Non-drug therapies for lower limb muscle cramps (Protocol)

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[Intervention Protocol]

Non-drug therapies for lower limb muscle cramps

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness of non-pharmacological interventions for lower limb muscle cramps.

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BACKGROUND

Description of the condition

Muscle cramps are sudden, involuntary, painful contractions of skeletal muscle (Norris 1957; Jansen 1991a; El-Tawil 2004) that are characterised electrically by repetitive firing of motor unit action potentials at high rates up to 150 per second (Miller 2005). Cramps can be excruciatingly painful (Kanaan 2001; Jansen 2002) and can cause delayed onset muscle soreness (a type of painful muscle damage that typically produces pain for 2 to 14 days) (Leung 1999; Jansen 2002). Muscle cramps can also interfere with sleep (Gootnick 1943; Gentili 1997; Gulich 1998) and activities of daily living (Matsumoto 2009); cause distress (Naylor 1994; Butler 2002); reduce quality of life (Kanaan 2001; Miller 2005; Shaker 2005; Kobrin 2007); limit sports participation and performance; and lead to chronic underdialysis in people undergoing haemodialysis (Canzanello 1992; Kobrin 2007). In one of the earliest case reports, Gootnick 1943 reported three people whose sleep was so troubled by cramps during the night that they had been unable to sleep for months except in an armchair.

Muscle cramp can occur at any time throughout the day or night (Abdulla 1999) and can affect people of any age (Jansen 1991; Miller 2005), although they occur uncommonly in children less that eight years of age (Leung 1999). Cramps usually affect muscles of the legs (Naylor 1994; Hirai 2000), particularly the calf muscles (Jansen 1991; Manjra 1996; Abdulla 1999; Leung 1999). Most cramps resolve spontaneously within 10 minutes (Naylor 1994; Abdulla 1999) but are reported to last up to one hour (Abdulla 1999). In most cases, cramps occur irregularly; often appearing and disappearing spontaneously for long periods, irrespective of treatment (Jansen 1999).

No large, random-sampled population studies have been conducted to determine the prevalence of lower limb muscle cramps. In a nationwide, randomised study of general muscle cramps in nearly 2000 Dutch adults, approximately one in every three people reported at least one muscle cramp during the prior year (Jansen 1991a). Similarly, of over 1000 people surveyed in southern Germany, approximately one in every three people reported a history of nocturnal calf cramp and one in every four had experienced cramp within the four weeks prior to completing the questionnaire (Gulich 1998). In a separate study of 365 people aged 65 years and over, one in two people reported leg cramps at rest (e.g. while sleeping) (Abdulla 1999).

Compared to the general population, leg cramps are more prevalent in pregnant women (Jansen 1991; Jansen 1991a); people over 60 years of age (Naylor 1994; Gulich 1998; Hirai 2000); people undergoing haemodialysis (Canzanello 1992; Kobrin 2007); people with cirrhosis (Angeli 1996), fibromyalgia (Yunus 1996), arthritis (Yunus 1996; Abdulla 1999), lower motor neuron disease (e.g. amyotrophic lateral sclerosis) (Forshew 2003), lumbar spinal canal stenosis (Matsumoto 2009), peripheral neurological deficit (Haskell 1997), paraesthesia (Yunus 1996) or varicose veins (Gulich 1998; Hirai 2000); and children and adults with Charcot-Marie-Tooth disease (Burns 2009; Redmond 2009). There is no consistent relationship between cramp prevalence and being female versus male (Jansen 1991; Naylor 1994; Manjra 1996; Gulich 1998; Abdulla 1999; Hirai 2000), serum electrolyte levels (Oboler 1991; Haskell 1997; Sulzer 2005), dehydration (Manjra 1996; Sulzer 2005; Schwellnus 2007), heart disease (Oboler 1991; Haskell 1997; Gulich 1998; Abdulla 1999) or diabetes mellitus (Oboler 1991; Gulich 1998).

