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Randomised controlled trial of hydroquinine in muscle cramps

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Summary

Background Although quinine and hydroquinine are commonly prescribed for muscle cramps, controlled clinical trials of these drugs have reported mixed findings about efficacy. We investigated hydroquinine therapy in otherwise healthy adults who had frequent, ordinary muscle cramps.

Methods This randomised, double-blind, placebo-controlled, parallel-group trial consisted of three consecutive 2-week periods: qualification, treatment, and washout. 68 women and 44 men who had at least three muscle cramps per week were enrolled. During the treatment period, participants were randomly assigned 300 mg daily dose of hydroquinine hydrobromide dihydrate (54 participants) or placebo (58). The frequency, severity (1-10), duration, and location of muscle cramps, as well as any side-effects, were recorded by participants in daily diaries. The primary outcome measures were the number of muscle cramps and the number of days during which the participants had muscle cramps (cramp-days).

Findings We excluded five participants from both groups from the analysis. Thus, data from 49 hydroquinine-group participants and 53 placebo-group participants were analysed. In both groups the total number of muscle cramps and the number of cramp-days decreased during the treatment period compared with the qualification period. However, these improvements were greater in the hydroquinine group than in the placebo group. The

hydroquinine-group participants reported a median of 8 (95% CI 7-12) fewer cramps and median of 3 (1-4) fewer cramp-days, whereas those on placebo reported only 3 (0-5) fewer cramps and 1 (0-5) fewer cramp-days. 32 (65%) of participants in the hydroquinine group had a 50% or greater reduction in the number of muscle cramps. After the onset of cramps, hydroquinine did not reduce the severity or duration of cramps. We also found a sustained effect after treatment had stopped. Hydroquinine was well tolerated, and resulted in only mild side-effects.

Interpretation In our study, 300 mg hydroquinine was safe to take in the short-term and significantly more effective than placebo in the prevention of frequent, ordinary muscle cramps. This therapeutic effect outlasted the duration of treatment.

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Introduction

In 1988, a survey in the Netherlands reported that 36% of adults had had at least one muscle cramp in that year, and 2% reported having weekly cramps.¹ Surveys in the UK and Switzerland gave similar findings.²⁻³ The pathophysiology of muscle cramp is little understood.⁴ Current evidence points to a distal origin in the intramuscular motor-nerve terminals.⁵

The treatment of muscle cramps remains empiric. For more than 50 years, quinine and its derivatives, hydroquinine and quinidine, have been commonly prescribed to prevent muscle cramps. These drugs exert a curare-like action on skeletal muscle and the neuromuscular junction, but the mechanism is not understood. Although quinine and derivatives are widely used, the clinical efficacy in muscle cramps is not yet established. Initial trials were uncontrolled and recent studies were small or of questionable design. In addition, potentially serious side-effects such as hypersensitivity

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reactions and dose-related cinchonism can occur.⁶⁻¹⁰ Resolution of these efficacy and safety concerns are crucial for the continued use of quinine derivatives for a benign indication such as muscle cramps. We conducted a randomised double-blind parallel-group trial of hydroquinine in adults with frequent muscle cramps.

Methods

The trial was conducted between October, 1993, and December, 1994. We recruited volunteers through notices in regional newspapers and posters in libraries and pharmacies. Eligible participants were those aged 18 years or older who were in good general health, had at least three muscle cramps per week during activity or at rest, and did not take any medication for cramps. We defined muscle cramp as a sudden, involuntary, painful muscle contraction which was accompanied by muscle hardening and lasted no longer than 10 min.¹¹ Muscle cramps are self-limiting and resolve over seconds to minutes.¹² We limited the maximum duration of a muscle cramp to 10 min to distinguish cramps from painful muscle stiffness.

Exclusion criteria were: a history of alcohol or drug use that would interfere with participation; objection of the family physician to treatment with hydroquinine; suspicion of contraindications or allergy to hydroquinine; concurrent therapy with a drug that might interact with hydroquinine; pregnancy or lactation; and lack of contraception in women of childbearing age.

At enrolment, volunteers were examined by a neurologist (PHPJ) to keep to a minimum the possibility that muscle cramps might be a symptom of an underlying neuromuscular disease.

