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MANAGEMENT OF MUSCLE CRAMPS IN THE ELDERLY

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Abstract

Management of muscle cramps in the elderly is complicated by unique physiological and pathological considerations contributing to symptomatology as well as altered pharmacokinetics and polypharmacy affecting treatment options. Muscle cramps should prompt a focused history, medication review, physical examination and basic screening investigations to identify physiologic or secondary causes. In this population, treatment of underlying conditions together with lifestyle and non-prescription treatment options should be trialed first. Prescription medications should be considered in cases where symptoms are persistent and refractory to conservative treatments.

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Introduction

Muscle cramps are defined as sustained, painful contractions of a muscle or muscle group that result from high-frequency firing of motor neurons. Their initiation and spread is mediated by multiple physiological and pathological factors[1]. In the elderly, muscle cramps are influenced by unique factors such as the drop out of motor neurons[2,3] as well as mechanical effects including muscle length and prolonged inactivity[1,4]. The management of muscle cramps in the elderly is further complicated by the higher prevalence of predisposing conditions such as polyneuropathy as well as use of medications contributing to development of muscle cramps.

Muscle cramps are especially common in the elderly with a prevalence of 50% in patients over 65[5] and are associated with significant morbidity with detrimental effects on sleep and quality of life[6]. This review will focus on the management of neurogenic muscle cramps in the elderly.

Work-up

The evaluation of muscle cramps begins with a focused history, review of medications and physical examination followed by targeted investigations to differentiate cramps from mimics and to identify potential underlying conditions. In the elderly, rigidity and stiffness can arise from extrapyramidal disorders such as Parkinson's disease, as well as dystonia (a hyperkinetic movement disorder that consists of sustained or intermittent muscle contraction). Vascular claudication and myopathic cramps due to inherited metabolic myopathies typically occur bilaterally and consistently after exercise, but may also resemble neurogenic muscles cramps.

The majority of muscle cramps are neurogenic in nature and are a feature of disorders affecting lower motor neurons[2]. These include conditions such as polyneuropathy, radiculopathy and motor neuron disease. Of these, polyneuropathy is especially common in the elderly with a prevalence of 4.4% between the ages of 70-80 years and 13.2% over the age of 80[7]. The main causes of polyneuropathy in the middle-aged and elderly population are diabetes and idiopathic polyneuropathy[7].

Outside the setting of polyneuropathy, primary medical conditions to consider in the elderly with muscle cramps include diabetes, hepatic dysfunction and renal disturbance, which have all been associated with muscle cramps[8,9,10]. Patients with malabsorption or malnutrition are also susceptible to muscle cramps due to deficiencies of electrolytes and vitamins, namely vitamins B or D[1,11]. If found, further tests to identify the underlying causes of deficiency can be considered on a case-by-case basis taking into account the broader clinical picture. Toxic exposures such as alcohol can also contribute to neuropathy and cramps. Physiological factors such as exercise, electrolyte disturbance, volume depletion and heat also increase the risk of cramping[12].

With regards to offending medications, long-acting beta agonists, potassium sparing and thiazide diuretics have been associated with the initiation of Quinine as a surrogate for muscle cramps in a population-based study[13]. Despite this finding and the plausible mechanisms surrounding volume contraction and electrolyte abnormalities, the role of diuretics in muscle cramps has previously been questioned as no association was found in earlier studies[14]. Cramps and stiffness are the most common side effects reported by patients on lipid lowering therapy[15] and have been associated with muscle cramps based on information provided in a population-based study[13]. An elevated creatine kinase (CK) is not a prerequisite to making this association clinically as cramps may occur outside the setting of toxic statin myopathy characterized by pain, increased CK and weakness. Cholinesterase inhibitors used in dementia[16] as well as those used to treat neuromuscular disorders such as myasthenia gravis can also cause muscle cramps. A list of common medications associated with muscle cramps are found in Table 1.

Table 1.

Medications associated with muscle cramps in the elderly
Long acting β2-agonists
Thiazide-like diuretics
Potassium-sparing diuretics
Loop diuretics
Statins
Cholinesterase inhibitors

Muscle cramps are considered to be idiopathic when no underlying physiological, medical or neurological process can be identified[1]. Idiopathic cramps are often nocturnal, more common in the legs particularly involving the calves or intrinsic foot muscles and occur in 38-50% of the elderly[5,17,18]. Periodic leg movements (PLM) and restless legs syndrome (RLS) are two nocturnal syndromes that can co-exist but should be distinguished from muscle cramps as treatments may be different. PLM can often be distinguished from muscle cramps as they are less often painful and RLS presents with positive sensory symptoms including a creeping and crawling dysesthesia in the legs rather than a contraction of muscles.