Description of the intervention

Many interventions are available for lower limb muscle cramps. The most common interventions can be broadly categorised as pharmacological or non-pharmacological. Common pharmacological interventions include quinine sulphate (Man-Son-Hing 1998), gabapentin (Miller 2005), magnesium (Frusso 1999; Roffe 2002; Sohrabvand 2006), Vitamin E (Connolly 1992; Burnakis 2000), calcium channel blockers (Baltodano 1988), naftidrofuryl oxalate (Young 1993) and calcium (Sohrabvand 2006). In clinical trials, none of these has demonstrated consistent effectiveness and safety for muscle cramps and none is approved by the American Food and Drug administration for nocturnal leg cramps (The Journal of Family Practice 2008). In a landmark systematic review of the effectiveness of quinine for nocturnal leg cramps, the reviewers concluded that, due to the unclear risk/benefit ratio of quinine, non-pharmacological interventions should be prescribed as a first line therapy and before pharmacological intervention (Man-Son-Hing 1998). This recommendation is widely supported in the medical literature (Leclerc 1996; Kanaan 2001; Miller 2005). Non-pharmacological interventions reported in the literature include: muscle stretching (Daniell 1979; Jones 1983; Simchak 1991; Leclerc 1996; Leung 1999; Kanaan 2001; Miller 2005; Matsumoto 2009); massage (Jones 1983; Kanaan 2001; Matsumoto 2009); relaxation (Joekes 1982); sensory nerve stimulation (Bentley 1996); footwear changes (Roberts 1965); weight loss (Roberts 1965); physical exercise (Miller 2005); avoiding physical fatigue (Roberts 1965); heat therapy (Jones 1983); compression garments (Young 2009); night ankle dorsiflexion splints (Miller 2005); placebo (Miller 2005); reassurance (Butler 2002); and changes to sleeping (Gootnick 1943; Moss 1948; Cutler 1984; Warburton 1987; Abdulla 1999; Leung 1999; Kanaan 2001) and sitting (Roberts 1965) position. More controversial historical interventions include sleeping with a horseshoe (Simchak 1991), a magnet (Fowler 1973), corks (Warburton 1987) or potatoes (Warburton 1987) beneath the mattress.

Why it is important to do this review

Many interventions are available for lower limb muscle cramps, but not all are efficacious or supported by evidence (Leclerc 1996;

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Abdulla 1999). Many treatments are controversial (Roberts 1965; Abdulla 1999; Sallis 2002) and no treatment guidelines exist (The Journal of Family Practice 2008). As a result, management of leg cramps can be frustrating (Riley 1995) and difficult (Butler 2002) for physicians and patients alike. Many people experience no benefit from the interventions prescribed (Sontag 1988; Abdulla 1999; Miller 2005) and many more receive no intervention at all (Naylor 1994; Gulich 1998; Abdulla 1999). A systematic review of non-pharmacological interventions for lower limb muscle cramps will serve two purposes. Firstly, it will enable healthcare providers, users, and policy decision makers to make better informed decisions about the treatment of lower limb muscle cramps. Secondly, it will identify for researchers interventions that require further evaluation in clinical trials.

Only one Cochrane systematic review has focused on interventions for muscle cramps. This review assessed the treatment of muscle cramps in pregnancy (Young 2002). Two other reviews, currently in protocol stage, will evaluate intervention for muscle cramp in amyotrophic lateral sclerosis (Weber 2003) and the use of quinine for all types of muscle cramps (El-Tawil 2004).

OBJECTIVES

To evaluate the effectiveness of non-pharmacological interventions for lower limb muscle cramps.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials of non-pharmacological interventions for the prevention of lower limb muscle cramps. Trials of acute treatment of muscle cramps will be excluded. As there is no universally agreed upon definition for cramp, we will accept any diagnosis of cramp unless there is clear contradiction with the broad definition used in this review (cramp as a sudden, involuntary, painful contraction of skeletal muscle). Any exclusion based on definition will be clearly explained in the table 'Characteristics of Excluded Studies'. All definitions of 'cramp' used in included studies will be reported in the table 'Characteristics of Included Studies'. We will contact authors for clarification if: (1) 'cramp' is diagnosed but not defined; (2) authors diagnose commonly used synonyms for cramp (for example, spasm or charley horse); or (3) authors describe the problem in such a way that we suspect muscle cramp (for example, if the problem is described as a sudden, painful contraction of skeletal muscle).

