Citocinas Pró-Inflamatórias em Pacientes com Dor Neuropática Submetidos a Tratamento com Tramadol*

Proinflammatory Cytokines in Patients with Neuropathic Pain Treated with Tramadol

Durval Campos Kraychete, TSA[1], Rioko Kimiko Sakata, TSA[2], Adriana Machado Issy[3], Olívia Bacellar[4], Rogério Santos Jesus[5], Edgar M Carvalho[6]

RESUMO

Kraychete DC, Sakata RK, Issy AM, Bacellar O, Jesus RS, Carvalho EM - Citocinas Pró-Inflamatórias em Pacientes com Dor Neuropática Submetidos a Tratamento com Tramadol.

JUSTIFICATIVA E OBJETIVOS*: As citocinas pró-inflamatórias têm função importante na fisiopatologia das síndromes dolorosas neuropáticas. O objetivo desse estudo foi avaliar os níveis plasmáticos de citocinas pró-inflamatórias antes e após o tratamento com tramadol em pacientes com hérnia discal e síndrome do túnel do carpo e compará-los com indivíduos normais.*

MÉTODO*: Investigou-se 38 pacientes com dor neuropática por hérnia discal ou síndrome do túnel do carpo. Todos os pacientes foram tratados com tramadol de liberação controlada (100 mg em 12h) durante 10 dias. Realizaram-se coletas de sangue venoso (5 mL), no período matutino, antes do tratamento e no 11º dia e as amostras foram armazenadas até análise (-70ºC). Foram utilizados testes enzimáticos ELISA para dosagem de citocinas plasmáticas (TNF-α, IL-1, IL-6) e receptores sTNF-R1, (R & D Systems). Realizou-se dosagem de citocinas em soro de 10 voluntários sadios.*

RESULTADOS*: A concentração de TNF-α antes (5,8 ± 2,8 pg.mL^{-1}) foi significativamente maior que após o tramadol (4,8 ± 2,1 pg.mL^{-1}; p = 0,04, Teste Mann-Whitney). Não houve diferença significativa de IL-1β, IL-6 e sTNF-R1 antes e após o tratamento. As concentrações plasmáticas de TNF-α (sadios: 1,4 ± 0,5; pacientes com dor: 5,8 ± 2,8 pg.mL^{-1}; p = 0.01) e IL-6 (sadios: 1,2 ± 0,8; pacientes com dor: 3,5 ± 2,6 pg.mL^{-1}; p = 0,01) foram significativamente maiores nos pacientes com dor neuropática que nos voluntários, Teste de Mann-Whitney.*

CONCLUSÕES*: Nos pacientes com hérnia discal e síndrome do túnel do carpo as concentrações plasmáticas de TNF-α e IL-6 foram maiores que em voluntários sadios, não havendo diferença das concentrações de sTNF-R e IL-1β. Houve redução da concentração plasmática de TNF-α após tratamento com tramadol (100 mg em 12h), mas não de IL-6, sTNF-R e IL-1β.*

Unitermos: ANALGÉSICO: tramadol; CITOCINAS: IL-1, IL-6, TNF-α, sTNF-R; DOR, neuropática: hérnia de disco, síndrome do túnel do carpo.

SUMMARY

Kraychete DC, Sakata RK, Issy AM, Bacellar O, Jesus RS, Carvalho EM – Proinflammatory Cytokines in Patients with Neuropathic Pain Treated with Tramadol.

BACKGROUND AND METHODS: *Proinflammatory cytokines play an important role in the pathophysiology of neuropathic pain syndromes. The objective of this study was to evaluate plasma levels of proinflammatory cytokines before and after treatment with tramadol in patients with herniated intervertebral disks and carpal tunnel syndrome, and to compare them with normal individuals.*

METHODS: *Thirty-eight patients with neuropathic pain secondary to herniated intervertebral disks or carpal tunnel syndrome participated in this study. All patients were treated with controlled release tramadol (100 mg every 12 hours) for 10 days. Venous blood (5 mL) was collected in the morning, before treatment and on the 11th day, and stored (-70° C) until analysis. ELISA was used to determine the plasma levels of cytokines (TNF-α, IL-1, IL-6) and receptors sTNF-R1 (R & D Systems). Plasma levels of cytokines of 10 healthy volunteers were also determined.*

