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Peripheral neuropathy in obstetrics: efficacy and safety of α-lipoic acid supplementation

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Abstract. – OBJECTIVE: Neuropathic pain during pregnancy is a common condition due to the physical changes and compression around pregnancy and childbirth that make pregnant women more prone to develop several medical conditions such as carpal tunnel syndrome, sciatica, meralgia paraesthetica and other nerve entrapment syndromes. Most of the treatments usually performed to counteract neuropathic pain are contraindicated in pregnancy so that, the management of these highly invalidating conditions remains an issue in the clinical practice. We aimed to review the efficacy and safety of alpha lipoic acid supplementation in the treatment of neuropathic pain.

DISCUSSION: Lipoic acid is a co-factor essential in the regulation of mitochondrial energy. It has been demonstrated that lipoic acid supplementation is involved in several biochemical processes and actions, exerting important antioxidant and anti-inflammatory activity and significantly improving pain and paraesthesia in patients with sciatica, carpal tunnel syndrome and diabetic neuropathy.

CONCLUSIONS: Efficacy of lipoic acid is combined with a high safety profile, making this molecule a novel candidate for the management of several diseases. Data reported so far are promising and dietary supplementation with lipoic acid seems a useful tool to contrast neuropathic pain during pregnancy.

Key Words:
Neuropathic pain, Nerve entrapment syndromes, Pregnancy, Lipoic acid.

Introduction

Neuropathic pain is common during pregnancy. Pregnant women are particularly prone to the development of neuropathies such as carpal tunnel syndrome, sciatica, meralgia paraesthetica and other nerve entrapment syndromes. There are a number of factors that make pregnant women more prone to the development of neuropathic syndromes. First and foremost, the physical changes caused by the enlargement of the uterus and the development of the foetus cause postural changes and nutation of the pelvic girdle that facilitate the development of low back pain and entrapment neuropathies. The mutation of the pelvic girdle is favoured during pregnancy also by the presence of high concentrations of relaxin, which is produced from the tenth week of gestation and causes a laxity in the joints not only in the pelvis, but also on a vertebral level, which makes pregnant women more prone to low back pain, sciatica and pelvic pain.

The data available in literature suggest there is a close relationship between low back or pelvic pain during and after pregnancy and physically demanding jobs, the presence of low back pain before pregnancy and pelvic pain during pregnancy. On the other hand, there would not appear to be any significant relationship with weight gain during pregnancy[1].

Most of the analgesic medications usually used to treat neuropathic pain are contraindicated in pregnancy, as is surgery to resolve the nerve impingement. The best approach to these often highly invalidating conditions during pregnancy, therefore, remains a matter for debate.

To restrict the administration of potentially dangerous medication, it is appropriate to intervene with rehabilitation therapies and consider administration of neuroprotectors, which are not contraindicated during pregnancy and have been seen to be efficacious in the treatment of pain and paraesthesia in peripheral neuropathies[2].

Alpha-lipoic acid (ALA), also known as thioctic acid, and its reduced form, dihydrolipoic acid (DHLA) are naturally occurring compounds with one chiral centre (Figure 1). The *R* form is the only enantiomer synthetized and used in the bio-

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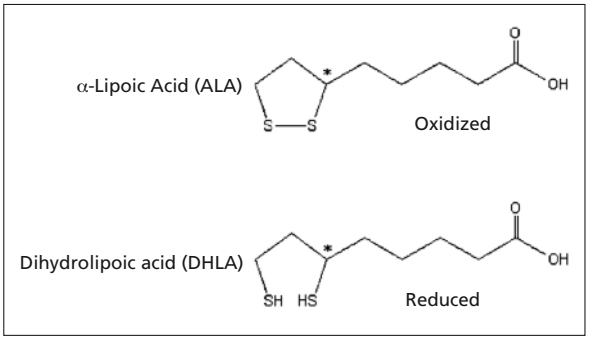

Figure 1. The oxidized and reduced forms of lipoic acid.

logical system as a co-factor essential to α-ketoacid dehydrogenase activity, playing a fundamental role in regulating mitochondrial energy metabolism. In addition to being synthesised inside the body, ALA can also be taken in through food or dietary supplements and it has been observed that, following absorption, it is involved in a number of biochemical processes and actions, rather than being used as a co-factor[3].

