

# The use of oxytocin and relaxin in the treatment of refractory chronic pain with mixed characteristics (neuropathic and myofascial pain). Case report

*O uso de oxitocina e relaxina para o tratamento de dor crônica refratária de características mistas (dor neuropática e miofascial). Relato de caso*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES:** Some studies have related the use of synthetic oxytocin for the treatment of painful syndromes that relies on central and peripheral modulation mechanisms of pain. Thus, the objective of this study was to report a case of a patient with a refractory chronic pain of mixed characteristics (myofascial and neuropathic pain) who responded to the treatment with synthetic oxytocin and relaxin.

**CASE REPORT:** Female patient, 41 years old, presenting a 10-year history of right hemifacial pain after dental surgery, with neuropathic characteristics, diagnosed as atypical facial pain (atypical trigeminal neuralgia). Later, she developed pain in the right cervical region, radiating to the shoulder, with several muscle trigger points in the pericranial region, suggestive of myofascial pain. After treatment with antidepressants, neuromodulators, anesthetic blockade, capsaicin and topical lidocaine, with partial results and pain recurrence, she started treatment with intramuscular oxytocin and oral relaxin. Over the year she followed the proposed treatment, she presented light pain, greater pain-free intervals, reduced need of pain blockade, improved tolerance to physical exercise and of the local face allodynia.

**CONCLUSION:** Despite the new drugs, procedures, and protocols to treat chronic pain, the patients often present unsatisfactory outcomes. Many times, there are situations of mixed pain (neuropathic and myofascial pain) with central and peripheral sensitization, resulting in worse prognostic and refractoriness. In this case, synthetic oxytocin and relaxin presented a satisfactory response.

**Keywords:** Chronic pain, Oxytocin, Relaxin.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS:** Alguns estudos têm relacionado o uso de oxitocina sintética ao tratamento de síndromes dolorosas que se baseia em mecanismos de modulação central e periférica da dor. Assim, o objetivo deste estudo foi relatar um caso de uma paciente com dor crônica refratária de características mistas (dor neuropática e miofascial), que apresentou resposta ao tratamento com oxitocina e relaxina sintéticas.

**RELATO DO CASO:** Paciente do sexo feminino, 41 anos de idade, iniciou quadro de dor em hemiface direita há 10 anos, após uma cirurgia dentária, de características neuropáticas, diagnosticada como dor facial atípica (trigeminalgia atípica). Posteriormente, desenvolveu dor em região cervical direita, com irradiação para ombro, com múltiplos pontos-gatilho musculares em região pericraniana, sugestiva de dor miofascial. Após tratamento com antidepressivos, neuromoduladores, bloqueios anestésicos, capsaicina e lidocaína tópicas, com resultados parciais e recidiva de dor, foi submetida a tratamento com oxitocina por via intramuscular e relaxina por via oral. Durante um ano em que se submeteu ao tratamento proposto, apresentou dor leve, maiores intervalos livres de dor, diminuição da necessidade de bloqueios de dor, melhora da tolerância ao exercício físico e da alodínea local em face.

**CONCLUSÃO:** Embora se tenha novos fármacos, procedimentos e protocolos de tratamento para dores crônicas, frequentemente os pacientes apresentam resultados insatisfatórios. Muitas vezes, existem quadros de dores mistas (dor neuropática e miofascial) com sensibilização central e periférica, resultando em pior prognóstico e refratariedade. Neste caso, a oxitocina sintética e relaxina apresentaram uma resposta satisfatória.

**Descritores:** Dor crônica, Ocitocina, Relaxina.

## INTRODUCTION

Painful syndromes continue to be a major challenge today, since they encompass varied aspects, such as their manifestations and intensity in time, as well as subjective and multidimensional factors<sup>1-3</sup>. Chronic pain generates physical and emotional stress for patients and their caregivers, as well as financial and social damage to the population, and all aspects of the patient's life (physical, emotional, social and spiritual) contribute to the pain generation and the suffering manifestation<sup>4</sup>.

