Peripheral Oxidative Stress Blood Markers in Patients With Chronic Back or Neck Pain Treated With High-Velocity, Low-Amplitude Manipulation

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Abstract

Objective: The purpose of this study was to investigate oxidative-stress parameters in individuals with chronic neck or back pain after 5 weeks of treatment with high-velocity, low-amplitude (HVLA) spinal manipulation.

Methods: Twenty-three individuals aged 38.2 ± 11.7 years with nonspecific chronic neck or back pain verified by the Brazilian Portuguese version of the Chronic Pain Grade, with a sedentary lifestyle, no comorbidities, and not in adjuvant therapy, underwent treatment with HVLA chiropractic manipulation twice weekly for 5 weeks. Therapeutic procedures were carried out by an experienced chiropractor. Blood samples were assessed before and after treatment to determine the activities of the antioxidant enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), and the levels of nitric oxide metabolites and lipid hydroperoxides. These blood markers were analyzed by paired Student *t* test. Differences were considered statistically significant, when P was $<.05$.

Results: There was no change in catalase but an increase in SOD (0.35 ± 0.03 U SOD per milligram of protein vs 0.44 ± 0.04 U SOD per milligram of protein; $P < .05$) and GPx (7.91 ± 0.61 nmol/min per milligram of protein vs 14.07 ± 1.07 nmol/min per milligram of protein; $P < .001$) activities after the treatment. The nitric oxide metabolites and the lipid hydroperoxides did not change after treatment.

Conclusion: High-velocity, low-amplitude spinal manipulation twice weekly for 5 weeks increases the SOD and GPx activities. Previous studies have shown a relationship between pain and oxidative and nitrosative parameters; thus, it is possible that changes in these enzymes might be related to the analgesic effect of HVLA spinal manipulation. (J Manipulative Physiol Ther 2015;38:119-129)

Key Indexing Terms: *Antioxidant Enzymes; Oxidative Stress; Manipulation; Spinal; Manual Therapy; Chiropractic*

The physiologic effects of vertebral manipulation may result from its effect on the flow of information to the central nervous system.[1,2] It is suggested that the spinal biomechanical dysfunction known as vertebral subluxation disturbs the neurologic function by sensitizing paraspinal sensory afferents, especially the proprioceptors and nociceptors in joints and muscles.[3-6] This sensitization possibly leads to plastic changes in cells of the central nervous system.[6] On the other hand, high-velocity, low-amplitude (HVLA) spinal manipulation supposedly alters the central sensory processing by favoring a nociceptive modulation due to low-frequency stimulation of mechanonociceptors of paraspinal tissues, which contributes to analgesia.[4] This central modulation may also influence muscle and visceral reflex responses.[1,2,6]

The peripheral sensitization after activation of nociceptors and the subsequent central sensitization are associated with neuronal excitability and the presence of pronociceptive molecules locally.[7,8] In pain conditions, there is an increase in neural activity due to neuronal excitability, with more utilization of metabolic substrates and increased production of reactive oxygen and nitrogen species (RS).[9,10] RS, which include free radicals and peroxides, are normally formed in the cell respiration process and play an important role in both physiologic and pathologic conditions.[11]

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At moderate concentrations, the RS may act as important physiologic regulators in intracellular signaling pathways.[12,13] In the development of persistent pain states, as occurs in nerve injury or inflammatory insult, the increase in RS seems to be essential not only for the induction but also for the maintenance of central sensitization in the spinal cord.[13-16] It is thought that hydrogen peroxide (H_2O_2), nitric oxide (NO), and superoxide are the main RS involved in the central sensitization process.[17]

