TREATMENT POSSIBILITIES OF MUSCLE CRAMPS IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract

Muscle cramps appearing in liver cirrhosis substantially affect the quality of life of these patients. The prevalence of painful muscle cramps can be up to 88%. The exact mechanism by which these muscle cramps occur is unknown. The management of this symptom is not easy because there is no uniformly accepted recommendation about what kind of supplementation or medicine (or both) can be used exactly. The aim of our study is to review the treatment options for muscle cramps in liver cirrhosis.

We found in the literature (using the keywords „liver cirrhosis", „muscle cramps", „treatment" and „quality of life") 32 articles of this topic. Treatment options currently are: vitamin supplementations (vitamin E, 1 - α hydroxy vitamin D), amino acid supplementations (taurine, branched - chain amino acids, L - carnitine, albumin), mixed herbal medicines (Niuche-Shen-Qui-Wan), zinc and medications (eperisone hydrochloride, quinine and quinidine sulphate, baclofen, methocarbamol, orphenadrine). Vitamin supplementations and amino acid supplementations are targeting the possible pathophysiological causes of muscle cramps (nerve function or energy metabolism alterations which are unique to liver cirrhosis). New aspects started to use medications especially antispasmodic agents (methocarbamol, orphenadrine) and antispasticity agents (baclofen) to relieve muscle cramps. We also found a multicenter study and two systematic reviews (performed in 2013 and 2014). From 2014 there is no systematic article appeared in this topic and we considered it important to survey the new treatment options next to the treatment options already known.

Keywords: *liver cirrhosis, muscle cramps, treatment, quality of life.*

Rezumat

Crampele musculare care apar în ciroza hepatică afectează substanțial calitatea vieții acestor pacienți. Prevalența crampelor musculare dureroase poate fi de până la 88%. Mecanismul exact prin care apar crampele musculare este necunoscut, iar gestionarea acestui simptom nu este ușoară, deoarece nu există o recomandare uniform acceptată cu privire la suplimentele sau medicamentele (sau ambele) care pot fi utilizate. Scopul lucrării noastre este de a revizui opțiunile de tratament pentru crampele musculare din ciroza hepatică.

Am găsit în literatură (folosind cuvintele cheie „ciroză hepatică", „crampe musculare", „tratament" și „calitatea vieții") 32 de articole pe această temă. Opțiunile de tratament în prezent sunt: suplimente cu vitamine (vitamina E, 1 - α hidroxi vitamina D), suplimente cu



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aminoacizi (taurină, aminoacizi cu lanț ramificat, L - carnitină, albumină), medicamente pe bază de plante (Niuche-Shen-Qui-Wan), zinc și medicamente (clorhidrat de eperizonă, chinină și sulfat de chinidină, baclofen, metocarbamol, orfenadrină). Suplimentele de vitamine și suplimentele de aminoacizi vizează posibilele cauze fiziopatologice ale crampelor musculare (alterări ale funcției nervoase sau ale metabolismului energetic, care sunt unice pentru ciroza hepatică). Au început să se utilizeze și medicamente, în special relaxante musculare (metocarbamol, orfenadrină) și agenți antispastici (baclofen) pentru ameliorarea crampelor musculare. De asemenea, am găsit un studiu multicentric și două review-uri (realizate în 2013 și 2014). Din 2014 nu a apărut niciun articol sistematic pe această temă și am considerat important să cercetăm noile opțiuni de tratament, alături de cele deja cunoscute.

Cuvinte cheie: *ciroză hepatică, crampe musculare, tratament, calitatea vieții.*

Introduction

According to the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Glossary of Terms published in 2015, a „muscle cramp" is an involuntary, painful muscle contraction associated with electrical activity[1].

Firstly, we have to differentiate various muscle conditions: true muscle cramps, muscle contracture, dystonia and tetany.

In the case of a „muscle cramp" or also named a „true muscle cramp", the commencement is sudden, generally occurring at rest and often is nocturnal. The pain is intense but yet short. The contraction and the pain resolve on its own in seconds to several minutes. The most commonly affected area are the calves but cramps can also occur in the fingers and hands. „True muscle cramps" electromiographically present an increased frequency of motor unit action potentials. This spread throughout the muscle group and produce a sustained muscle contraction. Muscle contracture is an involuntary state of sustained muscle contraction. It has no associated action potentials, this means that is electrically silent and it has the impossibility of the muscle fibers to undergo relaxation. Dystonia is defined as a contemporaneous contraction of both agonist and antagonist muscle groups. Tetany is a syndrome of sensory and motor neuron hyperexcitability. This results a motor hyperactivity (muscle spasms) and sensory hyperactivity (paresthesia)[2].