Types of participants

All people (including men, women and children) who experience lower limb muscle cramp will be included.

Types of interventions

We will include all non-pharmacological interventions used for at least four weeks. These may include, but are not limited to, muscle stretching, splints, massage, warmth, change in sleeping position, placebo, relaxation, footwear, weight loss, compression garments, transcutaneous nerve stimulation and changes to physical activity.

We will exclude all pharmacological interventions. For this review, pharmacological intervention will include any intervention taken orally (e.g. tablets, capsules, tonics), by injection, by rectal or vaginal suppository and by inhalation. Topically applied medicines (e.g. glyceryl trinitrate patches) will also be excluded, however, topically applied preparations that are not thought to alter directly and independently body function (e.g. oils used in massage) will be included.

We will also exclude reflexology and invasive interventions including surgery and acupuncture.

We will only include trials that compare pharmacological and non-pharmacological interventions if a placebo group, no intervention group, or second non-pharmacological intervention group is included.

Types of outcome measures

Primary outcomes

- Cramp frequency, measured as number of cramps per week

When analysing cramp frequency, we will use change from baseline frequency where possible. If change scores with measures of variability are not available for all trials included in the same analysis, change scores and follow-up values will be combined using weighted mean differences.

Secondary outcomes

- Adverse outcomes
- Cramp severity, including pain severity (measured using any validated pain assessment tool, for example, a visual analogue scale) and duration of cramp (measured in seconds)
- Health-related quality of life (measured by any validated assessment tool, for example, SF-26 survey)
- Quality of sleep (measured by any validated assessment tool, for example, MOSleep survey)
- Participation in activities of daily living, including physical activity (measured by any validated assessment tool)

If data from only one study are included in an analysis, we will measure the outcome as per the timepoint used in the original

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study. If data from more than one trial are included in an analysis, we will group the outcomes in the timepoints 'four weeks to three months' and 'more than three months'. In this instance, the time point 'more than three months' will be the primary outcome and the timepoint 'four weeks to three months' will be a secondary outcome. All outcome data that are combined in meta-analysis will be standardised to an appropriate follow-up period, for example, cramps per week after four months combined with cramps per week after six months.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Neuromuscular Disease Group Trials Specialized Register using the terms: cramp, spasm, contracture, charley horse and lower limb, lower extremity, foot, calf, leg, thigh, gastrocnemius, hamstring, quadriceps. This will be adapted to search for RCTs in the following databases:

1. MEDLINE (January 1966 to present);
2. EMBASE (January 1980 to present);
3. Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue).

The search strategy for MEDLINE is in Appendix 1. There will be no language or publication restrictions.

Searching other resources

We will check the reference lists of all included studies for other suitable trials. The first authors of included trials will be contacted via e-mail to assist in identifying relevant unpublished and published trials.

Data collection and analysis

Selection of studies

To authors (FH and KW) will independently assess the titles and abstracts of all trials identified by the search. The same two authors will then independently assess for inclusion full-text copies of potentially relevant studies. Authorship and results will not be masked. Disagreements will be resolved by discussion between review authors or, if necessary, arbitration by a third review author (JB). If arbitration by the third reviewer does not resolve the dispute, the study authors will be contacted. If this is unsuccessful, the disagreement will be reported in the review.

Data extraction and management

One review author (FH) will extract data from published reports using standardised, pilot tested forms and a second review author (KW) will perform cross checks. We will contact study authors as necessary to provide missing information. Disagreements will be resolved by discussion between review authors or, if necessary, arbitration by a third review author (JB).

Assessment of risk of bias in included studies

Two review authors (FH and KW) will independently rate risk of bias of included trials using the following criteria as described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008):

1. sequence generation;
2. concealment of allocation;
3. blinding;
4. incomplete data;
5. selective outcome reporting;
6. other sources of bias, such as financial conflicts of interest and single author or single centre trials.

We will create a 'Risk of bias' table to present a description of what was reported within the published report for each criterion and to assign a judgement relating to the risk of bias for that entry. 'Yes' will indicate a low risk of bias, 'No' will indicate a high risk of bias and 'Unclear' will indicate an unclear or unknown risk of bias; or if an entry is not relevant to the study at hand. A 'Risk of bias summary' figure will be generated using Review Manager 5 to present all of the judgements in a cross-tabulation of study by entry.