An overwhelming production of reactive oxygen species can generate oxidative stress, leading to deleterious effects on cellular function.[18] Oxidative stress occurs as a result of an imbalance between increased production and/or reduced degradation of oxygen reactive species. It may lead to damage to lipids, protein, and DNA.[18] To counteract reactive oxygen species–induced cell damage, biological systems have evolved endogenous mechanisms to protect themselves in normal physiologic conditions.[19] The cellular antioxidant mechanisms involve nonenzymatic compounds and enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx).[19,20] Superoxide dismutase is specific to superoxide-radical detoxification. Superoxide dismutase can rapidly dismutate the superoxide radical, yielding H_2O_2 and oxygen.[21] Hydrogen peroxide is a diffusible reactive oxygen species that contributes to the development of pathologic pain states, not only by generating harmful reactive species but also by modulating synaptic plasticity.[22] The presence of H_2O_2 apparently affects the release of intracellular calcium, leading to neuronal sensitization and pronociceptive patterns in interneurons in the spinal cord dorsal horn.[15] Catalase activity, in turn, converts H_2O_2 to water.[23] Furthermore, GPx is an important enzymatic mechanism for the disposal of peroxides, producing water or alcohol and reduced glutathione.[24]

Nitric oxide may react with the superoxide radical and form peroxynitrite, a very deleterious nitrogen species, which may lead to lipid and protein peroxidation and damage.[17] In addition, NO has a modulatory role in pain states at both the central and peripheral levels.[25,26] Nitric oxide has been implicated in synaptic plasticity and multiple mechanisms involving central sensitization.[26] The involvement of NO in peripheral nociception is corroborated by data demonstrating the local release of NO by an inflammatory stimulus.[27] Nitric oxide plays a controversial role in pain modulation, that is, NO can mediate nociception or induce an antinociceptive effect.[26] The modulatory effect of NO may be related to neuronal excitability.[25]

In a previous study, we demonstrated a possible correlation between HVLA manipulation and oxidative-stress parameters. An increase in systemic catalase activity was demonstrated after 6 sessions of HVLA manipulation in 2 weeks of treatment.[28] Glutathione peroxidase activity, in turn, seemed to require a longer period of treatment (>2 weeks) because only a tendency to increased activity was found in the period considered.[29] These results led us to hypothesize that the effects of HVLA spinal manipulation on antioxidant activity may depend on the treatment period. Therefore, to provide more information about this hypothesis, the purpose of this study was to assess RS in blood of patients with nonspecific chronic neck or back pain treated by HVLA spinal manipulation for 5 weeks, twice a week, to analyze the activity of the antioxidant enzymes SOD, catalase and GPx, the levels of NO metabolites, and the formation of lipid hydroperoxides (LOOHs), which are formed by the action of reactive oxygen species on polyunsaturated fatty acids,[30] in the blood of the patients before and after the treatment.

Methods

Subjects

This study selected individuals with nonspecific[31] chronic neck or back pain as described by Guzman et al[32] and Lawrence et al,[33] respectively. The criteria for inclusion in the study were symptoms must be present for at least 90 days[34] and have an average intensity greater than 2 of 10 on a visual numerical pain scale.[35] The exclusion criteria were symptoms related to serious pathologies such as malignancy, infection, inflammatory disorder, or fracture. Patients were also excluded, when there were signs of lumbar or cervical spinal cord compromise or radiculopathy and/or a history of neck or back surgery. In addition, subjects were only eligible for trial inclusion if spinal manipulation was an appropriate therapy for their condition. The subjects had to be nonsmokers, not be on adjuvant therapy, and have a sedentary lifestyle because exercise can influence the biochemical parameters studied.[36,37]

Experimental Procedures

Fifty subjects (18-60 years old) with chronic neck pain or back pain were recruited through advertisements in the local newspapers of Vale dos Sinos (free distribution, 13 000 copies, May-July 2012; Jornal Bem Estar) and advertisements in public agencies (Agência do Sistema Nacional de Emprego e Fundação Gaúcha do Trabalho e Ação Social, June 2011-2012; and City Hall of Novo Hamburgo, August-December 2012). Each volunteer was identified by a code during the selection process; the same code was subsequently used to identify the records and blood samples. An inclusion/exclusion questionnaire was administered, and the history and a physical examination were used to screen the participants. The frequency, intensity, and disability of the symptoms were assessed by the Brazilian Portuguese version of the Chronic Pain Grade (CPG-Br), an adapted and validated version of the original graded chronic pain scale from Von Korff et al.[38,39] The CPG-Br evaluates self-perception of pain. The scale has 7 questions that assess pain intensity and disability. Six questions request numerical scores ranging from 0 to 10, including the pain intensity at the moment, in the worst phase, and the average pain intensity. An additional question