Many conditions are associated with muscle cramps:

- Idiopathic;
- Neurological conditions: motor neuron disease (eg. amyotrophic lateral sclerosis), radiculopathy (eg. spinal cord stenosis), peripheral neuropathy;
- Benign conditions: benign nocturnal muscle cramps in elderly people, exercise - induced muscle cramps, pregnancy - related muscle cramps;
- End - stage disease: liver cirrhosis, renal requiring hemodialysis;
- Cardiac disease: peripheral vascular disease (claudication);
- Various conditions: volume depletion, parenteral nutrition, adrenal deficiency, malignancy, uremia, hyponatremia;
- Medications: beta - blockers, calcium channel blockers, conjugated estrogens, raloxifene, levalbuterol, naproxen, diuretics, morphine, verapamil, intravenous iron sucrose, teriparatide, albuterol/ipratropium, pregabalin, bromocriptine, bupropion, celecoxib, cetirizine, chromium, cinacalcet, ciprofloxacin, citalopram, clonazepam, donepezil, eszopiclone, fluoxetine, gabapentin, lansoprazole, rivastigmine, sertraline, telmisartan, zolpidem[2,3,4].

Patients suffering in liver cirrhosis often experience muscle cramps. These kind of symptoms are described by the patients as „true muscle cramps": they are very painful, often occur at rest or during sleep and predominantly affect the hands, legs, feet, (but may also affect the neck, back and the sides) [5]. The association of liver cirrhosis with muscle cramps was first reported in 1986 by Konikoff and Theodor[6].

The mechanism behind the appearence of muscle cramps remains unclear. These muscle cramps are not accompained with progressive motor neuron disease or chronic neuromuscular disability. The prevalence is varried from 29% to 88%[7].

In liver cirrhosis, muscle cramps can significantly impair quality of life. They should be differentiated from myalgias, myositis and rhabdomyositis (by determining serum creatinine kinase and serum aldolase)[8].

Muscle cramps have an impact on physical functioning, sleep, general and mental health, energy levels and social isolation[9].

As mentioned above, in liver cirrhosis the pathophysiolagical mechanisms of muscle cramps are not completely elucidated. The possible mechanisms may be: alterations in nerve function, energy metabolism, plasma volume and electrolytes.

Nerve function

Oxidative stress can damage membrane conduction which causes the nerve dysfunction. Histologic studies find that patients with liver disease have thinly myelinated nerve fibers and axonal loss. Cirrhotic patients were also noticed to have involuntary bursts of action potentials. On electromyogram these action potentials appeared as fasciculations (with origin in the peripheral nerve). These suggests that patients with liver disease have a chronically depolarized and hyperexcitable motor neuron. These lesions can induce inadequate high – frequency and repetitive firing of the motor nerve action potentials which results the appearance of muscle cramps in liver cirrhosis[3].

Energy metabolism

In liver cirrhosis, there is a modification in the regulation of amino acid and protein



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metabolism, which causes decreased plasma and skeletal muscle concentrations of taurine (which can be found in high concentrations in skeletal muscle).

Modified taurine concentration appear as a result of decreased production (caused by an imbalance in the ratio of branched – chain amino acids to aromatic amino acids) and increased release from muscle. Taurine concentrations influence the voltage - dependent chloride channels and calcium - activated sodium and potassium channels. These channels modulate striated fiber electrical activity and stabilize the sarcolemma, so the result of taurine deficiency is a decrease in the threshold potential and hyperecitability of the skeletal muscle.

Yamamoto et al in 1994 measured the mean plasma taurine level in cirrhotic patients with and without muscle cramps in comparison with controls. The mean plasma taurine level in cirrhotic patients with muscle cramps was 56.9 nmol/mL. In cirrhotic patients without muscle cramps taurine level was 79.3 nmol/mL and healthy controls had a level of 90.1 nmol/mL. Taurine deficiency predispose cirrhotic patients to muscle cramps by altering the skeletal muscle electrical properties[3,10]. Altered energy metabolism in cirrhotic patients may also occur by a reduction in adenosine triphosphate (ATP) production[3].

Plasma volume, electrolytes and zinc

Hyponatremia, hypokalemia, hypomagnesemia and changes in plasma volume can have an impact on intracellular concentrations of electrolytes or cause hypovolemia, which can produce cramps. Many studies suggest that, in cirrhotic patients, shifts in plasma volume may contribute to muscle cramps (but plasma electrolyte concentrations and diuretic use do not directly influence the frequency of cramps)[3].

Treatment options

We searched in the bibliographical databases (for example:PUBMED), with the search terms of „liver cirrhosis”, „muscle cramps”, „treatment” and „quality of life”. Searches were resticted to adult human studies written in English.

In the literature we found 32 articles which focuses on the treatment of muscle cramps in liver cirrhosis. These 32 articles were corresponding by including the keywords: „liver cirrhosis”, „muscle cramps”, „treatment” and „quality of life”. Each treatment possibility is detailed below.

