-point descriptive scale.[17] We assessed overall symptom burden using the mean of three Likert scale scores assessing 'disrupted activity', 'sleep quality' (sleep disturbance is a recognised consequence of night cramps),[5] and 'overall problems with cramp in the past week' — all reported on a seven-point Likert scale following the same format as the MYMOP (Measure Yourself Medical Outcome Profile).[20] Quinine usage over the previous 4 weeks was also recorded.

The 6-week diary recorded daily cramp symptoms (in order to be able to document any rebound from quinine cessation), intervention compliance, and weekly symptom burden scores. The 12-week self-completion postal questionnaire recorded cramp symptoms in a similar manner to that at randomisation, quinine usage and frequency of taught exercises over the previous week.

Statistical tests

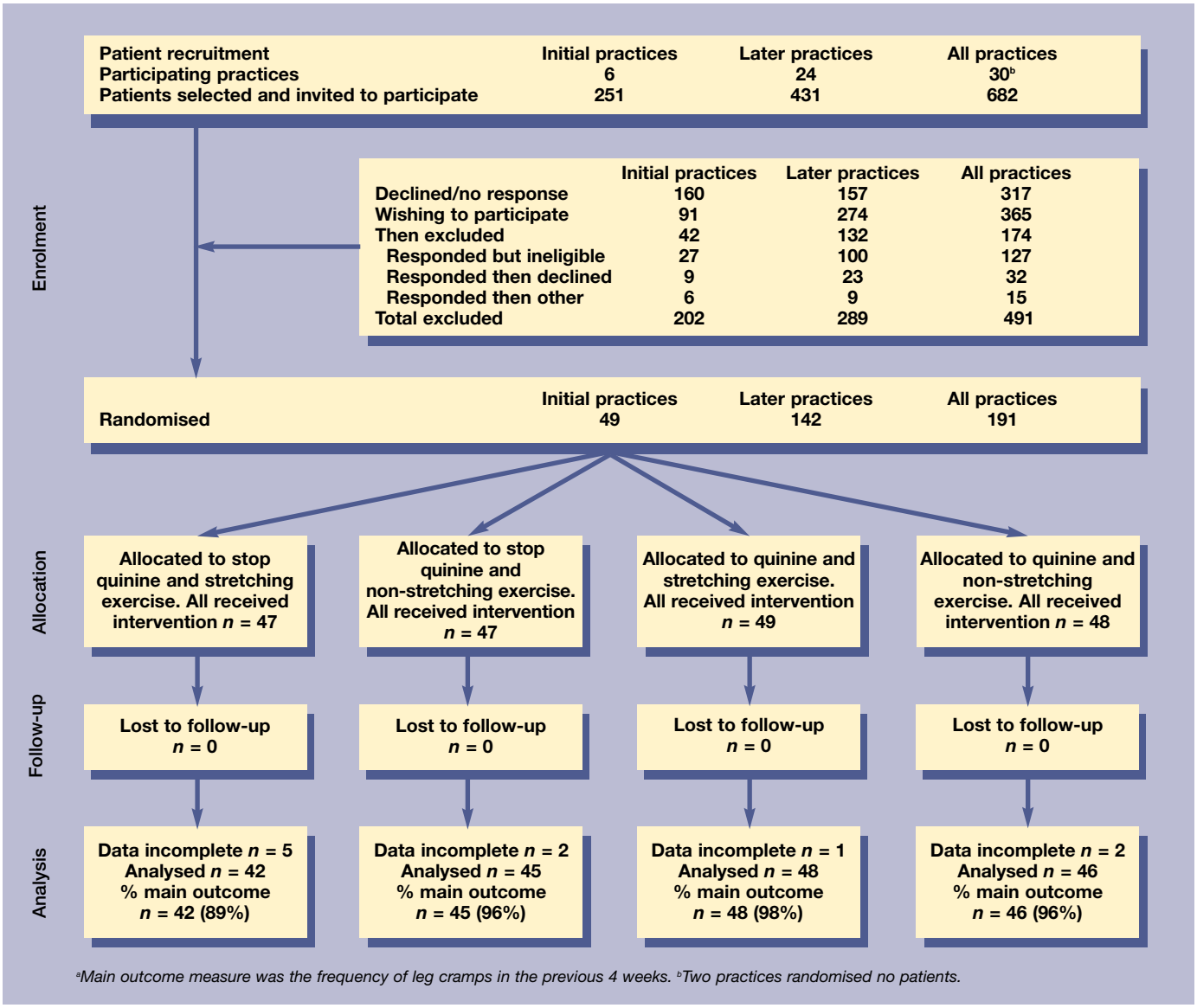
Sample size (for $\alpha = 0.05$ and $\beta = 0.2$). We performed two sample size calculations for the number of night cramps and for the number of patients reporting quinine use.