If study investigators are contacted for missing information, we will ask open-ended questions to reduce the risk of leading, for example the open-ended question 'How did you decide which treatment the next patient should receive?' will be used in preference to 'Did you conceal the allocation sequence?'.

Measures of treatment effect

Where possible, we will extract and analyse continuous data using mean differences (MD) and 95% confidence intervals (CI). When different measurement scales are used, we will perform standardised mean difference (SMD) analyses . We will analyse count data (e.g. number of muscle cramps) as continuous data (mean number of cramps per person).

Results for dichotomous data will be reported as risk ratios (RR) with 95% confidence intervals.

Unit of analysis issues

We will include cross-over trials; however, only data from the first phase of intervention will be considered, as clinical trials of interventions for muscle cramp have detected significant carryover effects (particularly for quinine) (Dunn 1993; Jansen 1997; Coppin

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2005) and the effectiveness of washout periods for interventions for muscle cramps is unknown. Due to the substantial and variable carryover effect of quinine, we will exclude studies that discontinue quinine less than three months prior to intervention within the trial.

Dealing with missing data

Where available, we will extract data from intention-to-treat analyses. If the original researchers did not perform intention-to-treat analyses and sufficient raw data are available, we will complete intention-to-treat analyses before entering data into RevMan, to limit attrition bias.

Assessment of heterogeneity

We will assess clinical heterogeneity across trials and if trials are sufficiently clinically homogenous in terms of participants, interventions, and outcomes they will be included for meta-analysis.
We will quantify inter-trial statistical inconsistency using I^2 (Higgins 2008).
The I^2 value will be calculated by:
$I^2 = 100\%[(Q-df)/Q]$
where Q is Cochran's heterogeneity, Chi-squared statistic and df is the degrees of freedom. The Cochran's Q will be determined by summing the squared deviations of each trial's estimate from the overall meta-analytic estimate and a P value obtained by comparing the statistic with a x^2 distribution with k - 1 degrees of freedom (where k is the number of trials). The following guide will be used to interpret the I^2 values:

- 0-40% might not be important;
- 30-60% may represent moderate heterogeneity;
- 50-90% may represent substantial heterogeneity;
- 75-100% considerable heterogeneity.

When there is heterogeneity that cannot readily be explained, we will use a random-effects model to incorporate heterogeneous trials in meta-analysis.

Data synthesis

We will use the Cochrane statistical package, Review Manager 5 (RevMan 2008), for statistical analyses. One author will enter statistical data into Review Manager 5 and a second author will check the data.

Subgroup analysis and investigation of heterogeneity

Providing sufficient data are available, we will perform subgroup analysis according to cramp type/aetiology, for example, rest cramp versus exercise associated cramp versus haemodialysis cramp versus cramp in people with neuromuscular disease.
Meta-analyses of subgroups will follow the same methodological principles as the primary analysis. If meta-analyses are performed within multiple subgroups, the magnitude of effect estimates for subgroups will be compared informally between groups. Non-overlap of summary estimate confidence intervals will be considered to indicate statistical significance. If confidence intervals overlap to a small degree the possibility of a statistically significant difference will be considered (Higgins 2008).
We will not compare the statistical significance of the pooled effect estimates for individual subgroups as the likely unequal information loading subgroups will affect the power to detect effects (Higgins 2008).

Sensitivity analysis

We will perform sensitivity analyses by including only studies of high methodological quality (low to moderate risk of bias). If all trials are found to have a high risk of bias, we will perform sensitivity analyses by excluding trials not concealing allocation or blinding the participants.
If one or more outliers are found to contribute to heterogeneity, and a reason for the outlying result is apparent, analyses both with and without outlying trials will be performed as a component of sensitivity analysis (Higgins 2008).

REFERENCES

Additional references

Abdulla 1999
Abdulla A, Jones P, Pearce V. Leg cramps in the elderly: prevalence, drug and disease associations. *International Journal of Clinical Practice* 1999;**53**(7):494–6.