The trial consisted of three consecutive periods: a 2-week qualification period, during which the baseline frequency of muscle cramps was assessed; a 2-week treatment period, during which participants were randomly allocated hydroquinine or placebo; and a 2-week washout period, during which clinical after-effects were assessed and the target symptoms allowed to return to pretreatment levels. We limited active treatment to 2 weeks in accordance with guidelines on the hydroquinine package insert.

The trial was conducted according to the European Guidelines for Good Clinical Research Practice and followed the 1983 revised provisions of the 1975 Declaration of Helsinki. The protocol was approved by the ethics committee of our hospital. All participants gave written informed consent to take part. In addition, the participants' family physicians were asked to declare in writing that they did not object to their patient's participation.

Treatment

We used a standard regimen of two 100 mg hydroquinine or placebo tablets to be taken with the evening meal plus one 100 mg hydroquinine or placebo tablet at bed-time. We asked the participants to swallow the tablets whole, without chewing them. Participants were given an excess of medication and asked to return the unused tablets. Compliance was tested by comparison of the number of tablets returned with the number prescribed.

We chose hydroquinine hydrobromide dihydrate (Inhibin sugar-coated tablets) because of availability; this compound is the only quinine derivative registered in the Netherlands for the prevention of muscle cramps. Hydroquinine and placebo tablets were supplied in coded containers by the manufacturer (ASTA Medica BV, Diemen, Netherlands).

Randomisation

The hospital pharmacists received two coded containers, marked A and B, holding boxes with hydroquinine or placebo tablets, and did not know which container held the active treatment. An independent investigator (ThdB) used the random-number generator of the SAS program to create the randomisation schedule. He separately assigned men and women to treatment in blocks of four. We used separate randomisation to avoid the problem that had arisen in the earlier pilot study, in which all the men had been assigned, by chance, to the placebo group.¹³ Randomisation in blocks was used to keep to a minimum possible

time effects. Thereafter, the investigator linked the participants' numbers to treatment A or B according to the randomisation list, and marked the boxes with the participant number alone. Another investigator (KCWV) assigned consecutive participant's numbers to each individual participant in order of entry to the trial.

The hydroquinine and placebo tablets were identical in appearance. All investigators involved in the study and all participants were unaware of the treatment allocation. During the trial, the randomisation code was kept by the independent investigator (ThdB). The manufacturer kept the code for treatments A and B. At the end of the trial, after all data were collected, the independent investigator disclosed the code of randomisation. After the final analysis, the code for A and B was revealed.

Outcome measures

The primary outcome measures were the number of muscle cramps and the number of days during which the participant had muscle cramps (cramp-days). Participants used a daily diary to record the number, severity (on a scale of 1 to 10), duration, and location of muscle cramps for the entire 6 weeks. We also asked participants to record in the diary any possible side-effects of treatment. The use of a daily diary to record muscle cramps has been previously validated.¹³

Follow-up

We interviewed participants at enrolment, before the treatment period (week 2), and after the treatment period (week 5). During each interview, the participant's diary was reviewed and a history was taken (by KCWV) that focused on the clinical details of the muscle cramps. Participants were encouraged to describe their symptoms and any side-effects.

Data from the participants' diaries and interviews were collected on standard forms, checked for accuracy, entered into computer, and double-checked.

Statistical analyses

We calculated our sample size on the basis of data from our pilot-study.¹³ We estimated that 38 participants were required in each treatment group to give a power of 90% and a significance level of 0.05 in detecting a between-group difference of at least a 30% reduction in the number of muscle cramps.

Although the minimum clinically important differences (MCID) in the numbers of cramps and cramp days between study periods and treatment groups may differ with each individual, we defined the MCID as a decrease of two cramps per week and one cramp-day per week.

We used SAS software for the analysis. The primary analysis of the rate of treatment success—expressed as the decreases in the number of muscle cramps and cramp-days—was intention to treat, and included data from all study periods for which end-of-period data were available.

Because most of the data did not satisfy a normal distribution, the results are given as the numbers of muscle cramps and cramp-days with median values and IQRs. Percentages were first calculated for each participant and then the medians were calculated for treatment groups and study periods.