RESULTS: *The concentration of TNF-α before (5.8 ± 2.8 pg.mL-^{1}) was significantly higher than after treatment with tramadol (4.8 ± 2.1 pg.mL^{-1}; p = 0.04, Mann-Whitney test). The levels of IL-1β, IL-6, and sTNF-R1 before and after treatment with tramadol showed no significant differences. Plasma levels of TNF-α (healthy individuals: 1.4 ± 0.5; pain patients: 5.8 ± 2.8 pg.mL^{-1}; p = 0.01) and IL-6 (healthy individuals: 1.2 ± 0.8; pain patients: 3.5 ± 2.6 pg.mL^{-1}; p = 0.01) were significantly higher in patients with neuropathic pain, Mann-Whitney Test.*

CONCLUSIONS: *In patients with herniated intervertebral disks and carpal tunnel syndrome, plasma levels of TNF-α and IL-6 were higher than in healthy volunteers, while differences in the concentrations of sTNF-R and IL-1β were not observed. Plasma levels of TNF-α, but not of IL-6, sTNF-R, and IL-1β, decreased after treatment with tramadol (100 mg every 12 hours).*

Keywords: ANALGESIC: tramadol; CYTOKINES: IL-1, IL-6, TNF-α, sTNF-R; PAIN, neuropathic: herniated intervertebral disk, carpal tunnel syndrome.

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INTRODUCTION

Recent studies that have established the relationship between neuroimmune function and nociception are focused on understanding the role of cytokines, chemokines, and neurotrophins on the development and maintenance of chronic pain syndromes, especially neuropathic pain [1-3].

Experimental models in vertebrates and invertebrates also suggest the presence of modulation of synaptic activity by cytokines (IL-1β, TNF-α, IL-6, and IL-8) when they are administered by different routes (peritoneal [4], plantar [5], subcutaneous [6], neural [7], and epineural [8]), increasing the efficacy of nerve transmission, similarly to what is seen in neuropathic pain syndromes, i.e., a reduction in the nociceptive response threshold and generation of ectopic neuronal activity in sensitive afferents Aδ and C fibers [9].

TNF-α is considered the prototype proinflammatory cytokine due to its ability of direct activation of signal transducers, receptors, and channels in nociceptive afferent fibers and other cytokines [10], neurotrophic factors [11], bradykinin [12], and the neurovegetative system [13], and of changing synaptic plasticity into a state of long-term facilitation [5]. Tumor necrosis factor-α can be released by different cells, including Schwann cells, and exert its actions by interacting with type 1 TNF-α receptor (sTNF-R1), whose expression is increased after neuronal damage [4].

Several studies have emphasized the prevalence of elevated levels of proinflammatory cytokines in the CSF, plasma, or at the site of tissue damage in patients with chronic pain [1-3,15]. Those authors tried to correlate plasma levels of cytokines with pain intensity or symptom severity; however, those studies had a small population, which hinders analysis of the data. The importance of associating elevated serum levels of kinins with chronic pain would indicate a new therapeutic approach, stimulating clinical and experimental studies with antagonists of those substances.

The objective of this study was to evaluate the prevalence of elevated plasma levels of proinflammatory cytokines (IL-1β, TNF-α, IL-6) and receptors sTNF-R1 in patients with chronic muscle-skeletal and neuropathic pain and compare them with normal individuals, as well as to observe the level of those substances after treatment with tramadol hydrochloride.

METHODS

After approval by the Ethics Committee and signing of the informed consent, an exploratory, transversal study was conducted with 38 patients, ages 18 to 65 years, who had pain greater than four in the verbal numeric scale for more than three months.

Patients were admitted in the study sequentially; history and standardized general physical, orthopedic, and neurological exams aiming at pain evaluation were conducted. Patients with herniated lumbar or cervical disks, confirmed by MRI, or with carpal tunnel syndrome confirmed by electroneuromyography were included in the study. Patients with psychiatric, systemic inflammatory, viral, parasitic, bacterial, or hepatic diseases, as well as those with a history of allergies and cancer, were excluded from the study.