Chronic pain prevalence, defined in general population by World Health Organization (WHO), varies around 37% in de-

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veloped countries and around 41% in developing countries, with an average age between 45 and 65 years and a predominance in women<sup>2</sup>. In the United States, approximately \$ 89 billion is spent annually on pain handling and benefits to workers resulting from their physical disability<sup>3</sup>. Although there are new drugs, procedures and treatment protocols for chronic pain, patients often have unsatisfactory results. Some studies have related the use of synthetic oxytocin to the treatment of painful syndromes, which is based on central and peripheral modulation mechanisms of pain<sup>6</sup>.

### Oxytocin

Oxytocin is a neuropeptide synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and released into the circulation via the neurohypophysis, acting as a neuromodulator. In humans, it acts as a modulator in the limbic system (amygdala), a region related to social behaviors, and also related to pregnancy and breastfeeding, inducing uterine contractions during childbirth and during lactation<sup>6</sup>.

In non-human mammals, oxytocin receptors are then distributed across several brain regions, associated with central nervous control of stress and anxiety, as well as social behaviors (including parental care, bonding, social memory, and aggression to others)<sup>7</sup>.

There are some hypotheses that corroborate the use of oxytocin as a treatment for chronic pain. Firstly, oxytocin acts on the hypothalamic-pituitary-adrenal axis, decreasing the production of the cortisol hormone, reducing symptoms related to stress and the perception of pain intensity<sup>6</sup>. In addition, oxytocin participates in the regulation of spinal cord dorsal horn neurons, modulating the sensory process, the pain perception and also endogenous opioid receptors<sup>7-10</sup>.

### Relaxin

Human relaxin is a hormone made up of 53 amino acids produced by corpus luteum and present in the blood in the last days of the menstrual cycle and during gestation. It is known due to its effects on reproduction and pregnancy, causing relaxation in musculoskeletal tissues such as the pelvis bones and in the woman's preparation for childbirth. Its action on other targets has now been demonstrated, including cardiovascular, central and peripheral nervous system, muscle system and skin. It plays an important role in extracellular matrix remodeling, inhibiting the fibrosis process, inflammatory activity, and the myofascial nociceptors sensitization. Most of these effects have been studied in animal models, but there is positive evidence in some studies in humans, suggesting their possible therapeutic fields of application<sup>11</sup>.

This study aimed to report a case of a patient with refractory chronic pain of mixed characteristics (neuropathic and myofascial pain), who presented a response to treatment with synthetic oxytocin and relaxin.

### CASE REPORT

A female patient, 41 years old, started with pain in the right hemiface 10 years ago, after dental surgery. The pain was located

in the right hemiface, with sharp and burning characteristic, presence of local trigger points (TP) (gingival region), of intensity 8 in the numerical visual scale (NVS). The pain was continuous, without autonomic signs, without nausea, photophobia or phonophobia and in daily frequency. The patient denied a history of headaches. A few months later, she developed pain in the right cervical region, radiating to the right shoulder. At that moment, the physical examination showed pain in several pericranial and cervical muscles, besides mechanical allodynia in the face.

In the investigation, the nuclear magnetic resonance (NMR) of the encephalon and the electroneuromyography of upper limbs were normal. The cervical spine MNR revealed incipient disc protrusion between the 6<sup>th</sup> and 7<sup>th</sup> cervical vertebrae, which did not compress nerve structures. Thermography showed several myofascial TPs in right temporalis muscles, right splenius, right sternocleidomastoid and right trapezius.

As treatment, it was used venlafaxine (150mg daily), amitriptyline (50mg daily), nortriptyline (50mg daily), duloxetine (60mg daily), pregabalin (300mg daily), topiramate (100 mg daily), oxcarbazepine (900mg daily), topical capsaicin (0.025µg) and topical lidocaine at 5% local. All these drugs have been used for more than six months. Several pain blocks were performed: cervical epidural, Gasser, suprascapular nerve, pericranial and cervical muscle's TP, major and minor occipital nerves to the right, which presented partial response but recurrence of pain.

The hypothesis was atypical facial pain (atypical trigeminal neuralgia) after dental surgery and refractory chronic myofascial pain.

As an alternative, oxytocin treatment by intramuscular route and oral relaxin (oxytocin 10 intramuscular units every 3 days and relaxin - 20µg 2 times a day) was proposed. There were no adverse effects reported during the use of the drugs for one year.