The primary outcome measures were analysed by Wilcoxon's signed-rank test for paired data and Wilcoxon's two-sample test for unpaired data. A two-sided *p* value of less than 0.05 was considered significant. For the comparison of data from the qualification and treatment periods, diary entries for days 1 and 15 were excluded because 15 participants had not made a diary entry on day 1, had not taken their first dose of medication until the evening of day 15, or both. To have equal study periods for the qualification and washout periods, diary entries for days 1, 13, 14, 29, 41, and 42 were excluded from the analysis because seven participants had not completed their diary entries on day 1, or on days 41 and 42, or both. The individual effects of potential confounding factors, such as age and body-mass index, were analysed by stepwise regression.

	Hydroquinine group (n=49)	Placebo group (n=53)
Sex (m/f)	18/31	20/33
Age on July 7, 1994 (years)	54 (20-77)	47 (17-87)
Height (cm)	172 (154-196)	173 (158-190)
Bodyweight (kg)	74 (46-113)	72 (56-108)
Smoking		
Current smokers	13 (27%)	15 (28%)
Number of cigarettes per day	10 (3-40)	15 (1-25)
Alcohol intake		
Drinkers	26 (53%)	26 (49%)
Number of drinks per week	5.5 (1-32)	10 (1-35)
History of muscle cramps (years)		
<1	2 (4%)	2 (4%)
1-5	15 (31%)	13 (25%)
5-10	9 (18%)	11 (21%)
>10	19 (39%)	27 (51%)
Tonic water intake		
1 glass per week	1 (2%)	1 (2%)
2 glasses per week	3 (6%)	1 (2%)
Previous sciatia		
Yes	8 (16%)	16 (30%)
No	41 (84%)	37 (70%)
Muscle cramps		
Duration (min)	1.5 (0.3-6.1)	1.7 (0.1-5.5)
Severity (numerical scale 0-10)	4.6 (1.6-8.8)	4.1 (1.5-8.4)

Values are median (IQR).

Table 1: Baseline characteristics of participants

Results

382 volunteers responded to the recruitment notices and posters. Of these responders, 270 were excluded because they did not fulfil the inclusion criteria or met one or more of the exclusion criteria. Thus, 112 volunteers were enrolled. 54 participants (34 women and 20 men) were randomly assigned to hydroquinine, and 58 (34 women and 24 men) to placebo (figure 1). The two groups were well matched in baseline characteristics (table 1).

Of the 112 participants, 101 completed the trial. During the qualification period, six participants were withdrawn because of failure to practise contraception (one woman in hydroquinine group), only one muscle cramp reported during the qualification period (one woman in hydroquinine group), and inability to comply with the guidelines for diary-keeping (two in hydroquinine group and two in placebo group). During the treatment period, five participants were withdrawn. Treatment was stopped because of side-effects in one woman and two men in the placebo group and in one woman in the hydroquinine group. One man in the placebo group, who had a history of sporadic gout attacks, was withdrawn from the study because he required concurrent analgesic medication. Of these five drop-outs, the woman in the hydroquinine group and two placebo-group participants had sufficient data, assuming unchanged mean cramp frequency, to allow extrapolation to the end of the treatment period (day 28). There were no drop-outs during the washout period, although two participants were excluded after this period because they did not have complete diary records. Thus, data from 49 participants in the hydroquinine group and 53 placebo-group participants were included in the intention-to-treat analysis of the qualification and treatment periods (figure 1). Data from one man were omitted because he became ill during the washout period and reported a substantial increase in frequency of cramp. Data from 98 participants (47 hydroquinine, 51 placebo)