Management

Lifestyle

Since the publication of a systematic review encompassing all randomized controlled trials (RCTs) of non-drug interventions in 2012[19], new evidence has emerged to support stretching as a cramp prophylactic. Hallegraeff and colleagues conducted a randomized control trial in patients over the age of 55 with nocturnal leg cramps. Those in the intervention group received a 45-minute training session with a physiotherapist and were taught to perform three exercises nightly; a standing calf stretch, standing hamstring stretch and a seated calf/hamstring stretch. In contrast to previous evidence, stretching led to a modest but significant reduction in cramp frequency and severity – in patients with a mean of 3.4 cramps/night, muscle cramps were reduced by a mean of 1.2 cramps per night[17]. Based on this evidence, stretches targeting the calves and hamstrings done nightly with proper instruction present a reasonable conservative measure. Although there is no evidence, we would also recommend the maintenance of good hydration. Similarly, in patients with underlying medical conditions, appropriate fluid balance should be preserved as this is in concordance with the literature on hemodialysis-induced cramps[20] and cramps in cirrhosis, where fluid shifts have been proposed to contribute to the development of cramps[21].

Non-prescription

Magnesium is commonly promoted as a non-prescription cramp prophylactic. While there is evidence to support its use in pregnancy and magnesium deficiency states[22,23], there is no strong evidence supporting its use in the general population[24]. Nevertheless, some patients do experience benefit and it is possible a clinically meaningful reduction in cramps may have been missed in studies by the short duration of studies and slow equilibration of magnesium within different tissue compartments[25,26]. As such, a short trial of magnesium daily over 2-3 weeks should be considered keeping in mind side effects such as diarrhea, particularly in the elderly. As a guide, published trials of oral magnesium in non-pregnant patients used formulations of magnesium citrate 300 mg[27] and 900 mg BID[24,28] for periods of approximately 4-6 weeks. Magnesium supplementation may need to be avoided in patients with significant renal dysfunction.

Vitamin B complex also has evidence to support its use in muscle cramps. A randomized double blind placebo control study in patients over the age of 65 (n=28) found that vitamin B complex consisting of fursulthiamine 50 mg, hydroxocobalamin 250 µg, pyridoxal phosphate 30 mg and riboflavin 5 mg resulted in a clinically significant reduction in cramps while adverse effects were the same in both groups[29]. Other non-prescription options with evidence in hemodialysis-induced cramps include vitamin B complex used together with vitamin E 400 mg and vitamin C 250 mg[9].

Prescription

Quinine derivatives represent one of the most effective agents used to treat muscle cramps. Proposed mechanisms include increasing the refractory period of muscle and reducing excitability of the motor end plate[30]. When considering its use in the elderly, in addition to dose independent adverse effects, further concern arises from altered pharmacokinetics. The most commonly prescribed dose for muscle cramps in studies is 300 mg/day ranging from 200-500 mg[31]. By comparison, tonic water contains 40-80 mg/L of Quinine and the dosage for malaria is 600 mg every eight hours[31]. Quinine is predominantly excreted by the liver and in variable amounts by the kidney. Its half-life is estimated to be 10 hours but can extend to 18 hours in healthy elderly patients[32]. The half-life of Quinine is also markedly increased in hepatic impairment[33] and although it has been used in patients with Pugh's classification A and B, patients with class C or alcoholic cirrhosis were not studied[34]. Therefore, caution should be used when considering quinine sulphate in elderly patients with severe hepatic dysfunction and avoided if possible, and although the elimination half-life is increased in people with mild to moderate hepatic impairment, dosage adjustment is not needed as weight-adjusted clearance remains the same. When used prior to hemodialysis at doses of 320 mg no adverse hematological, auditory or visual effects were noted, and as such this medication at the usual dose of 300 mg qhs can be considered in elderly patients on hemodialysis[35]. In contrast, given that the half-life in people with severe renal impairment who are not on dialysis is increased to 26 hours, a lower dose of quinine of less than half the normal dose is recommended in people with severe renal impairment not on dialysis.

A Cochrane review published in 2015 consisted primarily of older patients with the mean age from all studies being 58 years. Quinine significantly reduced cramp number, cramp intensity and cramp days[31]. Of the studies classified as class 1 in the report by the American Academy of Neurology (AAN) in 2010, only one study included patients over the age of 70[36]. In this study, 300 mg of hydroquinine hydrobromide resulted in five fewer cramps compared to placebo over a two-week period in patients who prior to treatment had a minimum of three cramps per week, which translated to a 36% reduction in the mean number of cramps[37].

Quinine is associated with a broad range of dose independent reactions. These include drug-induced thrombocytopenia and drug-induced thrombotic microangiopathy[38]. Other serious side effects include thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC) and bleeding diathesis[36]. Most of these symptoms have been described to resolve after discontinuation of quinine[31].

