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A Comprehensive Review on the Mechanism, Risk Factors, and Management of Muscle Cramping

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Abstract

Muscle cramps are sudden, involuntary, and painful spasms of skeletal muscles. This condition affects 37% of the general population each year. It is a common complaint in practice. Muscle cramps occur suddenly and can last for a few seconds to a few minutes. They can be associated with exercise or rest, or can be a manifestation of a medical condition. There is controversy regarding the pathophysiology of muscle cramps. Two theories have been advanced in the literature to explain muscle cramps. They include the dehydration/electrolyte imbalance hypothesis and the altered neuromuscular control hypothesis. This paper provides a comprehensive overview of the current literature on the pathophysiology, risk factors, and management of muscle cramps. The literature suggests that exercise-associated muscle cramps (EAMCs) result from a variety of factors. It is suggested that muscle cramps result from a combination of intrinsic and extrinsic factors. One such factor is neuromuscular fatigue. Passive stretching is the mainstay in the management of muscle cramps. Similarly, prevention is also individualized according to the risk factors. Pharmacological agents such as methocarbamol, orphan Adrien, and taurine are effective in patients with cirrhosis.

Keywords

muscle cramps, exercise-associated muscle cramps, pathophysiology, risk factors, neuromuscular control

1. Introduction

Muscle cramps are among the most common neuromuscular complaints faced by individuals and athletes alike; however, they are not well understood by many medical practitioners. The symptoms of muscle cramping include sudden pain, loss of agility, and failure of muscle contraction [1]. The significance of muscle cramps goes beyond the pain and discomfort they cause. In sports medicine, exercise-associated muscle cramps (EAMCs) are the most common condition for which athletes seek medical attention during or after sports events. The incidence of EAMCs varies by sport, age group, and sex. In a four-year investigation of ultramarathon runners, the incidence of serious EAMCs ranged between 1.01 and 2.2 cases of EAMCs per 1,000 race starters [2]. The incidence was higher among less experienced runners, older runners, and runners with faster running speeds. In American football players, EAMCs are common during the hottest months of the year, with an incidence of 3.07 cases per 1,000 athlete-exposures. Outside the realm of sports medicine, the effect of MC on quality of life in other patient populations is considerable. For example, in cirrhotic patients with MC, the effect on quality of life is considerable. However, in this patient

population, widely accepted clinical practice guidelines for the management of EAMC are still lacking. Other patient populations that are adversely affected by MC include individuals undergoing hemodialysis, pregnant women in the later stages of gestation, and individuals with thyroid disorders or upper motor neuron lesions. The confusion and debate regarding the pathophysiology, management, and prevention of EAMC have persisted for decades. For example, in the past, the fluid and electrolyte imbalance theory caused by sweating during EAMC has been the most widely accepted explanation of the phenomenon. Although this theory is somewhat intuitive, it is not well supported by scientific data. More recently, the altered neuromuscular control theory has gained considerable support as the most likely explanation for EAMC. The theory is based on the imbalance between the excitatory drive from the muscle spindle to the alpha motor neuron and the inhibitory drive from the Golgi tendon organ to the alpha motor neuron, most likely due to neuromuscular fatigue. This paper aims to provide a comprehensive review of the literature on muscle cramps, including evidence supporting various pathophysiological theories, risk factors across populations, pharmacological and non-pharmacological treatments, and evidence-based recommendations. By synthesizing the literature across various clinical settings, from healthy athletes to patients with cirrhosis or neurological disorders, this review aims to guide readers on the prevention and treatment of muscle cramps in different individuals.

2. Literature Review

2.1 Historical Perspectives and Evolving Theories

Significant advances have been made in the pathophysiology of muscle cramps over the last century. Initially, observations made in the early 1900s through occupational medicine practices linked muscle cramps to hot work environments. This led to the general acceptance of the dehydration/electrolyte depletion theory, which suggested that dehydration and sodium ion depletion under extreme heat are both responsible for muscle cramping. However, “heat cramps” is a misnomer, since muscle cramps are unrelated to temperature; they can occur in different environmental conditions, are not associated with heating, and cannot be relieved by cooling. Moreover, there is semantic confusion with the use of the terms “cramp,” “spasm,” “contracture,” and “fasciculation,” which are often used synonymously despite their different meanings.