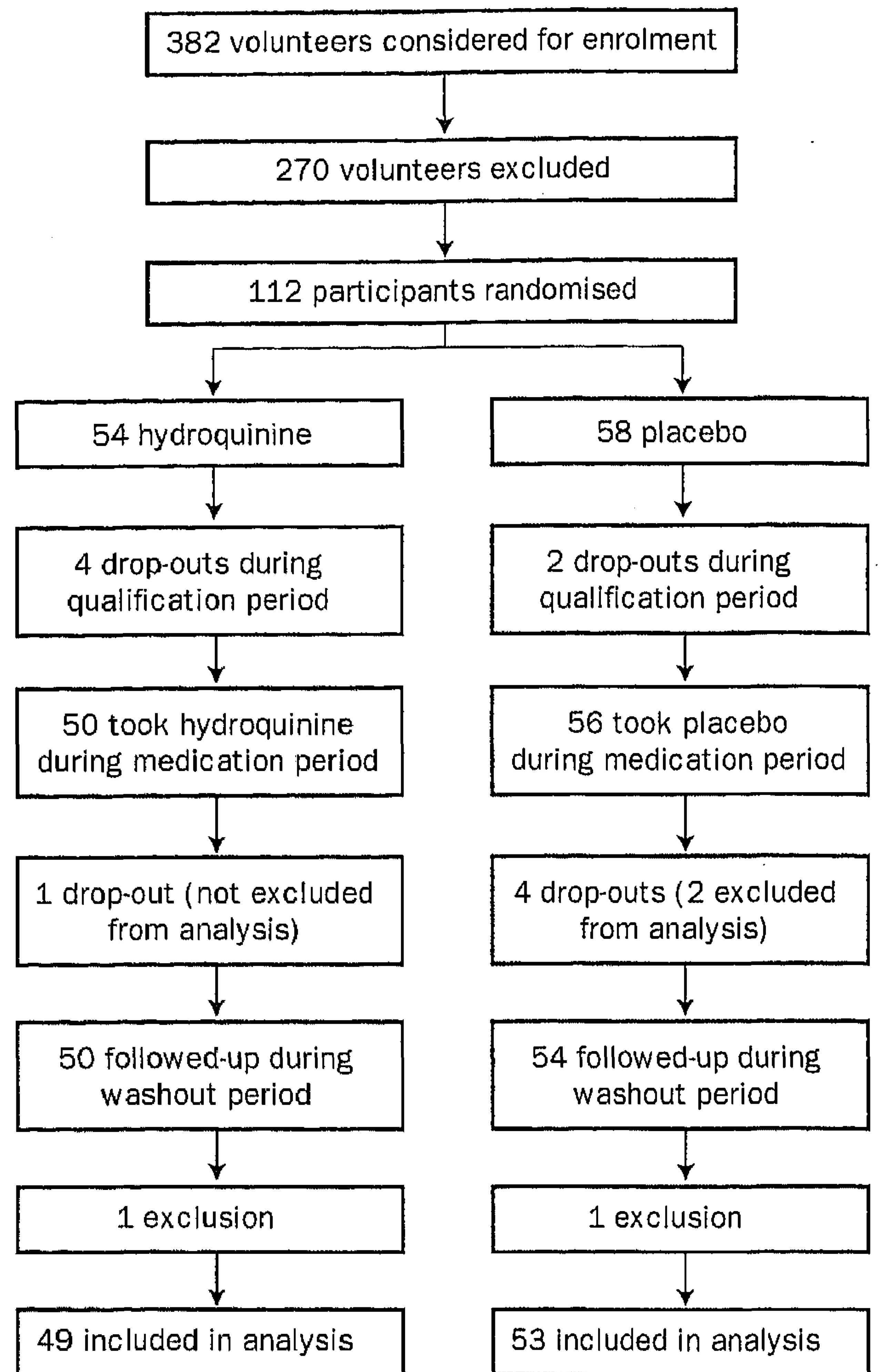


Figure 1: Trial profile

were included in the comparison of the qualification and washout periods.

Compliance was good (>90% pills taken) and the number of returned tablets did not differ significantly between the hydroquinine and placebo groups: 47 participants (98%), and 51 participants (100%), respectively.

Table 2 shows the between-group differences in the median number of cramps and cramp-days during the study periods. During the treatment period, the median difference in the number of cramps and cramp-days between the hydroquinine and placebo groups was 5 (95% CI 2-8) and 1 (0-3), respectively.

Study period	Hydroquinine group	Placebo group	Median difference (95% CI)
Qualification			
Number of participants	49	53	
Cramps	17 (10-31)	17 (10-22)	-1 (-6 to 3)
Cramp-days	8 (7-12)	8 (7-11)	0 (-1 to 1)
Treatment			
Number of participants	49	53	
Cramps	7 (4-11)	13 (6-18)	5 (2 to 8)
Cramp-days	5 (3-7)	7 (4-10)	1 (0 to 3)
Washout			
Number of participants	47	51	
Cramps	9 (5-17)	8 (5-22)	-1 (-4 to 3)
Cramp-days	6 (4-9)	5 (3-8)	-1 (-2 to 0)

Number of cramps and cramp-days are median (IQR).