Older patients are particularly at risk for dose related side effects given altered pharmacokinetics. Based on a recent Cochrane review, common adverse events for quinine include gastrointestinal side effects and cinchonism (see https://en.wikipedia.org/wiki/Cinchonism). The constellation of symptoms linked to long-term Quinine use include nausea, vomiting, vertigo, visual disturbances, tinnitus and hearing impairment[31]. Adverse effects that are more likely at higher serum concentrations include visual impairment and cardiac arrhythmias[39]. Comorbidities should also be taken into consideration. Looking at heart failure specifically, a Danish observational study found that quinine use was associated with increased mortality, particularly in patients that were also on β-Blockers[40]. Polypharmacy is also a concern in the elderly.

Quinine concentration is increased when used together with CYP3A4 inhibitors[41]. Isomers of quinine used concurrently with drugs that prolong the QT interval increase the risk of drug induced torsades de pointe[42]. Quinine has also been shown to elevate digoxin concentration[43].

As outlined by the AAN in their report from 2010, although there is level A evidence to suggest that quinine and quinine derivatives are effective in the treatment of muscle cramps, they should only be considered when cramps are disabling and no other agents provide relief[36]. While it is banned from being marketed for muscle cramps by the FDA in the USA[44], it remains used by neurologists with good tolerability in Canada[45] and other countries worldwide. In the elderly, the presence of impaired elimination processes, medical co-morbidities and polypharmacy emphasize the need for special caution. Furthermore, pre-existing hearing impairment in the elderly may obscure symptoms such as tinnitus and hearing loss suggestive of cinchonism[18].

A similar agent to quinine with recent evidence is mexiletine, an analog of lidocaine. At doses of 300 mg and 600 mg daily, mexilitine has been shown to suppress currents in human motor axons and decreased the mean pain/muscle cramp disability score following 2-3 months of treatment in a trial of 20 patients[46]. More recently in a phase 2 randomized control trial in ALS, muscle cramp frequency and severity were significantly lower when compared to placebo[47].

There is also evidence to support calcium channel blockers such as diltiazem and verapamil. A crossover study of 13 patients with a mean age of 64 years showed that diltiazem hydrochloride 30 mg before bed resulted in a reduction in cramp frequency[48]. Notably, patients with cardiac conditions such as heart block, sick sinus syndrome, as well as cardiac failure were excluded. An open label study of eight elderly patients refractory to quinine with nocturnal leg cramps experienced improvement with verapamil 120 mg[49].

Baclofen is among the most commonly prescribed agents for managing cramps in ALS and in patients in general[45,50] and was recently shown to be effective in treating muscle cramps in hepatic cirrhosis[51]. Extra caution is advised when considering its use in the elderly due to adverse effects such as drowsiness. A trial of baclofen in geriatric stroke patients without severe renal or hepatic impairment was discontinued due to intolerable drowsiness[52]. Unless new evidence is presented, neither gabapentin nor cannabinoids should be used in patients with cramps alone, particularly in the elderly, as trials for each in the ALS population were negative[53,54].

Antiepileptic sodium channel blockers such as phenytoin and carbamazepine have been used as therapy for muscle cramps, particularly in patients with cramp fasciculation syndromes or refractory muscle cramps[55]. In addition, a small pilot trial in the ALS population suggests that levetiracetam is effective in treating muscle cramps[56]. This option may also have significant neurological side effects (e.g., decreased cognition, impaired balance, rashes and dizziness) and in some cases require ongoing monitoring, particularly in the elderly, and as such, should be used judiciously and only under careful supervision.

When considering any treatment option for muscle cramps, assessing the clinical response a minimum interval of two weeks after initiation of therapy or longer in patients with less frequent cramps is recommended, as this allows for adequate patient assessment of the frequency and characteristics of the cramps. At present, no guidelines exist to determine what constitutes a clinically meaningful response. Parameters such as cramp frequency, cramp duration, cramp severity, sleep disturbance and cramp days can be used to guide therapy.

Conclusion

Muscle cramps are common in the elderly and can be idiopathic or secondary to underlying neurologic or medical conditions. Not all patients require electrophysiological investigation; however, muscle cramps should

prompt a focused history, medication review, physical examination and basic screening investigations to identify physiologic or secondary causes. Suggested investigations include electrolytes, magnesium, calcium, liver function tests, creatinine and fasting glucose. Features suggestive of a secondary cause such as polyneuropathy should prompt further investigations. Despite limited supportive evidence, conservative measures such as stretching, magnesium and vitamin B complex should be trialed initially in the treatment of muscle cramps. Quinine sulphate remains the medication with the greatest evidence for efficacy in treatment of muscle cramps; however, potential adverse effects should be taken into account before prescribing this medication, particularly in the elderly. Other pharmacological agents with some evidence such as calcium channel blockers may be worth considering for treatment given their preferable risk profile. In the end physicians must work together with their patients in establishing a management plan.

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