2.2 The Dehydration and Electrolyte Depletion Hypothesis

The dehydration and electrolyte depletion hypothesis has been the most commonly cited theory in this regard. Evidence cited includes decreased EAMCs in patients receiving saline infusions in initial case series, and that tennis players and American football players with a history of cramps have higher sweat rates (approximately 2.5 L/h) and sodium loss (up to 2.7 g/h) compared with those without a history of cramps. One study of American football players found that those with sweat sodium loss rates of more than 1.18 g/h or sweat chloride loss rates of more than 2.3 g/h during a workout were approximately nine times more likely to have a history of muscle cramps. Some experimental evidence has also been cited in this regard. Ohno et al. induced hamstring cramps in men by passive dehydration in a sauna and noted that no muscle cramps occurred with 0.5% or 1% body mass dehydration. Still, three out of five participants experienced muscle cramps with 2% or 3% body mass dehydration. However, expert opinion and stronger evidence have been cited increasingly in opposition to this theory. Schwellnus, in a landmark evidence-based review, noted that “there is limited evidence to support the electrolyte depletion and dehydration hypotheses, and this is based on anecdotal reports and case series of only 18 patients, and a small case-control study of 10 patients” [3]. Importantly, results of four prospective cohort studies have failed to show evidence for this hypothesis. The theory is also flawed in that “salty sweaters” have high sweat rates and thus high plasma osmolality, causing fluid shifts from interstitial compartments into the vasculature. Conversely, “salty sweaters” have high sodium loss and thus low plasma osmolality, causing no fluid shifts from interstitial compartments into the vasculature.

2.3 Altered Neuromuscular Control Hypothesis

The altered neuromuscular control hypothesis has been identified as the best pathophysiological basis for EAMCs. This hypothesis states that muscle cramps are due to an imbalance between the excitatory input from muscle spindles (type Ia and II afferents) and the inhibitory input to alpha motor neurons from Golgi tendon

organs (type Ib afferents), which are altered by neuromuscular overload and fatigue, especially of muscles crossing two or more joints and frequently contracting during exercise [4].Scientific evidence for this hypothesis was obtained from human studies of muscle cramping. Studies of human models of muscle cramping have shown that muscle cramps can be induced by repetitive maximal voluntary contractions, especially when muscles are shortened. Epidemiological studies of muscle cramping in athletes have identified neuromuscular fatigue as a common risk factor. Animal experimental studies have further elucidated the reflex mechanisms underlying cramp pathogenesis. Nelson and colleagues, in their narrative review article, emphasized that EAMC has multiple causes and is not just due to dehydration and/or electrolyte deficits, but rather to an imbalance in neuromuscular control. This pathophysiological basis of EAMC explains many of the clinicians' observations and experiences [5].

2.4 Cramps in Special Populations

Aside from exercise-associated cramps in healthy individuals, several clinical conditions are associated with muscle cramps. For patients with cirrhosis, the occurrence of cramps is highly prevalent, which significantly affects health-related quality of life. A systematic review of randomized controlled trials in patients with cirrhosis reported 13 interventions, including acetaminophen, methocarbamol, orphenadrine, and taurine supplements, which were effective in comparison with the placebo group [6]. In patients with upper motor neuron disorders, such as spinal cord injury, cerebral palsy, traumatic brain injury, and stroke, the relationship between cramps and spasms is not well understood. However, a scoping review by Therkildsen et al. reported that muscle cramps and spasms are probably related and share common pathophysiological mechanisms [7].Moreover, it was reported that some spasms may be considered as cramps. Other patients at increased risk for developing muscle cramps include pregnant women in the final months, patients with hemodialysis, patients with thyroid dysfunction or hypothyroidism, patients taking medications such as diuretics, and patients with alcohol use disorders and vitamin D deficiency.

2.5 Gaps in Current Research

Despite extensive research in this area, major knowledge gaps persist in the muscle cramp literature. The research in this area has been marred by a small number of participants, definitions of muscle cramps, and outcome measures. The absence of widely accepted clinical practice guidelines for treating muscle cramps, even in well-defined patient groups such as those with cirrhosis, is a reflection of this. Research in this area has been dominated by exercise-associated muscle cramps in athletes, with other patient groups relatively ignored. There is an urgent need for well-designed randomized controlled trials that compare interventions, assess optimal dose and duration of treatment, and long-term safety.

3. Discussion

3.1 Interpretation of Findings

Recent studies have found that our current understanding of muscle cramp has shifted quite substantially. We have moved away from the dehydration/electrolyte imbalance hypothesis and now understand a more complex role for neuromuscular factors [8].This has important implications. A common theme across groups, such as athletes, patients with cirrhosis, and patients with nocturnal muscle cramps, is that stretching is always effective at stopping acute muscle cramps. This supports the neuromuscular hypothesis, since stretching activates the Golgi tendon organs, increasing the activity of the inhibitory Ib afferent input to alpha motor neurons to counterbalance the excessive excitation thought to cause the muscle cramp. This would not be expected if muscle cramps are due to dehydration/electrolyte imbalance. One important aspect is that, despite a lack of evidence for the dehydration/electrolyte imbalance hypothesis in large prospective studies, which would be necessary to confirm it, this hypothesis has persisted for a long time. This is a good example of how evidence-based medicine is more important than tradition or anecdotal evidence. While electrolyte imbalance may play a role in muscle cramps in certain circumstances, such as “salty sweaters” or patients with an electrolyte imbalance disorder, it is clearly not a major contributor to muscle cramps in most patients. A more modern hypothesis is more consistent with current understanding. This hypothesis is multifactorial; it recognizes that a single syndrome can have multiple causes. This means that muscle cramps can be caused by a variety of factors, such as