Table 2: Number of cramps and cramp-days during qualification, treatment, and washout periods

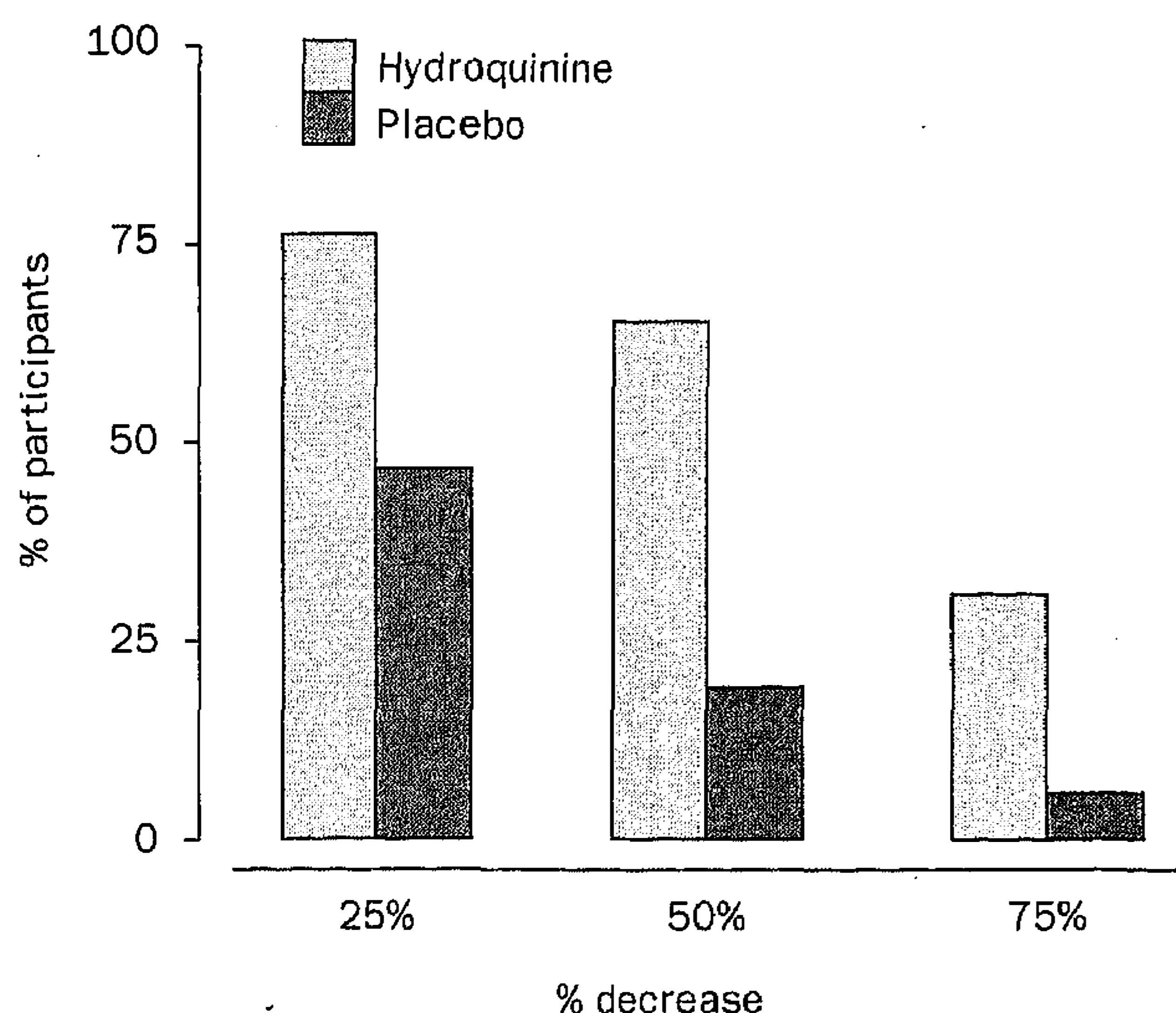


Figure 2: Percentage decrease in number of muscle cramps in hydroquinine and placebo groups during treatment period

Figure 2 shows the percentage decrease in the number of muscle cramps during the treatment period between hydroquinine and placebo groups: 37 (76%) *vs* 25 (47%) had a 25% decrease; 32 (65%) *vs* 10 (19%) had a 50% decrease; and 15 (31%) *vs* 3 (6%) had a 75% decrease.