Vitamin E

Vitamin E (RRR – alpha – tocopherol) is an important antioxidant in the cell membrane. It could be considered as a scavenger of free

radicals. In humans, the liver is an important organ for vitamin E metabolism. After absorption in the duodenum by the lymphatic pathway, it is transported in association with chylomicrons, so vitamin E arrives mainly to hepatocytes. From hepatic parenchyma cells, alpha - tocopherol is secreted in association with VLDL (very low density lipoprotein) and it is also found in HDL (high density lipoprotein) and LDL (low density lipoprotein) in plasma. In skeletal muscle and adipose tissue is deposited unmodified the most of the incorporated alpha – tocopherol. Von Herbay et al in their study demonstrated that lower serum vitamin E levels can be found in patients with Wilson`s disease, alcoholic liver disease, hemochromatosis compared with the healthy controls[11].

Howard et al. in 2011 report that their findings strongly confirm that vitamin E helps membrane repair, as a membrane - based antioxidant, that is the reason why vitamin E is essential to muscle homeostasis[12].

Two additional studies have reported the effects of supplementation with vitamin E on painful muscle cramps in cirrhotic patients[3,9]. Konikoff et al in their study examined 29 cirrhotic patients and found 23 with muscle cramps. Patients with cramps had a lower serum vitamin E levels than those who did not experience muscle cramps. 13 of these patients were treated with 200 mg vitamin E three times per day for 4 weeks and had a significant improvement in cramp severity, frequency and duration. There were no reported adverse events[3,9,13]. Chandok et al reported in a randomized, double-blinded, placebo controlled, cross-over pilot study on the effects of vitamin E supplementation on muscle cramps in 9 patients with cirrhosis and found no statistical significance between vitamin E and placebo in the frequency, duration or severity of cramps. The dosage and duration of the treatment was not documented[14].

Taurine

We found 9 articles in the literature which report the effects of oral taurine supplementation on muscle cramps in liver cirrhosis.

The first study published by Matsuzaki et al in 1990 describes a case report in which taurine was administered for a 64-year-old female cirrhotic patient, who was admitted with bilateral pretibial edema and muscle cramp at upper and lower limbs (in neurological examination, an irregular muscle discharge was found). Irregular muscle contraction appeared after electric stimulation. Taurine was administered postprandially at doses of 3g, three times daily and muscle cramps disappeared. It reappeared after treatment, was discontinued, but after readministration it disappeared again. During taurine treatment, muscle cramp did not appear after electric stimulation on EMG. They continued to administer taurine to other 10 patients with muscle cramp in chronic liver disease and muscle cramp disappeared in 7 cases, and decreased in 3 cases[15].

In the second study (in 1993) Matsuzaki et al gave to 12 nonalcoholic cirrhotic patients 6g taurine 3 times daily for 4 weeks. 8 patients had complete resolution of cramps, and 4 patients had a significant decrease in cramp severity by 1 month. No adverse effects were observed[3,9,16].

Yamamoto et al reported their experiences about taurine administration in cirrhotic patients with muscle cramps in 4 studies[9,10,17,18,19] and Alturi et al in one single study[20]. The number of participants was small in all of these reports. There was no comparison with a palcebo group or randomisation. Cirrhotic patients with muscle



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cramps received taurine supplementation with or without low serum taurine levels. The dosage was 3-18g taurine daily from 4 weeks to 24 months. All of these studies reported a decrease in the incidence and severity of muscle cramps in patients who were treated with taurine. There were no side effects reported[9,10,17,18,19,20].

Vidot et al published their results and experiences in a placebo - controlled randomized clinical trial in 2018. They demonstrated that 2g taurine per day orally ameliorates the frequency, duration and intensity of painful muscle cramps[21].

A single-arm pilot study was published recently, in 2021 by Jang et al, who evaluated the effects of taurine supplementation in Korean cirrhotic patients with muscle cramps. 10 patients were enrolled in this study and they received oral taurine solution (1g/50 ml) three times per day for 4 weeks. Muscle cramp scores (frequency × intensity) decreased in 7 patients by weeks 4 and 8 after the treatment was started. Five patients whose baseline plasma taurine levels were below the normal limit showed increased taurine levels at week 4 (and 60% of them experienced improvements in their muscle cramps). Of the five patients who had normal or higher taurine plasma levels, 80% experienced an improvement at week 4[22].

As we mentioned in the introduction, taurine is essential in the energy metabolism. Taurine is a membrane stabilizer sulfur - containing amino acid, which modulates calcium transport. It is also able to dissipate the toxic effects of hypochlorous acid (HOCl). Taurine is a normal component of the human diet. This diet ensures most taurine either directly or by synthesis in the liver and brain[53]. Methionine metabolism leads to the formation of taurine and cystine[54].

1 – α hydroxy vitamin D

Okajima et al reported about the use of 1 - α hydroxy vitamin D for treating muscle cramps in patients with liver cirrhosis. 24 cirrhotic patients with muscle cramps received either 0,5 or 1,0 μg of 1 - α hydroxy vitamin D for 2 weeks. But there was no randomization and no placebo group. In 46% of the patients muscle cramps disappeared and the frequency was reduced in the remaining 54%. There were no side effects reported[9,23].