Pain was evaluated by a numeric scale (0 to 10) where zero represents absence of pain and ten is the worst possible pain.

Sample size was based on literature reports and on a preliminary study with 10 patients, ages between 18 and 65 years, with herniated lumbar disk (n = 7) or carpal tunnel syndrome (n = 3), with severe pain, in which TNF-α levels were 1.68 to 10.7 times greater than the standard level, which was 1.25 $pg.mL^{-1}$.

Patients were selected among those treated at the outpatient clinic.

They were treated with 100 mg of slow release tramadol hydrochloride every 12 hours for 10 days.

Before institution of the treatment and on the 11th day, 5 mL of venous blood were collected in a simple tube, without anticoagulant, centrifuged to remove the plasma, and stored at –70°C until they were analyzed. ELISA tests were used to determine the plasma levels of cytokines (TNF-α, IL-1, and IL-6) and their receptors, sTNFR1 (R & D Systems).

Exams were conducted at the Immunology Department of the Hospital Universitário Professor Edgard Santos (Salvador, Bahia, Brazil).

Plasma cytokines levels of 10 healthy individuals, ages 18 to 65 years, were also measured for comparison.

The Mann-Whitney test (abnormal distribution curve) was used to compare cytokine levels among patients and the control group and to evaluate the intragroup difference in mean cytokines levels of dichotomic categorical variables. The Wilcoxon test was used for paired analysis. Spearman's coefficient was used to determine the correlation among cytokines and clinical parameters related to continuous variables. The software SPSS version 9.0 was used, and on statistical analysis the probability of a type I error ≤ 5% ($p \leq 0.05$) was considered significant.

RESULTS

Out of 38 patients, 26 (76.3%) had herniated lumbar (n = 26) or cervical (n = 3) disks, and nine (23.7%) had carpal tunnel syndrome. Due to the size of the study sample, patients were analyzed as a single group. Patients had a mean age of 42 ± 9 years; mean weight 66 ± 11 kg; height of 163 ± 9 cm; and body mass index of 25 ± 4 $kg.m^{-2}$. As for gender, 36.8% were males and 63.2% females.

Changes in physical exam included: hypoesthesia (22 patients), decreased muscle strength (9 patients), changes in tendon reflexes (6 patients), and muscular atrophy (1 patient). Twenty-seven patients finished the study.

Pain severity was of 9 ± 2 by the numeric scale and it had a duration of 88 ± 114 months.

Plasma levels of TNF-α and IL-6 were significantly higher in patients than in the control group (Table I). The levels of

Table I – Levels of Cytokines and Receptors in the Control Group and Patients with Chronic Pain (lumbosciatalgia, cervicobrachialgia, and carpal tunnel syndrome)

Cytokines ($pg.mL^{-1}$)	Control (n = 10)	Patients (n = 38)	p
TNF-α	1.4 ± 0.5	5.8 ± 2.7 *	0.01
IL-1β	0.5 ± 0.1	0.5 ± 0.3	0.82
sTNF-R	581.0 ± 49.5	574.0 ± 42.5	0.83
IL-6	1.2 ± 0.8	3.5 ± 2.6 *	0.01

*$p \leq 0.05$; Mann Whitney test
TNF-α = tumor necrosis factor alpha; IL-1β = interleukin-1 beta; IL-6 = inteleukin-6; sTNF-R = soluble tumor necrosis factor receptor; n = number of patients

Table II – Levels of Cytokines and Receptors in Patients with Chronic Pain (lumbosciatalgia, cervicobrachialgia, and carpal tunnel syndrome) before and After Treatment with Tramadol Hydrochloride

Cytokines ($pg.mL^{-1}$)	Before (n = 27)	After (n = 27)	p
TNF-α	5.8 ± 2.8 *	4.8 ± 2.1	0.04
IL-1β	0.5 ± 0.3	0.6 ± 0.5	0.39
sTNF-R	573.9 ± 41.4	577.5 ± 41.1	0.76
IL-6	3.8 ± 2.9	4.3 ± 3.3	0.232