The proportions of men and women with reductions in the number of muscle cramps from the start of the qualification to the end of the treatment period were similar in both groups ($p=0.8$ in hydroquinine group, $p=0.7$ in placebo group).

Differences in severity and duration of muscle cramps between the two groups were small and did not achieve significance ($p>0.1$). Similarly, in both groups, differences in severity and duration of muscle cramps between the qualification and the treatment periods were not significant ($p>0.1$).

Stepwise regression of the data from the hydroquinine group showed that body height and body-mass index had a significant effect on response ($p<0.01$). A body-mass index of more than 25 kg/m² was associated with a greater percentage decrease in the number of cramps, whereas body height was negatively correlated to the percentage decrease in the number of cramps.

Table 3 shows the side-effects in both groups. The only side-effect definitely related to hydroquinine was a bitter

Side-effects	Hydroquinine group (n=49)	Placebo group (n=53)
Definitely hydroquinine-related		
Bitter taste, dry mouth	10 (20%)	0
Tinnitus	1 (2%)	0
Possibly hydroquinine-related		
Nausea, vomiting	7 (14%)	4 (8%)
Headache	5 (10%)	3 (6%)
Dizziness	3 (6%)	5 (9%)
Diarrhoea, abnormal stool	3 (6%)	1 (2%)
Unrest, perspiration, tremor	2 (4%)	0
Itching, blushing	2 (4%)	0
Visual complaints	1 (2%)	0
Irregular heartbeat	1 (2%)	0
Bleeding gums	1 (2%)	0
Not hydroquinine-related		
Musculoskeletal pain	3 (6%)	3 (6%)
Fatigue, somnolence	2 (4%)	0
Muscular twitching, stiffness	1 (2%)	1 (2%)
Swollen joint	0	1 (2%)
Cough	1 (2%)	0

Table 3: Side-effects

taste or dry mouth (ten participants) and one case of tinnitus. There were no significant differences in age, sex, compliance, or percentage decrease in median number of muscle cramps between participants who reported side-effects and those who did not. However, hydroquinine-group participants who reported side-effects were slightly heavier than those who did not (mean body weight 80 [15] *vs* 70 kg [11], respectively), and also had a higher body-mass index (26.8 [4.5] *vs* 23.8 kg/m² [3.8]).

Discussion

A crossover design is suitable for drugs with effects that fade rapidly after treatment has been stopped. The effects of drugs such as quinine and hydroquinine may outlast their administration by at least a week,¹³ thus, a crossover design would be inappropriate unless an adequate washout is scheduled before crossover. Dunn¹⁴ reported a significant carryover effect of quinine for night cramps. Hing and Well's meta-analysis¹⁵ of six small crossover trials concluded that treatment with quinine for 4 weeks resulted in a significant reduction in the number of nocturnal leg cramps and nights with cramps compared with placebo. However, a meta-analysis cannot be considered as a substitute for a large, well-designed, and carefully conducted trial.^{16,17}

A parallel-group trial may, therefore, be preferable to assess the effects of quinine and its derivatives in individuals with muscle cramps. There have only been two parallel-group trials of quinine for muscle cramps. Görlich's study¹⁸ was designed to investigate a possible improvement in the effects of quinine by theophylline ethylene diamine. Our previous study¹³ was able to assess the effects of hydroquinine only in women because of an unlucky randomisation procedure.

In our parallel-group trial in otherwise healthy adults with frequent ordinary muscle cramps, the low confidence limits we found for the total decrease in the median number of cramps (eight cramps) and cramp-days (three cramp-days) in the hydroquinine group are clinically relevant (table 2). Although both hydroquinine and placebo significantly reduced the number of muscle cramps and cramp-days, the improvement was greater in hydroquinine-group participants. 32 (65%) participants in the hydroquinine group, compared with only 10 (19%) placebo-group participants, had a 50% or greater reduction in the number of muscle cramps.