Several studies indicate that the intake of ALA supplements provides various therapeutic options, given its potent antioxidant and detoxifying actions, which help to overcome cardiovascular, cognitive and neuromuscular deficits and modulate various inflammatory pathways. ALA inhibits the production of vascular and intracellular adhesion molecules (VCAM-1 and ICAM-1), reduces the expression of CD4 on the surface of blood mononuclear cells, reduces the secretion of tumour necrosis factor (TNF)-α and inhibits the activation and cytotoxicity of natural killer (NK) cells[4]. In addition, given inflammation's oxidative nature and considering that the events related to it are associated with the activation of the transcription factor NF-κB, ALA's anti-inflammatory action has also been evaluated in terms of its direct inhibitory action against this factor. NF-κB plays a fundamental role in the expression of various genes involved in inflammatory response and in cell apoptosis processes. Its activation is connected to the cell's exposure to lipopolysaccharides, inflammatory cytokines (TNF-α and interleukin-1), growth factors, lymphokines, free radicals and many other physiological and non-physiological stimuli. It has been observed that treatment with ALA causes a down-regulation of NF-κB, which, being a redox-sensitive molecule, suffers its oxidative effects. In particular, acute treatments with ALA have been found to be effective both in inhibiting the degradation of the IκB, a protein that inhibits NF-κB, and in directly reducing the expression of NF-κB and of MMP-9s (matrix metalloproteinase-9), an enzyme responsible for the degradation of the extracellular matrix[5].

On the basis of these mechanisms, ALA supplementation has been seen to exert important antioxidant and anti-inflammatory activity and to significantly improve pain and paraesthesia in patients with sciatica, carpal tunnel syndrome and diabetic neuropathy[6-9].

Low Back Pain and Sciatica

Epidemiological studies have shown that 49-56% of pregnant women suffer from low back pain; in most cases the pain appears between the 5th and 7th month of pregnancy. Another interesting fact is that the pain often does not disappear after childbirth, rather it tends to become chronic.

The causes of low back pain include the increase in the biomechanical load that alters the normal load balances on the spine and the increase in the laxity of the collagen tissue, due to the action of relaxin, which acts above all on the sacroiliac joint and on the pubic symphysis, but may also affect the spine, causing articular problems also in the lumbar region.

In some cases, simple low back pain can be associated with a radicular syndrome, sciatica. Sciatica is a form of peripheral neuropathy characterised by pain in the lumbar and lumbosacral spine that irradiates to the lower limb in the sciatic nerve territory. Sciatica is the most common cause of neuropathic pain. The involvement of the sciatic nerve, due to the impingement of the sensory nerve roots in the intervertebral disk spaces (primarily L4-L5 or L5-S1), characterises the clinical presentation of the sciatica. In this case, the low back pain irradiates to the gluteus and leg. The pain caused by nerve impingement (radicular pain) is associated with numbness, tingling, weakness and movement difficulties, particularly after long periods of sitting. The most common cause is the loss of the intervertebral disks' cushioning function. The intervertebral disks are essential for absorbing the pressure produced by spine movements and their degeneration greatly reduce spinal mobility and favours friction between vertebral bodies and the crushing of the nerve roots passing through the intervertebral foramens[10,11].

In sensitive/motor radiculopathies, the clinical presentation is characterised by acute pain symptoms that often require the use of nonsteroidal

anti-inflammatory drugs (NSAIDs) or other types of painkillers. In these cases, once the acute phase has passed, or even in association with the same analgesics, it is useful to introduce substances with an antioxidant and, therefore, anti-inflammatory and neurotrophic action.

Supplementation with antioxidants and neurotrophic agents is a pathogenetic approach, as opposed to the purely symptomatic approach adopted when using analgesics, and not only reduces symptoms, but also avoids the progression of the condition to the point in which it becomes chronic.

Pathogenetic treatments can also act on the various clinical presentations of the neuropathy, which helps to resolve the sensitive, motor and autonomic problems caused by the nerve conduction deficit.

Various studies have been conducted to evaluate the effects of ALA administration in patients with sciatica. In one randomized, double-blind study, 64 patients with sciatica were treated with l-acetyl-carnitine (ALC) 1180 mg/day or ALA 600 mg/day for 60 days. ALA 600 mg/day was seen to be significantly superior to ALC in the treatment of sciatica, with an improvement in symptom scores and a reduced need for analgesia. ALA also improved nerve conduction velocity[12].

Other studies on patients with radiculopathies evaluated the combination of physical and neurotrophic and antioxidant therapies. One report on patients with radiculopathies evaluated treatment with a combination of 600 mg/day of ALA, gamma-linolenic acid and vitamins with oxygen-ozone therapy compared to oxygen-ozone therapy alone[13], whereas in another study the evaluation was conducted on patients treated with rehabilitation physiotherapy[14]. In both cases, a synergetic action was observed between the administration of ALA and the combined therapy, with significantly superior results on both symptoms and functional deficits in the groups treated with ALA.