Angeli 1996
Angeli P, Albino G, Carraro P, Dalla Pria M, Merkel C, Caregaro L, et al.Cirrhosis and muscle cramps: evidence of a causal relationship. *Hepatology* 1996;**23**(2):264–73.

Baltodano 1988
Baltodano N, Gallo BV, Weidler DJ. Verapamil vs quinine in recumbent nocturnal leg cramps in the elderly. *Archives of Internal Medicine* 1988;**148**(9):1969–70.

Bentley 1996
Bentley S. Exercise-induced muscle cramp. Proposed mechanisms and management. *Sports Medicine* 1996;**21**(6):409–20.

Burnakis 2000
Burnakis GT. Gabapentin for leg cramps: muscling in on quinine. *Hospital Pharmacy* 2000;**35**(8):887–90.

Burns 2009
Burns J, Ryan MM, Ouvrier RA. Evolution of foot and ankle manifestations in children with CMT1A. *Muscle & Nerve* 2009;**39**(2):158–66.

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Butler 2002
Butler JV, Mulkerrin EC, O'Keeffe ST. Nocturnal leg cramps in older people. *Postgraduate Medical Journal* 2002;**78**(924):596–8.

Canzanello 1992
Canzanello V, Burkart J. Hemodialysis-associated muscle cramps. *Seminars in dialysis* 1992;**5**:299–304.

Connolly 1992
Connolly P, Shirley E, Wasson J, Nierenberg D. Treatment of nocturnal leg cramps. A crossover trial of quinine vs vitamin E. *Archives of Internal Medicine* 1992;**152**(9):1877–81.

Coppin 2005
Coppin R, Little P. Managing nocturnal leg cramps - calf-stretching exercises and cessation of quinine treatment: a factorial randomised controlled trial. *British Journal of General Practice* 2005;**55**(512): 186–91.

Cutler 1984
Cutler P. Cramps in the legs and feet. *Journal of the American Medical Association* 1984;**252**(1):98.

Daniell 1979
Daniell HW. Simple cure for nocturnal leg cramps. *New England Journal of Medicine* 1979;**301**(4):216.

Dunn 1993
Dunn NR. Effectiveness of quinine for night cramps. *British Journal of General Practice* 1993;**43**(368):127–8.

El-Tawil 2004
El-Tawil S, Musa TA, El-Tawil Z, Weber M. Quinine for muscle cramps (Protocol). *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD005044]

Forshew 2003
Forshew DA, Bromberg MB. A survey of clinicians' practice in the symptomatic treatment of ALS. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 2003;**4**(4):258–63.

Fowler 1973
Fowler AW. Relief of cramp. *Lancet* 1973;**1**(7794):99.

Frusso 1999
Frusso R, Zárate M, Augustovski F, Rubinstein A. Magnesium for the treatment of nocturnal leg cramps: a crossover randomized trial. *Journal of Family Practice* 1999;**48**(11):868–71.

Gentili 1997
Gentili A, Weiner DK, Kuchibhatil M, Edinger JD. Factors that disturb sleep in nursing home residents. *Aging* 1997;**9**(3):207–13.

Gootnick 1943
Gootnick A. Night cramps and quinine. *Archives of Internal Medicine* 1943;**71**(4):555–62.

Gulich 1998
Gulich M, Heil P, Zeitler H-P. Epidemiology and determinants of nocturnal calf cramps. *European Journal of General Practice* 1998;**4** (3):109–13.

Haskell 1997
Haskell SG, Fiebach NH. Clinical epidemiology of nocturnal leg cramps in male veterans. *American Journal of the Medical Sciences* 1997;**313**(4):210–4.

Higgins 2008
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1*. The Cochrane Collaboration, 2008 Available from www.cochrane–handbook.org.

Hirai 2000
Hirai M. Prevalence and characteristics of muscle cramps in patients with varicose veins. *VASA* 2000;**29**(4):269–73.

Jansen 1991
Jansen PH, Joosten EM, Van Dijck J, Verbeek AL, Durian FW. The incidence of muscle cramp. *Journal of Neurology, Neurosurgery and Psychiatry* 1991;**54**(12):1124–5.