The perceived placebo effect in the placebo group was equivalent to a mean percentage decrease of 14% in the number of muscle cramps. Subtraction of this placebo effect from the treatment effect in the hydroquinine group (50%) yields a 36% mean percentage decrease in the number of muscle cramps. Thus, the effect of hydroquinine was almost three times greater than that of placebo.

We did not find any significant changes in the estimated duration and severity of cramps between the groups. This finding may be because these variables are more subjective and difficult to quantify than, for example, the number of cramps, and thus only large differences will be observable. This finding accords with data reported in earlier crossover trials.^{15,19}

Our finding that ten participants complained of a bitter taste during hydroquinine therapy raises the question of whether these individuals were aware of treatment allocation. During the design of the trial, it proved to be

technically unfeasible to produce a placebo with a bitter taste. However, participants were presumably unaware of this property of hydroquinine and were unable to compare the taste of active medication with that of placebo. Furthermore, since the hydroquinine tablets were sugar-coated and subjects were told to swallow the tablet whole, any bitter taste would have been perceived only after drug absorption. Thus, we believe that any difference in taste between hydroquinine and placebo was unlikely to have biased participants' reporting of treatment effects.

Several studies point to increased quinine efficacy with a longer duration of therapy, and suggest that it may be necessary to administer quinine for 4 weeks to achieve optimum therapeutic benefits.^{15,18-20} Nevertheless, the 2-week treatment period in our study was long enough to confirm the clinical efficacy of hydroquinine.

In Connolly and colleagues' study,¹⁹ 500 mg quinine daily resulted in a 50% or greater reduction in the number of muscle cramps in 13 (48%) of 27 men. By contrast, we obtained a 65% response rate with a standard daily regimen of 300 mg hydroquinine. Variability between individuals may result from differences in bioavailability and drug absorption.¹³ Thus, the benefits of (hydro)quinine therapy might be improved by monitoring drug levels.

In this study, we found that during the washout period participants in both groups recorded sustained percentage decreases in the number of cramps. Cessation of (hydro)quinine therapy may be followed by sustained relief from muscle cramps, even for several months.¹³ This clinical after-effect may be responsible for carryover effects in crossover trials that do not have a sufficiently long washout before crossover. Furthermore, because of the duration of the after-effect, and our observation that placebo as well as active treatment had beneficial effects that outlasted administration, it is questionable whether this clinical after-effect reflects a pharmacological action.

Our findings are consistent with the hypothesis that relief from frequent muscle cramps in itself may prevent the recurrence of cramps by a physiological mechanism that interrupts the cycle of cramps. After a cramp, delayed localised soreness does not usually appear for 24-48 h and is accompanied by involuntary tonic muscle-spasm, which could precipitate another cramp by mechanical or chemical irritation.²¹ Irrespective of the mechanism of sustained relief of cramps, it seems reasonable to exploit this effect in clinical practice by interrupting (hydro)quinine treatment.

The benefits of hydroquinine should be weighed against the risk of side-effects. Previous trials reported only mild side-effects associated with quinine derivatives. Hing and Wells' meta-analysis¹⁵ reported that only one of 107 participants in six studies had serious side-effects (nausea, myalgia, leucopenia, and thrombocytopenia), which resolved 3 days after treatment had stopped. In our study, hydroquinine was well tolerated by most participants: only 11 reported mild side-effects. Hydroquinine-related side-effects (bitter taste, nausea) necessitated cessation of treatment in only one participant.

We do not know why body height and body-mass index emerged as explanatory variables in the stepwise regression analysis. A body-mass index of more than

25 kg/m² was associated with a greater therapeutic effect at the cost of increased side-effects; it is unlikely that this finding can be attributed to storage of hydroquinine or metabolites in body fat or fluids. Studies are needed to assess whether dose adjustments according to body-weight or body surface area are warranted.

In conclusion, the results of this study confirmed that a daily dose of 300 mg hydroquinine dihydrate is safe to take on a short-term basis, and is significantly more effective than placebo in the prevention of frequent, ordinary muscle cramps in otherwise healthy adults. Because hydroquinine did not ameliorate the severity or duration of muscle cramps once they had occurred, we believe that the drug should be prescribed on a regular rather than on an as-needed basis.

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