Branched-chain amino acids (BCAA)

Studies had reported about the administration of branched-chain amino acids (isoleucine, leucine and valine) in liver cirrhosis. BCAA supplementation has many benefits: improves serum albumin levels, increases taurine concentration and decreases progression of liver disease[3,24,25,26]. Oral BCAA supplementation was given to cirrhotic patients to normalize amino acid profiles and nutritional status. Controlled

trials (performed in Italy and in Japan) on BCAA supplementation demonstrated that BCAA given orally for cirrhotic patients improves not only nutritional status but also prognosis and quality of life (muscle cramps)[55].

Harushige et al gave to 15 malnourished cirrhotic patients 12 g BCAA granules daily for 3 years and 9 patients of this group experienced painful muscle cramps before the intervention. 4 patients of the 9 (44%) reported no cramps at the end of the treatment and 3 (33%) experienced a reduction in muscle cramps[9,27].

Sako et al studied the effects of nocturnal supplementation with BCAA in 8 patients with advanced hepatic cirrhosis and muscle cramps (these patients had also other complications such as ascites). The treatment period was 3 months. They observed a significantly increase in the concentration of serum albumin (2.8± 0.3 vs. 3.1± 0.2 g/dl, P< 0.002) and in the activity of serum cholin esterase (54±13 vs. 67±17 IU/l, P<0.02).

Fischer's ratio also increased (1.3±0.9 vs. 1.4±0.9, P<0.005). Blood ammonia levels did not change (137±41 vs. 115±27 µg/dl, P=0.0541). The frequency of muscle cramps decreased also significantly (7.4±2.0 vs. 0.3±0.5 times/week, P<0.0001)[28]. Fischer's ratio is the molar ratio of branched-chain AAs (leucine, valine, isoleucine) to aromatic AAs (phenylalanine, tyrosine). This ratio evaluates the liver metabolism, hepatic functional reserve and the severity of liver dysfunction[29].

Hidaka et al performed a small multicenter randomized study with 37 patients and compared daytime and nocturnal branched-chain amino acid supplementation for 3 months. The frequency of muscle cramps decreased in both groups (daytime vs. nocturnal) and no adverse effects were reported[3,9,30].

Intravenous albumin replacement

A single small study published by Angeli et al reported about the use of intravenous albumin to treat cirrhotic patients with muscle cramps. 12 patients received placebo or 100 ml 25% human albumin solution intravenously once weekly for 4 weeks. 9 participants (75%) reported a decrease in the frequency of muscle cramps and 2 of these patients reported no cramps during the treatment period. There were no adverse events during the treatment period. After cessation of the treatment, there was a gradual increase in cramps severity and duration in all participants[3,9,31].

L-carnitine

L–carnitine (4-N-trimethyl ammonium 3-hydroxybutyric acid) is a nutrient, which is greatly obtained from meat and dairy products, but also naturally produced from the amino acids lysine and methionine in the human liver, brain and kidney[32]. Total carnitine of the body mostly is found in skeletal and cardiac muscle (98%) and the liver contains only 1,6%[33]. This L-carnitine transfer long-chain fatty acids across the mitochondrial membrane, enabling oxidative release of energy. Tsuda et al reported in a study their experience of L-carnitine supplementation on muscle cramps in 23 patients with cirrhosis. Patients were treated with 300 mg L-carnitine twice a day. Muscle cramps were significantly improved in 90% of patients after 1 month of treatment (p<0.01). They also monitored the serum CK-level, blood platelet count, serum ammonia, prothrombin time, serum albumin and bilirubin level. No adverse events appeared in this study[34].



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Nakanishi et al performed a prospective study in which they used also L-carnitine to treat muscle cramps in cirrhotic patients. A total of 42 patients with cirrhosis that was complicated by muscle cramps were enrolled in this study. 19 patients received L-carnitine 300 mg 3 times/day (900 mg/day) and 23 patients 300 mg 4 times/day (1200 mg/day) for 8 weeks.

The frequency of muscle cramps was assessed by questionnaires. The degree of muscle cramping was valued by using the VAS (visual analogue scale). Muscle cramps were reduced in 88,1% of all the participants and disappeared for 28,6% of the patients at the end of the 8 weeks. The dose of L-carnitine was associated with percentages of patients with reduced muscle cramps after the treatment period: 43.5% in the 1200 mg/day group vs 10.5% in the 900 mg/day group. VAS scores at 8 weeks were: 9.9 ± 13.5 in the 1200 mg/day group vs 39.6 ± 31.9 in the 900 mg/day group. No adverse effects were found. There was no control group, and the patients were not randomized into 2 doses. So, the preliminary results suggest a dose-dependent effect of L-carnitine[35].

In 2019, Hiraoka et al studied the efficacy of the combination of L-carnitine and exercise in cirrhotic patients who received branched-chain amino acid supplementation, reported to prevent muscle wasting, for muscle complications (function, volume and cramping). 18 patients with liver cirrhosis who received branched-chain amino acid granule supplementation (12.45 g/day) were enrolled in the study.

