

**Areas of Capsaicin-Induced Secondary Hyperalgesia and Alloodynia Are Reduced by a Single Chiropractic Adjustment: A Preliminary Study**

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**ABSTRACT**

**Introduction:** The aim of the study was to investigate the hypoalgesic effects of a single spinal manipulation treatment on acute inflammatory reactions and pain induced by cutaneous application of capsaicin.

**Methods:** Twenty healthy subjects participated in the experiment, which consisted of 2 sessions. In both sessions, following control measurements, topical capsaicin was applied to the right or left forearm to induce cutaneous inflammatory reactions. The cream was removed after 20 minutes. Then subjects received either spinal manipulation treatment (SMT) or “nonspinal manipulation treatment” (N-SMT), respectively. In control as well as pretreatment and posttreatment intervals, the following tests were performed: measurement of the areas of mechanical hyperalgesia and stroking allodynia, assessment of spontaneous pain, and measurement of blood flow.

**Results:** The results confirmed that topical capsaicin induced inflammatory reactions based on occurrence of hyperalgesia and allodynia, augmented pain perception, and increased blood flow following capsaicin application compared with the control session. When compared with N-SMT, spontaneous pain was rated significantly lower post-SMT ($P < .014$). In addition, areas of both secondary hyperalgesia and allodynia decreased after SMT (hyperalgesia: $P < .007$; allodynia: $P < .003$). However, there was no significant treatment effect for local blood flow.

**Conclusion:** These results suggest hypoalgesic effects following a single SMT. As local vascular parameter was not affected by the single SMT, the hypoalgesic effects appear to be due to central mechanisms. (*J Manipulative Physiol Ther 2004;27:381-7*)

**Key Indexing Terms:** Chiropractic Manipulation; Hyperalgesia; Allodynia; Pain

**INTRODUCTION**

Numerous studies have investigated the basic mechanisms underlying spinal manipulation treatment (SMT) on pain and inflammatory reactions. Vernon et al demonstrated that the pain-relieving effect of manipulation is partly due to a short-term increase of beta-endorphin levels. Subsequent studies failed to replicate these findings while demonstrating hypoalgesic effects of SMT. Furthermore, plasma cortisol and adrenocorticotropic hormone (ACTH) levels did not differ pre-SMT and post-SMT and also when compared with sham treatment. Salivary cortisol level was also shown to remain constant following SMT.

Using visual analog scales, menstrual distress questionnaire, and prostaglandin plasma levels, Kokjohn et al demonstrated in menstruating women that both pain and menstrual distress were significantly reduced following SMT. In this study, the authors also showed a significant reduction of prostaglandin plasma level in the sham group, indicating that a placebo effect was associated with a single sham intervention.

The conflicting results described above clearly indicate that further studies are needed to investigate the physiological mechanisms underlying the effects of spinal manipulation on pain perception and inflammatory reactions. In all recent
Fig 1. An overview of the experimental procedure. SMT, spinal manipulation treatment; N-SMT, nonspinal manipulation treatment.

studies, either patients or healthy volunteers were tested. However, SMT has not been examined in experimental models of human pain/inflammation. Among such models that have been successfully applied to induce inflammatory reactions and pain is the intradermal or topical application of capsaicin, the active ingredient of chili pepper. This technique induces a controlled neurogenic inflammation that allows repetitive and gradual assessment of both sensory and local vascular changes. Capsaicin predominantly activates nerve endings of unmyelinated nociceptive afferents. It causes neuropeptide release (such as substance P), resulting in the development of many signs of acute inflammation, eg, hyperalgesia (an increased response to previously noxious stimuli) and allodynia (pain perception induced by innocuous stimuli), vasodilation, increased blood flow, and elevated skin temperature.16,17

The aim of the study was to investigate the hypoalgesic effects of a single SMT on acute inflammatory reactions and pain induced by capsaicin. These effects were assessed by measuring both sensory (allodynia, hyperalgesia, spontaneous pain intensity) and local vascular parameters (blood flow). Long et al that patients receiving prior SMT would not influence the patient’s recognition of the treatment. To not bias the subjects, treatments were explained in a broad sense only. Prior to participation, all volunteers signed an informed consent form. The study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects (Edinburgh amendment). The proposal was approved by the Institutional Review Board of Cleveland Chiropractic College, Los Angeles Campus.