Number of night cramps. There have been no studies that have published the means and standard deviations (SDs) for the number of night cramps experienced by patients who are stable on treatment. We used the SDs of night cramps, our principal outcome measure, which had been recorded previously in newly diagnosed patients[17] (SD = 6.6). For a 0.5 change in SD (three to four cramps in 4 weeks assuming SD = 7, or seven cramps assuming SD = 14), then 128 patients with complete outcomes (or 160 allowing for 20% loss to follow-up of diaries) would be required — in either case considerably smaller than the 17 cramp change observed with quinine in the previous study. Changes much smaller than one cramp every 3 or 4 nights, i.e. seven to eight cramps in 4 weeks, are unlikely to be very important clinically.

Quinine use. Assuming at least 85% of those not asked to halt quinine treatment would still be taking it, 166 patients with complete outcomes would be needed (or 184 allowing 10% loss to follow-up of notes) to detect a 20% absolute difference in the number of patients requiring quinine in the 'stop quinine group' at the end of the study.

Analysis

Analysis was performed on an intention-to-treat basis. Our null hypotheses were that there would be no difference between advice to use stretching exercises and non-stretching exercises, or between advice to stop taking quinine for 6 weeks and no such advice for the main outcomes (reported cramp symptoms and quinine use). For continuous outcomes the analysis used general linear modelling for analysis of covariance for a factorial study in SPSS for Windows and Stata for Windows: this model uses the outcome at follow-up as the dependent variable and includes a term for each intervention factor and for the baseline value of the outcome as independent variables. We first assessed whether there was any interaction between intervention factors, and if no significant interaction was found we presented the main effects, that is, the mean difference attributable to one intervention when controlling for the other intervention. For dichotomous outcomes we used analagous logistic regression models. For the large numbers in this study testing differences in means between groups in analysis of covariance is robust to assumptions of the normality of the underlying distribution, but not to assumptions of homogeneity of variance. For each model the assumption of homogeneity of variance between groups was assessed using Levene's test. We also checked the inferences of the parametric models with non-parametric tests (Mann–Whitney U test).



[a]*Main outcome measure was the frequency of leg cramps in the previous 4 weeks.* [b]*Two practices randomised no patients.*

Figure 1. Flow and follow-up of participants.[a]

RESULTS

Patient recruitment

Overall, 191 subjects from 28 practices agreed to participate and were randomised. The main outcomes (cramp symptoms and quinine use after 12 weeks) were measured in 181 (95%) of patients (Figure 1) and these data have been analysed.

Baseline characteristics

There was no difference in baseline characteristics in the different groups (Table 1).

Compliance with exercises

By 12 weeks people performed the exercises 3–4 times per week, and although the non-stretch group did them slightly more frequently, this was not significant (placebo = 3.79 times per week, stretch = 3.07 times per week, $t = 1.71$, $P = 0.09$).

Adverse effects

There was no reporting of significant adverse effects from either intervention.

Main results

There was no evidence of heterogeneity of variance for any of the analysis of covariance models. There was also no evidence of interaction between the two factors (advice to undertake exercises for 6 weeks; advice to stop quinine for 6 weeks). There was little clinically important difference in the mean reporting of problems with cramp in week one for those advised to stop quinine (on a 7-point scale, mean difference = 0.43 points [95% confidence interval {CI} = -0.07 to 0.93], $P = 0.09$) or week two (mean difference = 0.51 points [95% CI = 0.05 to 0.97], $P = 0.03$). By 12 weeks (Table 2) there was no difference between both advice on stretching exercises and

Table 1. Baseline sociodemographic and symptom characteristics of factorial groups.[a]

	Factor 1		Factor 2	
	Stretch exercises	Placebo exercise	Stop quinine for 6 weeks	Not to stop quinine for 6 weeks
Male sex (*n* [%])	47 (49)	44 (47)	42 (45)	49 (51)
Age in years	74.4 (0.70)	75.0 (0.66)	75.1 (0.76)	74.3 (0.60)
Symptom burden score[b]	3.19 (0.14)	3.11 (0.15)	3.34 (0.14)	2.97 (0.14)
Night cramps in previous 4 weeks	10.8 (1.74)	9.3 (1.17)	9.7 (1.14)	10.4 (1.76)

[a]Figures are means (SEM) unless specified. [b]Range = 1–7. SEM = standard error of the mean.

advice to stop quinine in mean symptom burden, frequency of night cramps, or reported problems with cramps. To check the inferences of the analysis of covariance for the frequency of night cramps we also used square root transformed data and confirmed the inferences from the analysis of covariance using the Mann–Whitney U test.