After the evaluation of the average number of daily steps, the authors added oral L-carnitine supplementation (1000 mg/day) and additional exercise (plus 2000 steps/day) for 6 months. Every 4 weeks, a pedometer, a hand dynamometer, ergometer, and bioelectrical impedance analysis were used to evaluate daily steps, muscle function and muscle volume. Muscle cramps were inscribed using a numerical rating scale. Serum levels of total and free carnitine and average steps were increased after the treatment period.

There were no significant changes in the ratios of handgrip strength, leg strength, and muscle volume after 6 months. Muscle cramping complaints were reduced as compared with the start of therapy (baseline, 3 months, and 6 months: 6.3 ± 4.8, 3.1 ± 3.3, and 2.1 ± 2.0, respectively) (P=0.025, Holm's method), although numerical rating scale did not show any significant improvement. As a conclusion, they consider that in cirrhotic patients L-carnitine may have important impacts to prevent muscle wasting volume and function and improve muscle cramping[36].

Niuche-Shen-Qui-Wan (TJ-107)

Niuche-Shen-Qui-Wan (7.5 g) contains 4.5 g

of dried extract of mixed herbal medicines, the remaining 3.0 g is composed of lactose (98,5%), sucrose esters of fatty acids (0,5%) and magnesium stearate (1%). Motoo et al reported a case-series in 1997 about the oral supplementation with Niuche-Shen-Qui-Wan in cirrhotic patients with muscle cramps. They administered 7,5 g Niuche-Shen-Qui-Wan (2,5 g three times per day) to 12 patients with liver cirrhosis and painful muscle cramps. All of the participants reported the disappearing of muscle cramps after 7-28 days of treatment. One patient complained of epigastric discomfort. In this study there was no control group. This study suggests that Niuche-Shen-Qui-Wan may be useful in the treatment of muscle cramps in cirrhotic patients (but the results are still anecdotal). It is unclear if the effect is due to the combined effect of the preparation or to any component of the preparation, or the magnesium stearate component in responsible for the relief of muscle cramps[9,37].

Zinc

Kugelmas reported in 2000 about the beneficial effects of administering zinc sulfate to 12 cirrhotic patients with muscle cramps. These patients had low serum zinc levels and 5 of them were in Child's A, 3 patients in Child's B, and 4 participants in Child's C. They received 220 mg zinc sulfate orally twice daily for 12 weeks. After the treatment, muscle cramps completely resolved in 7 patients and improved in 3 patients. One patient complained of mild watery diarrhea that resolved after the cessation of zinc sulfate[38].

Eperisone hydrochloride

Kobayashi et al studied the effects of antispasmodic agent eperisone hydrochloride in patients with liver cirrhosis and muscle cramps. 21 patients were enrolled in this study. 150-300 mg eperisone hydrochloride were given to the patients daily, orally for 8 weeks. Of 18 patients who continued the treatment, in 11 patients the muscle cramps disappeared completely, in 6 cirrhotic patients the frequency decreased and in 1 patient were unaltered. In 4 patients were observed side effects: fatigue appeared in 1, epigastric discomfort in 2 and dizziness in 1 patient[39].

Quinine and quinidine sulphate

Quinine is a white crystalline alkaloid powder extracted from the bark of the cinchona tree. This cinchona tree is native to the Andes region of South America. Its mechanism of action is unknown. It is thought that quinine has a similar effect on the neuromuscular junction and muscles as curare. It diminishes the excitability of the motor end plate so there is a reduced response to nerve stimulation and acetylcholine and also increases the refractory period of muscle hereby reducing its response to repetitive stimulation. Quinine has derivates like quinine sulfate, hydroquinine and its optical isomer quinidine[40].

Quinine rarely causes hypersensitivity reactions or adverse effects. Cinchonism, hypoglycemia and hypotension is a triad of dose – related toxicities with overdose or when given at full therapeutic doses. From this triad cinchonism is reversible after drug withdrawal, symptoms can be: headache, vertigo, nausea, vomiting, abdominal pain, diarrhea, disturbed vision and tinnitus. Skin rushes and pruritus can also occur. Hypoglycemia reacts rapid and good to glucose infusion. Hypotension is rare if the drug is given orally.

Hypersensitivity reactions are rare: skin rashes, fever, gastrointestinal symptoms,



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visual and auditory changes, seizures and thrombocytopenia. More serious adverse effects (rare): haemolysis, disseminated intravascular coagulation, and the immune thrombocytopenia with haemolytic uremic syndrome. Cardiac effects and arrhythmias: tachycardia and ventricular fibrillation may result from an overdose or with high serum concentrations. From the point of view of the liver, the incidence of quinine hepatotoxicity is quoted as 2-2.2%.