During this period, prior to this treatment, she underwent 11 sessions of blockages at myofascial points and nerves. She obtained a partial response with short periods free of pain, but with recurrence. She also complained of sleep impairment, intolerance to physical exercise and impairment of daily and social activities, and maintained local allodynia in the face.

The following year, when she underwent oxytocin and relaxin treatment, she was submitted to 5 sessions of myofascial point blocks. She had milder pain, NVS=4, greater pain-free intervals, improved sleep and daily activities, and began regular physical exercises. There was also improvement of local allodynia in the face.

### DISCUSSION

With regard to chronic pain treatment, there are often features of central and peripheral sensitization, resulting in worse prognosis and refractiveness. Thus, the description of new drugs that could potentially add to the already established treatments would be of fundamental importance.

Studies have related the use of synthetic oxytocin to the treatment of chronic pain syndromes. Cechetto and Saper<sup>8</sup> described that the oxytonergic neurons of the hypothalamus paraventricular nucleus have projections to spinal cord dorsal horn neurons, regulating the sensory process and the pain perception<sup>9,10</sup>. On the other

hand, oxytocin also acts on endogenous opioid receptors. The oxytocin administration in animal models in the region of periaqueductal gray matter results in an antinociceptive effect. This effect can be reversed by naloxone application (an opioid antagonist)<sup>10</sup>. Peripherally, oxytocin modulates the inflammatory response, improving the healing of cutaneous wounds<sup>12</sup>. In acute postoperative pain, the mechanical allodynia in scar is reduced in an experimental model<sup>13</sup>.

Another hypothesis concerns the psychological effects of oxytocin since this substance improves mood symptoms, such as anxious and depressive symptoms, as well as a decrease in the pain perception<sup>14</sup>. There is also a description that low serum levels of oxytocin in healthy women would be related to decreased pain tolerance for cold and ischemic stimuli<sup>15</sup>.

The use of intranasal oxytocin in women with a chronic migraine has reduced the frequency and intensity of seizures, and it is suggested that new studies should better explore the potential of oxytocin as prophylaxis to migraine. The hypothesis is that oxytocin would inhibit painful impulses in the trigeminal nucleus and also in neurons modulated by CGRP (Calcitonin Gene Related Peptide)<sup>16,17</sup>. On the other hand, the subarachnoid administration of oxytocin induces analgesia in patients with lumbar pain<sup>18</sup>, visceral pelvic and musculoskeletal pain with positive results<sup>19,20</sup>. Specific studies with neuropathic pain such as the present report have not been described.

Regarding the route of administration, some studies have attempted to standardize the intranasal use of oxytocin for the pain treatment; however, there is no consensus on adequate doses and routes of application, with nasal, subarachnoid, intravenous and intramuscular routes being described<sup>21</sup>.

Also analyzing the relaxin use, Bani, Yue and Bigazzi<sup>11</sup> have suggested its use for chronic pain treatment, since some studies point to its role as a modulator of inflammatory activity and muscle relaxant action since it acts on receptors in muscles<sup>11</sup>. Another study has shown that fibroblasts located in muscle fascia express estrogen and relaxin sex hormone receptors. Thus, these hormones play a fundamental role in the extracellular matrix remodeling, fibrosis inhibition, inflammatory activity and muscle rigidity, and may help explain the link between hormonal factors and myofascial pain<sup>22</sup>.

On the other hand, experimental studies in rats evidenced the presence of GPCR 135 (G-protein coupled receptor) receptor in areas of the somatosensory cortex, thalamus, and limbic system. The relaxin action in these regions could be related to central pain modulation<sup>23</sup>.

Considering the patient in question, during the use of synthetic oxytocin and relaxin, there was improvement of chronic refractory pain during the period of use of these drugs, including the pain's neuropathic symptoms, translated by less need for anesthetic blocks, lighter intensity of pain, longer pain-free intervals, improved sleep and daily activities. It remains to be described

that this patient had undergone several pharmacological and invasive treatments, with partial and insufficient answers.

## CONCLUSION

In the present case, synthetic oxytocin and relaxin promoted analgesia, being a therapeutic option that has to be better studied and explored.

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