More recent researches have also shown the positive effects of ALA administration, again with an oral dose of 600 mg/day, in patients with lower back pain[15] and in patients with cervicobrachial pain[16].

Carpal Tunnel Syndrome

Some 30-35% of pregnant women experience hand problems, which can often be attributed to carpal tunnel syndrome (CTS).

CTS is the most common canal syndrome and is caused by an increase in the pressure on the median nerve inside the carpal tunnel; it has a prevalence of 5-16% in the general population, with a female:male ratio of 3:1. Pregnant and perimenopausal women are particularly at risk, given the water retention related to the hormonal condition.

The incidence of CTS in pregnant women is 2 to 3 times higher than in women who are not pregnant.

CTS can be caused by any factor able to reduce the dimensions of the tunnel or increase the size of its content. The increase in pressure on the median nerve by the transverse ligament, particularly during the extension and flexion of the wrist and fingers, damages the local lesser circulation, causing the generation of spurious action potentials, demyelinization and axonal damage.

In the first phase of the condition (pain/irritation phase), the patient complains of tingling and burning or stabbing pain in the median nerve's distribution territory: thumb, index finger, middle finger and part of the ring finger. Pain occurs primarily at night-time, due to the lymphatic and circulatory stasis that occurs when the hand is immobile and with an intensity such as to repeatedly awaken the patient.

Subsequently, the condition may progress to the point where the patient complains of pain also during the daytime. The pain, accompanied by unpleasant paraesthesias, can irradiate to the whole of the upper limb and shoulder. The patient's quality of life suffers further because of the difficulties performing many movements and the frequent awakenings during the night. This phase is known as the paraesthesia-pain phase.

Lastly, a patient with advanced phase disease may present muscular hypotrophy of the hand's thenar eminence, with consequent deformation and paralysis and nail dystrophy (atrophy-paralysis phase).

The diagnosis of CTS is based on the presence of pain and paraesthesia in the median nerve distribution territory, the presence of nocturnal symptoms, muscle weakness of the thenar muscle and, above all, a positive Tinel's sign. This sign reveals median nerve irritation and is performed by tapping lightly on the flexor retinaculum to cause a tingling feeling in the nerve's distribution territory.

Another important test for the diagnosis of CTS is the Phalen's manoeuvre, which is per-

formed by flexing the wrist gently, as far as possible, and the holding the position until symptoms occur. In this case, the faster the numbness develops, the more advanced the condition.

Phalen's manoeuvre is defined as being positive when pain and/or paraesthesia develop in the fingers innervated by the median nerve after one minute of wrist flexion[17].

Lastly, the Durkan test involves the application of firm pressure on the palm above the nerve for a maximum of 30 seconds to cause the appearance of symptoms[18].

Median nerve decompression surgery is the treatment of election in most cases of CTS. However, the treatment of CTS in pregnant women is exclusively conservative.

As far as conservative treatment is concerned, one Cochrane review highlighted that the evidence on the efficacy of pharmacological treatments is unsatisfactory in the long term[19]. When managing pregnant CTS patients, intervention should focus on adequate ergonomic measures (braces), rehabilitation therapy and the administration of neuroprotectors.

An approach targeting the pathogenetic mechanisms of nerve damage in CTS has become more popular in recent years, as it can have a positive effect on median nerve damage and, therefore, on pain and paraesthesia symptoms and on nerve conduction deficits and the loss of hand function. More specifically, anti-oxidants and neurotrophic agents reduce symptoms and protect the nerve from further degeneration[20,21].

As far as carpal tunnel syndrome is concerned, ALA (600 mg/day) has been seen to significantly improve nerve conduction velocity and pain symptoms and paraesthesia after three months of treatment. One study on patients with carpal tunnel syndrome[8], compared the efficacy of a fixed combination of ALA 600 mg/day, EFAs 360 mg/day and vitamins B1, B2, B5, B6 and E and selenium (ALAnerv®, Alfa Wassermann) with a vitamin B complex preparation (Vit B6 150 mg, Vit B1 100 mg, Vit B12 500 g a day) for 90 days. A good reduction was observed in both symptom scores and functional deficit (Boston questionnaire) in the ALAnerv group, whereas the group treated with the vitamin B complex preparation showed a slight improvement in symptoms and a worsening in the function score. Electromyography also showed statistically significant improvements in the velocity of nerve conduction with ALAnerv®, but not with the vitamin B complex preparation.