Subjects were instructed not to take drugs 7 days prior to the experiment; in addition, they were asked not to drink caffeine or alcohol-containing beverages within 8 hours prior to the experiment. As we were interested in the response to a single SMT, subjects were also instructed not to receive chiropractic treatment within 30 days prior to the experiment.

Experimental Protocol

Subjects participated in 2 experimental sessions that were separated by at least 7 days. In each session (duration 60 minutes), subjects received either spinal manipulation treatment or a “nonspinal manipulation treatment” (N-SMT), respectively. The order of the 2 sessions was randomized across all participants. Randomization was performed using a computer-generated list that ensured a 1:1 allocation ratio. Only the treating doctor was aware of the randomization, and the investigator was blind to the applied treatment. Both the treating doctor and the investigator were not informed of the expected outcomes of the treatments.

To induce cutaneous inflammatory reactions, capsaicin cream was applied in each session to a premarked area randomized either to the right or left forearm, respectively. The cream was removed after 20 minutes using a swab. To
assure that the premarked area was not sensitized before the capsaicin application, a control session of 8 minutes duration was performed with the following tests: measurement of both the areas of stroking allodynia and hyperalgesia (in both primary [application site] and secondary areas [outside the application site]) and assessment of the spontaneous pain. In addition, a control session was performed only to measure the blood flow for a duration of 2 minutes (in both primary [application site] and secondary areas [2 cm from the application site]). Following control measurements, capsaicin cream was applied. After its removal, the measurements were repeated. Subsequently, subjects received SMT or N-SMT (approximately 15 minutes), respectively. Immediately after the SMT/N-SMT session, the same parameters were measured again (for graphical overview of the protocol, see Fig 1).

Capsaicin
Capsaicin (Sigma/Aldrich, Inc, St. Louis, MO) was dissolved in polysorbate 80 and mixed with a moisturising cream to reach a final concentration of 1%. The cream (1.5 g) was applied to an area of 4 × 4 cm (primary area: 16 cm²) at the right or left forearm.¹³ To minimize evaporation/increase penetration, the cream was applied for 20 minutes under occlusion with Tegaderm (3M, St. Paul, Minn).

Areas of Stroking Allodynia and Mechanical Hyperalgesia
To determine the areas of allodynia and hyperalgesia, 6 vectors (separated by 60°) of 6 cm length originating from the midpoint of application were marked on the forearm before the experiment started.¹³ The area of allodynia was tested by a swab stroked on the skin from the periphery along the vector in defined (1 cm) steps toward the center of capsaicin application until the subject reported pain. Distances between these points and the midpoint of application area were recorded. The area of mechanical hyperalgesia was tested using a von Frey hair¹⁹ (20.9 g) (Touch-Test Sensory Evaluator, Stoelting, Ill), which was punctuated on the skin in the same manner as described for stroking allodynia.

Spontaneous Pain Intensity
Subjects rated the intensity of spontaneous pain induced by capsaicin using a visual analogue scale (VAS) 10 cm in length (left-hand end: 0 = no pain; right-hand end: 10 = intolerable pain).

Blood Flow
Capillary blood flow was measured using a laser Doppler flowmeter (Moor Instruments, MULTI 2, Laser Doppler, Perfusion Monitor, United Kingdom) with 2 probes. One probe was placed in the center of the capsaicin application area and the second probe was positioned 2 cm from the edge of the application site, ie, 4 cm from the center. Measurements of blood flow were performed for 2 minutes. For statistical analysis, the mean values during the 2-minute recording were used.