After 12 weeks 26.5% (95% CI = 13.3% to 39.7%) more patients who had been advised to stop quinine for 6 weeks reported taking no quinine tablets in the previous week (advised to stop quinine for 6 weeks *n* = 43 [47.8%], not advised to stop quinine for 6 weeks *n* = 20 [21.3%]; odds ratio [OR] = 3.32 [range =1.37–8.06]; Wald test *P* = 0.008). There was no effect on the number reporting not taking quinine with advice to do stretching exercises (OR = 0.73 [range = 0.27–1.98]) (Table 2).

Validation of self-reported quinine use

In the validation sample of 46 patients randomised to advice to stop quinine, 12 (26%) had been issued with at least one prescription, of 44 patients randomised to continue quinine, 27 (61%) had been issued with a prescription, making a 35% difference, χ^2 = 11.4, *P*<0.001. Self-reported data were available for 82 of the 100 study patients from the same surgeries. Comparable figures were 9/40 (23%) versus 26/42 (62%), that is, a 39% difference, χ^2 = 13.0 *P*<0.001. These data demonstrate that self-reported quinine use in the study gave very similar results to prescribing data, and therefore validate the main self-report results.

Table 2. The effect on symptoms of advice to complete stretching exercises compared to placebo exercises, and advice to stop quinine treatment compared to no such advice.[a]

	Stretching exercises	*P*-value	Quinine cessation	*P*-value
Symptom burden score[b]	0.02 (-0.35 to 0.38)	0.93	0.04 (-0.33 to 0.40)	0.85
Night cramps in previous 4 weeks	1.95 (-3.01 to 6.90)	0.44	3.45 (-1.52 to 8.41)	0.17
Problems with cramps	0.02 (-0.42 to 0.46)	0.92	0.30 (-0.14 to 0.74)	0.17
Quinine tablets used in the previous week	0.33 (-0.56 to 1.22)	0.47	-1.85 (-2.75 to -0.95)	<0.001
Patients stopping quinine treatment (OR)[c]	0.73 (0.27–1.98)	0.54	3.32 (1.37–8.06)	0.008

[a]Figures shown are the mean differences estimated from analysis of covariance with 95% CIs unless specified. Analyses used analysis of covariance with 95% CIs for a factorial study to estimate mean differences for continuous outcomes. [b]Range = 1–7. [c]Logistic regression for a factorial study to estimate odds ratios for a dichotomous outcome was used. OR = odds ratio.

DISCUSSION

Summary of main findings

The results do not confirm that regular calf-stretching exercises are an effective intervention in reducing the frequency or severity of nocturnal leg cramps. However, a significant number of those on repeat prescriptions for quinine may be able to stop medication without major problems.

Study strengths and limitations

As a randomised trial this study has more robust findings than the previous, frequently cited observational study.[13] This was also a pragmatic trial, with advice (to undertake the exercises and to continue or stop quinine) being given in a manner comparable to that in a primary care consultation. It appears that most patients were able to undertake the exercises and did comply with the advice regarding quinine use.

Possible weaknesses in the design of our study were the nature of the placebo exercise and the fact that patients were not blinded to the interventions. Although it is not very plausible, the non-stretching, placebo exercise could have had some unrecognised effect that made it as effective as the stretching exercise. It could also be that the intensity of stretching or the frequency of the exercises were insufficient to demonstrate effectiveness. We did, however, copy Daniell's described intervention[13] in detail and therefore believe the comparison to be fair.

The reliability of the reporting method could be questioned but the use of self-reporting questionnaires in this age group have been shown to be reliable[21] and was validated by our comparison of reported quinine use with quinine prescriptions in a sub-sample. We identified patients taking quinine as a marker for those experiencing cramp. These results may not be generalisable to those with cramp who have not consulted their GP or those for whom a prescription for quinine was thought unnecessary. The mention of an 'exercise treatment' in the initial invitation, and the requirement for patients to attend the surgery

for the randomisation interview, may have tended to exclude those less ambulant from our sample. A minority of patients agreed to take part in the study, which would be expected from invitation by letter rather than in person, and where we did not know if all those invited were eligible.

Of particular concern is the possibility that those with severe cramp were put off by knowing that they might be advised to stop quinine. If so, then a drop in response would be expected following receipt of the information sheet, whereas for later practices, where the timing of the information sheet altered, recruitment did not fall. Furthermore, the baseline characteristics of our sample (Table 1) suggest we had patients who were still suffering significantly from cramp, with a mean of 10 cramps in the previous 4 weeks, and thus any such major selection bias seems unlikely. A potential weakness of our study was that the nurses who performed the intervention also executed the randomisation, with the potential for subversion of randomisation. However, there was no evidence of this either from the order of envelopes used, nor was there any evidence of subversion from the baseline characteristics.