Corbani et al in their article wrote about the use of quinine in the UK and in some other countries in patients with muscle cramps, because there is evidence from metaanalyses that in non-cirrhotic individuals quinine is effective. But, there are no trials about the use of quinine in cirrhotic patients[41].

The effects of quinidine (an optical isomer of quinine) was studied on muscle cramps in patients with non - alcoholic cirrhosis in a randomized - controlled trial reported by Lee et al. 31 patients were enrolled in this study. 16 individuals were treated with 400 mg quinidine sulfate/day orally vs placebo (15 patients). 88% of the quinidine - treated group had an improvement: it was a reduction in the incidence of muscle cramps greater than 50% compared with 13% in the placebo group. But, 31% of the people from the quinidine group experienced diarrhea (which resolved after quinidine was withdrawn)[42].

After these, the generally opinion is that the risk - benefit ratio for using quinine or quinidine in the treatment of muscle cramps in cirrhosis is unfavorable[3].

Baclofen

Baclofen is a derivative of gamma – aminobutyric acid. It was introduced firstly in 1966, as a possible treatment for spasticity due to corticospinal tract lesions[43].

It has been used in the treatment of cluster headaches, gastroesophageal reflux disease, chronic hiccups, cough[5], trigeminal neuralgia, acquired nystagmus, treatment of substance abuse, including alcohol or cocaine dependency[44] and multiple sclerosis[45].

Baclofen has low liver metabolism[5]. Other muscle relaxants are metabolized by the liver, but baclofen is primarily excreted by the kidneys in its unchanged form[44]. Another study reports that the kidneys are responsible for approximately 70% of baclofen's elimination[46]. But, patients with renal disease (diminished or absent kidney function) will increase baclofen plasma concentrations and these patients are at risk for developing baclofen toxicity[44,46]. Signs and symptoms of overdose are: hypotonia, hypothermia, impaired consciousness, respiratory depression and abnormal heart conductions. Patients with insufficient kidney function have been reported to develop baclofen induced

encephalopathy. There are no dosing recommendations for patients with renal dysfunction taking baclofen, but in literature appeared proposals to stop administering baclofen if the patient has glomerular filtration rate <30 mL/min/1.73m^2[46].

Sudden withdrawal of baclofen therapy may cause spasticity, pruritus, anxiety, disorientation, sedation, somnolence, and weakness[46].

Henry and Northup wrote in 2 studies about the safety and efficacy of baclofen for the treatment of muscle cramps in cirrhotic patients. They recommended a larger, randomized, placebo-controlled trial[47,56].

Elfert et al in 2016 reported a randomized placebo-controlled study about the use of baclofen in Egyptian cirrhotic patients with muscle cramps. 100 cirrhotic patients were enrolled in this study, 50 patients were treated with 30 mg baclofen/day 3 months (baclofen 10 mg tablet was administered orally, increased by 10 mg each week - baclofen therapy needs gradual titration) and 50 patients received placebo. After 3 months of baclofen therapy, muscle cramps disappeared completely in 72%, reduced in 20%, and there was no change in 8% of patients. In the placebo group there were no significant changes in the frequency, severity, and duration of muscle cramps. Mild side effects were reported such as dizziness, nausea and constipation[5].

Methocarbamol

Methocarbamol is a centrally acting muscle relaxant (antispasmodic agent). The mechanism of action is unknown but maybe it acts by depressing the general central nervous system. It is quickly and completely absorbed after oral administration. Methocarbamol is metabolized by dealkylation, hydroxylation and conjugation. The remaining unchanged methocarbamol and all metabolites are excreted in the urine. It has some special precautions such as the use in geriatrics, liver and renal impairment: literature recommends the use of lower initial doses and the gradually increase as needed or tolerated. Adverse effects can be drowsiness, dizziness, lightheadedness (clinical pearls: it may change the color of urine to brown, black or green)[45].

Abd - Elsalam et al reported in 2019 their results after performing a randomized, placebo - controlled, double - blinded trial about the use of methocarbamol for muscle cramps in cirrhotic patients. 100 patients were enrolled in the study. Group 1 (drug group): 50 patients received methocarbamol 500 mg twice daily for 1 month. Group 2 (placebo group): 50 participants received a placebo dose twice daily for 1 month. The pain score improved significantly from 6.52 ± 1.29 to 0.66 ± 1.18 ($p<0.001$). Frequency of muscle cramps decreased significantly from 11 ± 4 at baseline to 0.5 ± 1 per week ($p<0.001$). The duration of muscle cramps decreased from 4.22 ± 1.55 minutes to 0.71 ± 1.06 minutes after treatment ($p<0.001$). A few side effects were observed: dry mouth, drowsiness (in the methocarbamol group in comparison with the placebo group). Two weeks after the withdrawal of therapy, the frequency and severity of the muscle cramps returned (without a significant difference between the two groups)[48].