Jansen 1991a
Jansen PH, van Dijck JA, Verbeek AL, Durian FW, Joosten E M. Estimation of the frequency of the muscular pain-fasciculation syndrome and the muscular cramp-fasciculation syndrome in the adult population. *European Archives of Psychiatry and Clinical Neuroscience* 1991;**241**(2):102–4.

Jansen 1997
Jansen PH, Veenhuizen KC, Wesseling AI, de Boo T, Verbeek AL. Randomised controlled trial of hydroquinine in muscle cramps. *Lancet* 1997;**349**(9051):528–32.

Jansen 1999
Jansen PH, Lecluse RG, Verbeek AL. Past and current understanding of the pathophysiology of muscle cramps: why treatment of varicose veins does not relieve leg cramps. *Journal of the European Academy of Dermatology and Venereology* 1999;**12**(3): 222–9.

Jansen 2002
Jansen PH, Gabreëls FJ, van Engelen BG. Diagnosis and differential diagnosis of muscle cramps: a clinical approach. *Journal of Clinical Neuromuscular Disease* 2002;**4**(2):89–94.

Joekes 1982
Joekes AM. Cramp: a review. *Journal of the Royal Society of Medicine* 1982;**75**(7):546–9.

Jones 1983
Jones K, Castleden CM. A double-blind comparison of quinine sulphate and placebo in muscle cramps. *Age and Ageing* 1983;**12** (2):155–8.

Kanaan 2001
Kanaan N, Sawaya R. Nocturnal leg cramps. Clinically mysterious and painful-but manageable. *Geriatrics* 2001;**56**(6):34,39–42.

Kobrin 2007
Kobrin SM, Berns JS. Quinine - a tonic too bitter for hemodialysis-associated muscle cramps?. *Seminars in Dialysis* 2007;**20**(5): 396–401.

Leclerc 1996
Leclerc KM, Landry FJ. Benign nocturnal leg cramps. Current controversies over use of quinine. *Postgraduate Medicine* 1996;**99** (2):177-8, 181-4.

Leung 1999
Leung AK, Wong BE, Chan PY, Cho HY. Nocturnal leg cramps in children: incidence and clinical characteristics. *Journal of the National Medical Association* 1999;**91**(6):329–32.

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Man-Son-Hing 1998
Man-Son-Hing M, Wells G, Lau A. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *Journal of General Internal Medicine* 1998;**13**(9):600–6.

Manjra 1996
Manjra S, Schwellnus M, Noakes T. Risk factors for exercise associated muscle cramping (EAMC) in marathon runners. *Medicine and Science in Sports and Exercise* 1996;**28**(5 Supplement): S167.

Matsumoto 2009
Matsumoto M, Watanabe K, Tsuji T, Ishii K, Takaishi H, Nakamura M, et al.Nocturnal leg cramps: a common complaint in patients with lumbar spinal canal stenosis. *Spine* 2009;**34**(5): E189–94.

Miller 2005
Miller TM, Layzer RB, Miller M, Layzer Robert B. Muscle cramps. *Muscle and Nerve* 2005;**32**(4):431–42.

Moss 1948
Moss HK, Herrmann LG. Night cramps in human extremities: a clinical study of the physiologic action of quinine and prostigmine upon the spontaneous contraction of resting muscles. *American Heart Journal* 1948;**35**(3):403–8.

Naylor 1994
Naylor JR, Young JB. A general population survey of rest cramps. *Age and Ageing* 1994;**23**(5):418–20.

Norris 1957
Norris FH Jr, Gasteiger EL, Chatfield PO. An electromyographic study of induced and spontaneous muscle cramps. *Electroencephalography and Clinical Neurophysiology* 1957;**9**(1): 139–47.

Oboler 1991
Oboler SK, Prochazka AV, Meyer TJ. Leg symptoms in outpatient veterans.. *Western Journal of Medicine* 1991;**155**(3):256–9.

Redmond 2009
Redmond AC, Burns J, Ouvrier RA. Factors that influence health-related quality of life in Australian adults with Charcot-Marie-Tooth disease. *Neuromuscular Disorders* 2009;**18**(8):619–25.