Relationship to the existing literature

These data show that there is no difference between stretching and placebo exercises. This counters the previous study which suggested that stretching exercises are effective.[13]

Implications for future research and clinical practice

There was no effect on cramps, nor on symptom burden, of advice to stop quinine for 6 weeks. These data suggest that, for every four patients advised to cease treatment with quinine, one patient will still not be taking quinine 12 weeks later, and that there will be no undue symptom burden for patients. Clearly, more evidence is needed to confirm if this is genuinely a long-term effect. However, if it is, then there are considerable implications for saving health service resources such as medication costs and GP, nurse and pharmacist time.

Supplementary information

Additional information accompanies this article at http://www.rcgp.org.uk/journal/index.asp

Internation Standard Randomised Controlled Trial Number

ISRCTN26051665

Funding body and reference number

The study was funded by NHS Executive SE Project Grant SPGS787/SW

Ethics committee and reference number

South West Multicentre Research Ethics Committee (MREC/00/6/28), Bath Local Research Ethics Committee (BA 211/00-01), North and Mid Hampshire Local Research Ethics Committee (017/98H), Salisbury Local Research Ethics Committee (SA 52/99), Southampton and South West Hampshire Local Research Ethics Committee (049/00), Swindon Local Research Ethics Committee (SW 41/2000), West Berkshire Local Research Ethics Committee (20/00)

Conflicts of interest

None

Acknowledgements

We are grateful to all the patients who volunteered to help make this study possible. Our thanks are also due to Jane Garnett for administration and data entry, to Charlotte Rees for assistance in the initial stage of the study and to Professor Ann Ashburn for devising the non-stretching exercise. We also thank the GPs and particularly the study nurses in the participating practices.

REFERENCES

1. Naylor JR, Young JB. A general population survey of rest cramps. *Age Ageing* 1994; **23:** 418–420.
2. Gulich M, Heil P, Zeitler H. Epidemiology and determinants of nocturnal calf cramps. *Eur J Gen Pract* 1998; **4:** 109–113.
3. McGee SR. Muscle cramps. *Arch Intern Med* 1990; **150:** 511–518.
4. Sontag SJ, Wanner JN. The cause of leg cramps and knee pains: an hypothesis and effective treatment. *Med Hypotheses* 1988; **25:** 35–41.
5. Young G. Leg cramps. *Clinical Evidence* 2002; **8:** 1149–1155.
6. Mackie MA, Davidson J. Prescribing of quinine and cramp inducing drugs in general practice. *BMJ* 1995; **311:** 1541.
7. Man-Son-Hing M, Wells G, Lau A. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; **13:** 600–606.
8. Diener HC, Dethlefsen U, Dethlefsen-Gruber S, Verbeek P. Effectiveness of quinine in treating muscle cramps: a double-blind, placebo-controlled, parallel-group, multicentre trial. *Int J Clin Pract* 2002; **56:** 243–242.
9. Anonymous. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Federal Register* 1994; **59:** 43234–43252.
10. Hawkins G, McMahon A, Twaddle S, *et al.* Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003; **326:** 1115–1118.
11. Shapiro D, Hui KK, Oakley ME, *et al.* Reduction in drug requirements for hypertension by means of a cognitive-behavioural intervention. *Am J Hypertens* 1997; **10:** 9–17.
12. Young JB, Javid M, George J. Rest cramps in the elderly. *J R Coll Physicians Lond* 1989; **23:** 103–106.
13. Daniell HW. Simple cure for nocturnal leg cramps. *N Engl J Med* 1979; **301:** 216.
14. Sheehan, G. Six steps towards painless running. *Runner's World* 1975; **10:** 41.
15. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; **310:** 13–17.
16. Riley JD, Antony SJ. Leg cramps: differential diagnosis and management. *Am Fam Physician* 1995; **52:** 1794–1798.
17. Connolly PS, Shirley EA, Wasson JH, Nierenberg DW. Treatment of nocturnal leg cramps: a crossover trial of quinine vs vitamin E. *Arch Intern Med* 1992; **152:** 1877–1880.
18. Frusso R, Zarate M, Augustovski F, Rubinstein A. Magnesium for the treatment of nocturnal leg cramps a crossover randomised trial. *J Fam Pract* 1999; **48:** 868–871.
19. Coppin RJ, Wicke DM, Little PS. Recruitment of practices to primary care trials. *Br J Gen Pract* 2001; **51:** 758.
20. Paterson C. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. *BMJ* 1996; **312:** 1016–1020.
21. Smeeth L, Fletcher AE, Stirling S, *et al.* Randomised comparison of three methods of administering a screening questionnaire to elderly people: findings from the MRC trial of the assessment and management of older people in the community. *BMJ* 2001; **323:** 1403–1407.