Orphenadrine

Orphenadrine citrate is an analog of diphenhydramine. It is used to treat muscle spasm associated with acute painful musculoskeletal conditions. Orphenadrine indirectly relieves muscle pain through central atropine - like effects and it has some euphorigenic and analgesic characteristics. It



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undergoes extensive hepatic metabolism through the CYP450 enzyme system. Patients may experience palpitations and tachycardia, so, caution must be taken for patients with heart failure, tachycardia or cardiac arrhythmias. The use of orphenadrine is not recommended in the elderly (because of the anticholinergic side – effects). Common side effects are constipation, urinary retention and confusion[45].

In 2018, Abd – Elsalam et al studied the safety and efficacy of orphenadrine in the treatment of muscle cramps in patients with liver cirrhosis. 30 patients were enrolled in this study, 15 patients in the Group 1 were treated with 100 mg orphenadrine twice daily for 1 month and 15 patients in the Group 2 received calcium carbonate 500 mg twice daily for 1 month. After the treatment with orphenadrine for 1 month the frequency of muscle cramps decreased significantly to 0.6±0.74 per week compared to 12.53±6.01 at baseline ($p<0.001$). The pain score improved significantly from a score of 8/10 to 0/10 ($p<0.001$). The duration of muscle cramps decreased from 1 min to 0.1 min after treatment ($p<0.001$). The side effects were: dry mouth, drowsiness, and nausea[49].

Also Abd – Elsalam et al in 2019 reported another study about the use of orphenadrine in cirrhotic patients with muscle cramps. In this study a total of 124 patients were enrolled. Group 1 with 62 patients received a placebo tablet 100 mg twice daily for 1 month. Group 2 with also 62 patients were treated with orphenadrine 100 mg twice daily for 1 month. After the treatment, patients who were treated with orphenadrine had a significant decrease in the mean number of muscle cramps in from 11.08 ± 4.55 (median 13.0) to 0.91 ± 1.07 (median 1.00) per week ($P < 0.001$), in the mean duration also from 4.36 ± 1.24 (median 4.00) to 1.86 ± 2.25 (median 0.50) ($P <0.001$). They also presented significant improvement in the mean score of pain severity of cramps to 3.27± 3.46 (median 3.0) instead of 7.27 ± 2.38 (median 8.0) ($P < 0.001$).

The number of days until the improvement of cramps was lower in orphenadrine group (3.08 ± 1.01) in comparison to placebo group (11.66 ±8.18) (median 9.00) ($P < 0.001$). Side effects were: dry mouth in 5 patients (8.1%) ($P = 0.06$), drowsiness in 3 patients (4.8%) ($P = 0.24$), nausea in 5 patients (8.1%), and blurring of vision in 3 patients (4.8%) ($P = 0.079$)[50].

Multicenter study

Hiraoka et al performed a multicenter study in 2019. In this study 289 cirrhotic patients were questioned about the presence or absence of muscle cramps, including frequency and severity of related pain (using a visual analogue scale – VAS), cramp

Treatment	Authors and year
Vitamin E	Konikoff et al – 1991 (3,9,13) Chandok et al – 2011 (14)
Taurine	Matsuzaki et al – 1990 (15) Matsuzaki et al – 1993 (3,9,16) Yamamoto et al – 1994 (9,10) Yamamoto – 1994 (9,17) Yamamoto et al – 1994 (9,18) Yamamoto – 1996 (9,19) Alturi et al – 2013 (20) Vidot et al – 2018 (21) Jang et al – 2021 (22)
1-α hydroxy vitamin D	Okajima et al – 1994 (9,23)
Branched – chain amino acids (BCAA)	Harushige et al – 2002 (9,27) Sako et al – 2003 (28) Hidaka et al – 2013 (3,9,30)
Intravenous albumin replacement	Angeli et al – 1996 (3,9,31)
L-carnitine	Tsuda et al – 2013 (34) Nakanishi et al – 2015 (35) Hiraoka et al – 2019 (36)
Niuche-Shen-Qui-Wan (TJ-107)	Motoo et al – 1997 (9,37)
Zinc	Kugelmas – 2000 (38)
Eperisone hydrochloride	Kobayashi et al – 1992 (39)
Quinine and quinidine sulphate	Lee et al – 1991 (42)
Baclofen	Henry&Northup – 2014 (56) Henry&Northup – 2016 (47) Elfert et al – 2016 (5)
Methocarbamol	Abd – Elsalam et al – 2019 (48)
Orphenadrine	Abd – Elsalam et al – 2018 (49) Abd – Elsalam et al – 2019 (50)
Multicenter study	Hiraoka et al – 2019 (51)
Systematic reviews	Mehta&Fallon – 2013 (3) Vidot et al – 2014 (9)

Table 1. *Treatments used for muscle cramps in cirrhotic patients*



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locations, part of the day, duration, sleep disturbance, daily activity setback and being conscious of quality of life decline (this questionnaire was given again 3 or 4 months later to the patients who were treated with medication). 160 patients had muscle cramps, 82 of these patients with cramps received treatment with several types of medication, with L-carnitine (the most administered drug - 66 patients).
The authors observed that frequency, VAS, sleep disturbance, daily activity, duration of muscle cramps and being conscious of quality of life decline were ameliorated after the intervention[51].