RevMan 2008
Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.0.. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Riley 1995
Riley JD, Antony SJ. Leg cramps: differential diagnosis and management. *American Family Physician* 1995;**52**(6):1794–8.

Roberts 1965
Roberts H. Spontaneous leg cramps and 'restless legs' due to diabetogenic hyperinsulinism: observations on 131 patients. *Journal of the American Geriatrics Society* 1965;**13**(7):602–38.

Roffe 2002
Roffe C, Sills S, Crome P, Jones P. Randomised, cross-over, placebo controlled trial of magnesium citrate in the treatment of chronic persistent leg cramps. *Medical Science Monitor* 2002;**8**(5): CR326–30.

Sallis 2002
Sallis R, Clarkson P, Bergeron M, Schwellnus M. Sports related muscle cramps: science and clinical application. *Medicine and Science in Sports and Exercise* 2002;**34**(5):S88.

Schwellnus 2007
Schwellnus MP. Muscle cramping in the marathon: aetiology and risk factors. *Sports Medicine* 2007;**37**(4-5):364–7.

Shaker 2005
Shaker HK, Mackler L, Huber TE. What is the diagnostic approach to a patient with leg cramps?. *Journal of Family Practice* 2005;**54**(9):817–8.

Simchak 1991
Simchak AC, Pascuzzi RM. Muscle cramps. *Seminars in Neurology* 1991;**11**(3):281–7.

Sohrabvand 2006
Sohrabvand F, Shariat M, Haghollahi F. Vitamin B supplementation for leg cramps during pregnancy. *International Journal of Gynacology and Obstetrics* 2006;**95**(1):48–9.

Sontag 1988
Sontag SJ, Wanner JN. The cause of leg cramps and knee pains: an hypothesis and effective treatment. *Medical Hypotheses* 1988;**25**(1): 35–41.

Sulzer 2005
Sulzer NU, Schwellnus MP, Noakes TD. Serum electrolytes in ironman triathletes with exercise-associated muscle cramping. *Medicine and Science in Sports and Exercise* 2005;**37**(7):1081–5.

The Journal of Family Practice 2008
Identification and management of nighttime leg pain. *The Journal of Family Practice* 2008;**5**:S12–14.

Warburton 1987
Warburton A, Royston JP, O'Neill CJ, Nicholson PW, Jee RD, Denham MJ, et al.A quinine a day keeps the leg cramps away?. *British Journal of Clinical Pharmacology* 1987;**23**(4):459–65.

Weber 2003
Weber M, Feinberg D. Treatment for cramps in amyotrophic lateral sclerosis/motor neuron disease (Protocol). *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD004157]

Young 1993
Young JB, Connolly MJ. Naftidrofuryl treatment for rest cramp. *Postgraduate Medical Journal* 1993;**69**(814):624–6.

Young 2002
Young G, Jewell D. Interventions for leg cramps in pregnancy. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD000121]

Young 2009
Young G. Leg cramps. *Clinical Evidence* 2009;**03**(1113):1–10.

Yunus 1996
Yunus MB. Restless leg syndrome and leg cramps in fibromyalgia syndrome: a controlled study. *British Medical Journal* 1996;**312** (7042):1339.

* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. Ovid SP MEDLINE search strategy

1 muscle cramp/ or cramp$1.mp.
2 spasm/ or spasm.mp.
3 contracture/ or contracture.mp.
4 charley horse.mp.
5 or/1-4
6 lower limb.mp.
7 lower extremity/ or lower extemity.mp.
8 foot/ or foot.mp.
9 calf.mp.
10 leg.mp. or leg/
11 thigh.mp. or thigh/
12 gastrocnemius.mp.
13 hamstring.mp.
14 quadriceps.mp. or quadriceps muscle/
15 or/6-14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab.
19 placebo.ab.
20 drug therapy.fs.
21 randomly.ab.
22 trial.ab.
23 groups.ab.
24 or/16-23
25 (animals not (animals and humans)).sh.
26 24 not 25
27 5 and 15 and 26

HISTORY

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CONTRIBUTIONS OF AUTHORS

FH drafted the protocol. JB and VC suggested minor changes. All authors agreed on the final text.

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