*$p \leq 0.05$; Mann Whitney test
TNF-α = tumor necrosis factor alpha; IL-1β = interleukin-1 beta; IL-6 = inteleukin-6; sTNF-R = soluble tumor necrosis factor receptor; n = number of patients

Table III – Correlation between Cytokines and Pain Duration and Severity

Cytokines	Pain duration (months)	Pain severity (verbal numeric scale)
TNF-α	r = 0.04; p = 0.80	r = 0.15; p = 0.35
IL-1β	r = -0.14; p = 0.40	r = -0.13; p = 0.42
RTNF-α	r = 0.08; p = 0.61	r = -0.02; p = 0.89
IL-6	r = 0.16; p = 0.35	r = 0.16; p = 0.32

Significant correlation: $p \leq 0.05$
TNF-α = tumor necrosis factor alpha; IL-1β = interleukin-1 beta; IL-6 = interleukin-6

TNF-α decreased significantly after treatment with tramadol. Pre- and post-treatment levels of IL-1β, IL-6, and sTNF-R1 were not statistically significant (Table II).
According to Spearman's coefficient, pain severity and cytokine levels were not related (Table III).

DISCUSSION

In the present study, elevated plasma levels of IL-6 and TNF-α in patients with herniated intervertebral disks (lumbar or cervical) and carpal tunnel syndrome with moderate or severe pain were observed. Authors have correlated the increased plasma levels of cytokines, pain, and disease severity with osteoarticular pain [16] and complex regional pain syndrome [17]. One study demonstrated some association between increased levels of IL-6, low levels of cortisol, and symptom severity in patients with herniated intervertebral disks [16]. In another study, peak plasma levels of IL-6 were higher at night in the group of patients with sciatic pain and cortisol levels did not increase upon awakening, favoring the idea of a circadian level for cytokines release and possible dysfunction of the hypothalamic-hypophyseal axis for cortisol production [17]. An experimental study in animals showed that the peripheral administration of cytokines induces the expression of messenger RNA (c-fos) in hypothalamic nuclei responsible for the synthesis of corticotrophin-releasing hormone, and in central noradrenergic fibers that regulate the secretion of corticotrophin-releasing hormone [18]. Thus, cytokines could activate the neuro-endocrine axis, increasing the secretion of cortisol. This would modulate the hyperalgic response of cytokines, reducing pain, and would work as a negative-feedback system. Failure of this system could explain the prolonged release and increase in the secretion of those substances in the plasma. Another possibility would be an altered immune response, with a reduction in the production of IL-10 and IL-4, as has been demonstrated in the CSF or plasma of patients with chronic pain [19,20]. Those substances modulate the excessive or prolonged release of pro-inflammatory cytokines [21], and some authors demonstrated a reduction of hyperalgia after immunotherapy with IL-10 [22].

The interaction between the local production and plasma levels of cytokines in tissue trauma has not been explained. According to one of the hypothesis, there is a bidirectional communication between the peripheral and central nervous system on the perception of aggression, i.e., activation of a nociceptive fiber and the secretion of cytokines at the site of injury would cause those substances to be released into the blood stream, as well as other hypothalamic-hypophyseal hormones, especially in acute inflammation [23]. It is intriguing that, in the acute phase, the objective of hyperalgia is to maintain the patient immobilized in bed for a speedy recovery of organic homeostasis; however, in chronic pain, this would be physiologically illogical. To justify the relationship between the systemic increase in cytokines and localized pain, one should infer that circulating cytokines would only amplify the signal of the damaged nociceptive fiber, probably through the identification of surface markers on the nerve membrane. In the present study, a correlation between pain severity and duration and plasma levels of cytokines was not observed. Fixed pain scores (mode of 10) and the size of the study population could probably be confounding factors in the statistical analysis.
Plasma levels of IL-1β and sTNF-R1 within normal limits, different than the results reported by other authors [1,20] for neuropathic pain, could be explained by differences in the release sequence of those substances, internalization of the specific cytokine-receptor complex, modulation of cytokines secretion by other neuromediators, lack of proportion between the amount of cytokines and receptors, differences in genetic constitution, or failure in transduction signal mechanisms [24].
Treatment of osteomuscular and neuropathic pain involves the use of opioids, anticonvulsants, and antidepressants [25,26]. Tramadol exerts its actions in opioid and monoaminergic receptors, with therapeutic possibilities and advantages related with its low toxicity and addictive potential, and its side effects are well-tolerated [27]. Since this was an exploratory, transversal study and not a clinical assay, assumptions on the role of tramadol on the immune system and pain transmission cannot be made; however, the results obtained with tramadol favor the idea that it can be used in future clinical studies. Since this study did not have a placebo-controlled group, it is possible that pain relief was not promoted only by the use of tramadol; some of this effect could be due to the natural evolution of the disease.
It can be concluded that in patients with herniated intervertebral disks and carpal tunnel syndrome, plasma levels of TNF-α and IL-6 were higher than in normal individuals, while those of sTNF-R and IL-1β showed no differences. Plasma levels of TNF-α decreased after treatment with tramadol (100 mg every 12 hours), but not those of IL-6, sTNF-R, and IL-1β. Further studies are necessary to evaluate the relationship between plasma levels of proinflammatory cytokines and pain severity, activities of daily life, psychological profile, physical incapacity, prognosis, and response to treatment. This could validate cytokines as possible markers in the evalua-