Meralgia Paraesthetica

The entrapment of the lateral femoral cutaneous nerve (sensitive nerve) is known as meralgia paraesthetica and commonly occurs during the third trimester of pregnancy.

The symptoms of lateral femoral cutaneous nerve entrapment include loss of sensitivity, pain and dysaesthesia on the side of the thigh. Given the absence of muscular innervations, the syndrome is purely sensitive. Symptoms worsen when the subject is standing or walking. Patients complain of walking difficulties and knee instability, depending on the severity of the lesion.

The entrapment of the lateral femoral nerve usually occurs in the inguinal ligament and differential diagnosis includes lumbosacral radiculopathies and disk problems with impingement of the nerve roots in L2 and L3.

The causes of entrapment may be intrapelvic (pregnancy, abdominal tumours, uterine fibroids, diverticulosis or appendicitis) or extrapelvic (pelvic traumas, obesity or diabetic polyneuropathy).

In addition to pregnancy, the most frequent cause of femoral nerve neuropathy is diabetic amyotrophy. Nerve impingement and damage can also be caused when retractors are used during childbirth or pelvic surgery.

The treatment of meralgia paraesthetica during pregnancy can be tackled, as for other compression neuropathies (CTS, radiculopathies), with analgesics that are not contraindicated during pregnancy (paracetamol) combined with antioxidants and neurotrophic agents, such as ALA, as the pathogenetic mechanism underlying the neuropathy is common to the various forms of compression neuropathy[22].

Safe Use of ALA in Pregnancy

The use of ALA as a dietary supplement has risen greatly in recent years, and for this reason, various studies have been conducted to explore not only the efficacy, but also the safety of this substance. In humans, oral ALA supplementation at doses of up to 2400 mg/day has not shown any adverse effects. Intravenous administration of 600 mg/day has also been seen to be safe[5].

At the current time, there are currently no clinical studies available that show the safety of ALA in pregnant women; however, several studies highlight its positive effects in contrasting the weakening of human fetal membranes[23,24].

Furthermore, animal studies have shown that ALA has a protective effect on the foetus in mothers who are diabetic, alcoholic or exposed to toxic pollutants such as dioxin[25,26].

The data obtained in one recent study in animal models on the effects in foetuses whose mothers were exposed to dioxin showed that the suppression of pituitary gonadotropin biosynthesis in the foetus is mediated by the reduction in ALA levels caused by dioxin. ALA is fundamental for the production of the energy needed for gonadotropin biosynthesis. ALA deficiency is therefore responsible for the foetus' development deficit[27].

Another study on an animal model showed that the administration of ALA reduces the neuronal apoptosis that takes place in the foetus following alcohol consumption by the mother[28].

Alcohol has a neurotoxic effect as it increases oxidative stress and induces neuronal apoptosis.

Although it is appropriate to point out that the use of any dietary supplement must always be decided by the doctor based on a risk-benefit evaluation, it can be stated that use of ALA during pregnancy does not present contraindications. Furthermore, ALA supplementation plays an important role in the treatment of pain and lumbar and pelvic paraesthesia and in nerve entrapment syndromes, with an additional neuroprotective action on the foetus in conditions of increased oxidative stress (mothers who are diabetic, alcoholic or exposed to environmental pollutants).

Conclusions

Neurophatic pain is a common condition in pregnancy resulting in several medical conditions that negatively influence the quality of life of the patients. Drugs usually prescribed to counteract these medical conditions and reduce the symptoms are not indicated in pregnancy so that rehabilitation and the intake of neuroprotectors represent the best therapeutic choices. As reviewed herein, a growing body of evidence suggests that ALA significantly improve the neurophaties through a pathogenetic approach, as opposed to the purely symptomatic approach of analgesics.

A number of experimental as well as clinical trials report the usefulness and safety of ALA as a therapeutic agent for such medical conditions. The increase of oxidative stress could be one of the causes of the nerve damage responsible for neuropathies and the strong antioxidant nature of ALA combined with its anti-inflammatory activity may be the main mechanism through which this molecule exerts beneficial effects on these pathological conditions. Our review reports the importance of ALA in the treatment of peripheral nerve injuries, suggesting that its supplemetation may be appropriate even during pregnacy due to its high safety profile. However, additional long term and thorough clinical studies are needed to better explain the mechanisms of its neuroprotective effects and to further investigate the efficacy of its supplementation.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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