Spinal Manipulation Treatment/Nonspinal Manipulation Treatment
All chiropractic treatments were performed by the same chiropractor. SMT consisted of a short-lever, prestressed, high-velocity, low-amplitude sustained thrust and was applied at areas of vertebral subluxation in the thoracic spine.²⁰ Methods of determining areas of vertebral subluxation in this study included assessment for altered function of spinal motion segment by means of motion and static palpation. Patients received treatment in various postures (eg, seated, side posture, etc.) and at 1 or more spinal motion segments as determined by the chiropractor’s interpretation of palpation findings (not particularly at the level pertaining to the capsaicin stimulation).

The nonspinal treatment involved the same interaction between the chiropractor and the subjects as in the SMT treatment. It reproduced the manual contact and setting procedure used in the treatment but without the actual adjustment. Vicenzino et al²¹,²² applied a similar method as a placebo condition. A similar sham treatment was applied in another study where the subjects received only light physical contact (touch) at specific areas on the spine by the investigator. In chiropractic literature, as in the acupuncture studies,²³ there is controversy as to what exactly constitutes an ideal sham or placebo and also that further studies are needed to refine the placebo protocol to minimize specific effects while still maintaining blinding.²⁴

Table 1. Mean values of blood flow inside and outside the application area

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>SEM</th>
<th>M</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean values of blood flow in the application area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>30.8</td>
<td>2.9</td>
<td>Control</td>
<td>22.2</td>
</tr>
<tr>
<td>Pre-SMT</td>
<td>181</td>
<td>15.7</td>
<td>Pre-N-SMT</td>
<td>145.7</td>
</tr>
<tr>
<td>Post-SMT</td>
<td>211.5</td>
<td>14.0</td>
<td>Post-N-SMT</td>
<td>198.3</td>
</tr>
<tr>
<td>Mean values of blood flow outside the application area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>40.7</td>
<td>6.0</td>
<td>Control</td>
<td>33.8</td>
</tr>
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<td>Pre-SMT</td>
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<td>Pre-N-SMT</td>
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</tr>
<tr>
<td>Post-SMT</td>
<td>32.7</td>
<td>5.9</td>
<td>Post-N-SMT</td>
<td>22.6</td>
</tr>
</tbody>
</table>

n = 20.
In arbitrary units, AU.
Treatment had no significant effect on blood flow.
SMT, Spinal manipulation treatment; N-SMT, nonspinal manipulation treatment; M, mean value; SEM, standard error of mean.

Statistical Analysis
For statistical analyses, SPSS for Windows was used (Statistical Package for the Social Sciences, Version 10.0,
To minimize interindividual variance, differences were calculated between measures obtained during the posttreatment and the pretreatment conditions. To investigate treatment effects, analyses of variance were employed (repeated measures design, general linear model, within-subject factors “treatment” and “measurement”); degrees of freedom were adjusted according to Greenhouse-Geisser. In addition, paired t-tests were used for comparisons between treatments. P value below .05 was defined as statistically significant.

**Fig 2.** A and B. Areas of hyperalgesia and allodynia in the control as well as pretreatment and posttreatment intervals (mean values, standard error of mean, n = 20). Both the areas of hyperalgesia and allodynia continued to increase following the nonspinal manipulation treatment (N-SMT), while the areas of hyperalgesia and allodynia significantly decreased following the spinal manipulation treatment (SMT).
Fig 3. Ratings of spontaneous pain intensity in the control as well as pretreatment and posttreatment intervals (mean values, standard error of mean, \( n = 20 \)). The pain sensation continued to increase following the nonspinal manipulation treatment (N-SMT), while it significantly decreased following the spinal manipulation treatment (SMT).

RESULTS

Induction of Inflammation Through Capsaicin

A significant increase of blood flow in the application area was observed when comparing the blood flow measurements between the control session and the session after capsaicin was applied (\( F_{1,19} = 102.6, P < .001 \)) (Table 1). In addition, the occurrence of hyperalgesia and allodynia after capsaicin application indicated that inflammatory reactions were induced (Fig 2, A and B).