tion and measurement of chronic pain. Two causes of chronic pain were studied; therefore, there can be differences in the plasma levels of cytokines. Treatment of chronic pain is difficult and often frustrating. The discovery of new inhibitors or modulators of the production of cytokines represents a new possibility of clinical treatment, since current treatment options are limited.

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RESUMEN

Kraychete DC, Sakata RK, Issy AM, Bacellar O, Jesus RS, Carvalho EM - Interleucinas Proinflamatorias en Pacientes con Dolor Neuropático Sometidos a Tratamiento con Tramadol.

JUSTIFICATIVA Y OBJETIVOS*: Las interleucinas proinflamatorias tienen una función importante en la fisiopatología de los síndromes dolorosos neuropáticos. El objetivo de este estudio, fue evaluar los niveles plasmáticos de interleucinas proinflamatorias antes y después del tratamiento con tramadol en pacientes con hernia de disco y síndrome del túnel del carpo, y compararlos con individuos normales.*

MÉTODO*: Se investigaron 38 pacientes con dolor neuropático por hernia de disco o síndrome del túnel del carpo. Todos los pacientes fueron tratados con tramadol de liberación controlada (100 mg en 12h) durante 10 días. Se realizaron muestras de sangre venosa (5 mL), por la mañana, antes del tratamiento y en el 11º día, y las mismas se almacenaron para ser analizadas (-70ºC). Se utilizaron test enzimáticos ELISA para la dosificación de las interleucinas plasmáticas (TNF-α, IL-1, IL-6) y receptores sTNF-R1, (R & D Systems). Se realizó la dosificación de interleucinas en suero de 10 voluntarios sanos.*

RESULTADOS*: La concentración de TNF-α antes (5,8 ± 2,8 pg.mL^{-1}) fue significativamente mayor que después del tramadol (4,8 ± 2,1 pg.mL^{-1}; p = 0,04, Test de Mann-Whitney). No hubo diferencia significativa de IL-1β, IL-6 y sTNF-R1 antes y después del tratamiento. Las concentraciones plasmáticas de TNF-α (sanos: 1,4 ± 0,5; pacientes con dolor: 5,8 ± 2,8 pg.mL^{-1}; p = 0.01) y IL-6 (sanos: 1,2 ± 0,8; pacientes con dolor: 3.5 ± 2,6 pg.mL^{-1}; p = 0,01) fueron significativamente mayores en los pacientes con dolor neuropático que en los voluntarios, test de Mann-Whitney.*

CONCLUSIONES*: En los pacientes con hernia discal y síndrome del túnel del carpo, las concentraciones plasmáticas de TNF-α y IL-6, fueron más elevadas que en los voluntarios sanos, no habiendo ninguna diferencia en las concentraciones de sTNF-R y IL-1β. Hubo una reducción de la concentración plasmática de TNF-α; después del tratamiento con tramadol (100 mg en 12h), pero no de IL-6 sTNF-R y IL-1β.*