Systematic reviews

In the literature there are 2 systematic reviews about the treatment of muscle cramps in patients with cirrhosis. Mehta&Fallon in 2013 reported about the following treatment options which they found in the literature: vitamin E, quinine sulfate, eperisone hydrochloride, taurine, branched – chain amino acids, human albumin, electrolytes and zinc[3].
Vidot et al in 2014 wrote a more detailed review. They found studies in which the following medications were used for muscle cramps in cirrhotic patients: zinc, 1 – α Hydroxy vitamin D, vitamin E, branched – chain amino acids, taurine, L – carnitine, Niuche-Shen-Qui-Wan (TJ-107), eperisone hydrochloride, intravenous albumin replacement, quinidine[9].

Discussion

Muscle cramps, also known as „charley horses" are painful tonic muscle contractions that occur in rest or sleep[52]. Firstly, Konikoff and Theodor reported about the appearance of painful muscle cramps in patients with liver cirrhosis in 1986[6].
The aim of our study was to systematically review the treatment possibilities of muscle cramps in cirrhotic patients. We found in the literature 32 articles about this subject. Mehta and Fallon in 2013 and Vidot et al in 2014 reported 2 systematic reviews in which they evaluated the treatment options of muscle cramps in cirrhosis using the articles from the literature appeared until 2014.
In our paper, we wanted to overview of the recent literature (after 2014) about new treatment options of muscle cramps is cirrhosis and to systematically review in an updated general review. This article unites the treatment experiences before and after 2014 until nowadays. This would be useful for clinicians who combat with this symptom in cirrhotic patients in their everyday practice.
The use of vitamins (vitamin E and 1 - α hydroxy vitamin D), amino acids (taurine, BCAA, L-carnitine orally and intravenous

albumin) and mixed herbal medicines (Niuche-Shen-Qui-Wan) or zinc are useful in the treatment of muscle cramps with no side effects proved by the studies (these were only case - reports with no randomization or placebo group). Well designed, double - blinded, randomised - controlled trials are needed to evaluate the real usefulness and safety of these products.

The use of medications such as eperisone hydrochloride, quinine and quinidine sulphate, baclofen, methocarbamol, orphenadrine were studied in cirrhotic patients with muscle cramps. Some of these studies were randomized and placebo - controlled.

Patients who receive quinine or quinidine sulfate sometimes develop serious side-effects[40,41]. Eperisone hydrochloride can have also adverse effects[39]. Antispasmodic agents such as methocarbamol and orphenadrine are metabolized in the liver. If there is a liver or renal impairment, literature recommends the use of lower initial doses of methocarbamol and the gradually increase, as needed or tolerated[45]. But, the studies about these 2 medications report that they are safe in liver cirrhosis with muscle cramps[48,49,50].

If the liver cirrhosis worsens, the treatment with methocarbamol and orphenadrine should be evaluated (decrease of the doses or withdrawal). Baclofen is primarily excreted by the kidneys in its unchanged form[44]. So, because of its pharmacological properties, baclofen is extremely useful and safe in cirrhotic patients with muscle cramps (proved by the studies)[56,47,5]. We recommend also the decrease of the dosage or the withdrawal of baclofen if the patient develops hepato-renal syndrome during the disease course (because of the risk of baclofen toxicity).

These medications are useful in the treatment of muscle cramps in liver cirrhosis, demonstrated by the studies in the literature, but, it needs a strict follow-up of these patients during the treatments (if the liver cirrhosis decompensates, the use of these medications for muscle cramps should be evaluated).

These case-reports and studies enrolled a small number of cirrhotic patients. Only 7 studies from the 32 detailed that the cirrhotic patients what kind of Child-Pugh score had or what was the etiology of the liver cirrhosis. It is hard to compare patients if this information is missing.

Conclusions

To the best of our knowledge, there are no concrete protocols for the treatment of muscle cramps in cirrhotic patients. Only case-reports and a few randomized placebo-controlled studies, with few numbers of patients appear in the literature.

Treatment options found in the literature now are: vitamin supplementations (vitamin E, 1-α hydroxy vitamin D), amino acid supplementations (taurine, branched-chain amino acids, L-carnitine, albumin), mixed herbal medicines (Niuche-Shen-Qui-Wan), zinc and medications (eperisone hydrochloride, quinine and quinidine sulphate, baclofen, methocarbamol, orphenadrine).

In the near future, a combination of treatments may be more useful than the use of one single supplement or medication (because these case-reports and randomized studies with small numbers of patients proved the efficacy of each product administered alone). For example, a combination of a supplement with a medication: vitamin E with baclofen, amino



acids with baclofen/ methocarbamol/ orphenadrine should be evaluated. There will be a need of randomized placebo-controlled trials in this topic with a higher number of patients.

Conflicts of interest

There are no conflicts of interest.

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