Areas of Stroking Allodynia and Mechanical Hyperalgesia

The mean values of areas showed that the areas of hyperalgesia and allodynia decreased following SMT, while the opposite effect was observed after N-SMT (Fig 2, A and B). This indicated that the inflammatory reactions/effects lasted and even escalated throughout the experiment (significant effect of the factor “treatment” \( F_{2,38} = 11.86, P < .001 \); post hoc testing: area of stroking allodynia \( t = 3.37, P = .003 \), area of hyperalgesia \( t = 3.01, P = .007 \)).

Spontaneous Pain Intensity

Generally, subjects perceived the application of capsaicin cream as painful (Fig 3). In line with the results indicated above, spontaneous pain was rated lower following SMT, while it was rated as more painful after N-SMT. Statistical analysis indicated that compared with the N-SMT, intensity of spontaneous pain was rated significantly lower after SMT \( t = 2.70, df = 19, P = .014 \).

Blood Flow

While blood flow increased significantly after capsaicin application, no significant effects of the factor “treatment” were observed for blood flow (\( F_{1,19} = 1.22, P = .28 \)). That indicated that blood flow was affected by neither SMT nor N-SMT (Table 1).

DISCUSSION

As expected, topical capsaicin induced primary hyperalgesia in the application area and secondary hyperalgesia outside that area. While the local vascular parameter blood flow was not affected by a single SMT, the results indicated that sensory parameters (spontaneous pain perception and areas of both secondary hyperalgesia and allodynia) were significantly altered after spinal manipulation compared with N-SMT. These results clearly demonstrated that in contrast to the N-SMT condition, a single spinal manipulation triggered hypoalgesic effects.

In line with these findings, Glover et al.\(^25\) also reported a significant reduction of the size of pinprick pain following manipulation compared with a control group. Another study demonstrated the hypoalgesic effect of spinal manipulation on patients with acute low back pain.\(^6\) Terrett and Vernon\(^26\) reported a statistically significant increase of cutaneous pain thresholds in subjects receiving spinal manipulation compared with a control group. This finding was explained as an inhibitory effect of manipulation on spinal dorsal horn neurons.
In the present study, local blood flow was not affected by a single SMT. However, significant changes were observed on sensory parameters, supporting the hypothesis of centrally mediated effects of a single SMT. It is well known that secondary hyperalgesia appears to be due to central sensitization of the spinal dorsal horn neurons, while primary hyperalgesia is caused by nociceptor sensitization. It has also been discussed that mechanisms underlying allodynia are centrally mediated.

Our findings also confirm the view that the hypoalgesic effects of a single SMT might be due to central modulation. These effects could also be explained as a result of a stress reaction caused by spinal manipulation treatment. Nonetheless, the findings of previous studies led to inconclusive results in terms of plasma cortisol level. Other studies discussed that spinal manipulation stimulates mechanoreceptors of the spinal joints, resulting in afferent discharges and subsequently causing inhibitory reactions on the dorsal horn neurons.

Vicenzino et al demonstrated also a strong correlation between hypoalgesic and sympathoexcitatory effects, suggesting that a central control mechanism might be activated by manipulative therapy. While it is obvious that more studies are needed, previous studies as well as the present investigation (a preliminary study with a restricted study design) indicate that hypoalgesic effects of spinal manipulation are more likely mediated through central modulation.

**CONCLUSION**

The present study demonstrated hypoalgesic effects of a single spinal manipulation treatment. These effects appear to be due to central rather than peripheral mechanisms, especially as the local vascular parameter blood flow was not affected by single spinal manipulation treatment. The central effects are thought to relate to inhibitory effects in spinal dorsal horn neurons. Nevertheless, more studies are needed to investigate the central mechanisms of SMT.

**REFERENCES**