neuromuscular fatigue in athletes due to prolonged exercise, metabolic derangements, and possible alterations in neurotransmitter balance in patients with cirrhosis, or alterations in motor unit properties with aging in patients with nocturnal muscle cramp.

3.2 Clinical Implications

The results of this literature review support several practice recommendations. First, the assessment of patients with cramp symptoms must include a detailed history to identify possible risk factors, such as medications, co-existing medical conditions, and activity patterns. This individualized approach is more likely to result in successful prevention than general recommendations. Second, patient education must focus on the effectiveness and safety of stretching for the relief of acute cramp symptoms. This is a simple yet often unrecognized solution for patients with cramp symptoms. Third, pharmacologic interventions must be considered for patients with frequent debilitating cramp symptoms that do not respond to conservative measures. This must be individualized according to patients' co-existing conditions and risk factors. The strong recommendation against quinine use must be communicated to patients through various media. Some patients may be unaware that this recommendation is based on new evidence. Fourth, for patients with cirrhosis, emerging evidence on specific pharmacologic agents (methocarbamol, orphenadrine, taurine) offers new promise for more effective management of this condition.

3.3 Limitations

This review has several limitations. Firstly, the heterogeneity of the studies included in this review, which differed in their study designs, populations studied, definition of cramp, and outcome measures, makes it impossible to conduct a meta-analysis of the results. Secondly, most studies have been conducted in EAMCs among athletes, which may limit the generalizability of the results to other affected groups. Finally, the quality of the evidence for some of the issues discussed in this review varies widely, with some areas supported by small, poor-quality studies. Moreover, the pathophysiology of cramps in special populations such as pregnancy, cirrhosis, and neurological disorders is not well understood, and whether the pathophysiological mechanisms of cramp in athletes apply to these special populations is also unknown [9].

3.4 Future Research Directions

Based on gaps in current knowledge, several areas of future research have been identified. Further well-designed randomized controlled trials are required to establish the efficacy and safety of pharmacological interventions across different populations. Comparative effectiveness studies would also be beneficial for clinicians to select from the options currently available. Development of standardized outcome measures for cramp frequency, severity, and impact would be beneficial for comparing studies and conducting a meta-analysis. Biomarkers for predicting susceptibility to cramp or for selecting the most appropriate pharmacological agent would be a new frontier of research. Neurophysiological studies of motor neuron excitability in different cramp-susceptible populations could also provide new insights. The relationship between cramps and spasms in neurological disorders also warrants further investigation, which could lead to effective management of both symptoms in conditions such as spinal cord injury, stroke, and multiple sclerosis.

4. Conclusion

Muscle cramps are a common, painful, and potentially debilitating phenomenon that affects many different populations, from the athlete to the patient with chronic illness. This review synthesizes the current evidence on the pathophysiology, risk factors, and management of this common problem. The long-held belief that the primary etiology for cramps is dehydration and electrolyte loss has been replaced with the more sophisticated understanding that these are neuromuscular disorders. The current body of evidence clearly indicates that the pathophysiology of orders is sustained alpha motor neuron activity, most commonly due to neuromuscular fatigue syndromes, with electrolyte loss playing a secondary role in the etiology. Such an etiology is most consistent with the presentation, risk factors, and treatment response observed in muscle cramping. The first line of management for these disorders is the simple, safe, and extremely effective technique of passive stretching of the involved muscles. Prevention is achieved by assessing the patient's risk factors for these

disorders and implementing interventions to correct identified abnormalities. Although many agents are available for the management of these disorders, they should be used in patients in whom conservative measures have failed to provide relief. Even in such cases, the agent used should be based on the patient's individual factors. Despite decades of investigation into the etiology and management of these disorders, many unanswered questions regarding the pathophysiology of these disorders in special patient populations, such as pregnant women with cirrhosis or patients with neuromuscular disorders, remain. Further investigation is needed to establish the optimal pharmacologic management and the best approach to developing clinical practice guidelines for these disorders. As the understanding of these disorders continues to evolve with further research, the patient with these disorders, from the athlete to the patient with chronic illness, stands to benefit from the more sophisticated understanding that is to come.

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Conflicts of Interest

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