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PAIN IN EUROPE IV

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- Pain and the Individual
- Pain and the Brain
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- Pain and the Patient
- Pain and Society

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## Contents

### Reviews

Factors influencing the features of postherpetic neuralgia and outcome when treated with tricyclics  
David Bowsher 1

Disuse and deconditioning in chronic low back pain: concepts and hypotheses on contributing mechanisms  
Jeanine A. Verbunt, Henk A. Seelen, Johan W. Vlaeyen, Geert J. van de Heijden, Peter H. Heuts, Kees Pons and J. Andre Knottnerus 9

### Original Articles

Painful and non-painful neuropathy in HIV-infected patients: an analysis of somatosensory nerve function  
Claes Martin, Göran Solders, Anders Sönnerborg and Per Hansson 23

Implicit attitude towards pictures of back-stressing activities in pain-free subjects and patients with low back pain: an affective priming study  
Liesbet Geubert, Geert Crombez, Dirk Hermans and Guy Vanderstraeten 33

The treatment of complex regional pain syndrome (CRPS) involving upper extremity with continuous sensory analgesia  
Kristoslav Margić and Jelka Pirc 43

Comparison of the effect of video glasses and nitrous oxide analgesia on the perceived intensity of pain and unpleasantness evoked by dental sealing  
Bo Bensen, Ann Wenzel and Peter Svensson 49

Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation  
Peter Svensson, Timothy S. Miles, Darrin McKay and Michael C. Ridding 55
The significance of A-δ and C fibres for the perception of synthetic heat
Heinrich Fruhstorfer, Eva-Liz Harju and Ulf F. Lindblom

Experimental muscle pain provokes long-lasting alterations of thermal sensitivity in the referred pain area
B. Tuveson, U. Lindblom and H. Fruhstorfer

Induction of non-painful and painful intestinal sensations by hypertonic saline: a new human experimental model
Ashjorn M. Drewes, Liudmila Babenko, Lene Birket-Smith, Peter Funch-Jensen and Lars Arendt-Nielsen

Experimental pain by ischaemic contractions compared with pain by intramuscular infusions of adenosine and hypertonic saline
Thomas Graven-Nielsen, Ylva Jansson, Märta Segerdahl, Jens D. Kristensen, Siegfried Mense, Lars Arendt-Nielsen and Alf Sollevi

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Factors influencing the features of postherpetic neuralgia and outcome when treated with tricyclics

David Bowsher*

Pain Research Institute, Clinical Sciences Building, University Hospital Aintree, Liverpool L9 7AL, UK

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Abstract

This paper retrospectively reviews features of postherpetic neuralgia (PHN) in up to 279 personal patients in relation to treatment outcome when treated with tricyclic antidepressants (TCAs).

Factors affecting characteristics of PHN: (i) Patients with allodynia (89%) and/or burning pain (56%) have a much higher visual analogue pain intensity score than those without; (ii) Acyclovir (ACV) given for acute shingles (HZ) does not reduce the incidence of subsequent PHN, but reduces the pain intensity in PHN patients with allodynia; (iii) ACV given for acute HZ reduces the incidence of burning pain in subsequent PHN, but not of allodynia; (iv) ACV given for acute HZ reduces the incidence of clinically detectable sensory deficit in subsequent PHN.

Factors affecting outcome of TCA-treated PHN: (i) The point in time at which TCA treatment is commenced is by far the most critical factor; started between 3 and 12 months after acute HZ onset, more than two-thirds obtain pain relief (NNT = 1.8); between 13 and 24 months, two-fifths (41%) (NNT = 3.6); and more than two years, one-third (NNT = 8.3). Background and paroxysmal pain disappear earlier and are more susceptible of relief than allodynia. (ii) Twice as many (86%) of PHN patients without allodynia obtain pain relief with TCA treatment than those with (42%); (iii) the use of ACV for acute HZ more than halves the time-to-relief of PHN patients by TCAs; (iv) PHN patients with burning pain are significantly less likely to obtain pain relief with TCAs than those without (p < 0.0001).

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Keywords: Herpes zoster; Postherpetic neuralgia; Tricyclics; Antivirals

1. Introduction

The factors responsible for the development of postherpetic neuralgia (PHN) as a sequel of herpes zoster (HZ) have long engaged the attention of investigators. Many factors, such as age, have long been recognised and accepted; others such as prodromal pain (Choo et al., 1997; Whitley et al., 1998) and severity of antecedent HZ (Higa et al., 1997; Dworkin and Portenoy, 1996) have not yet reached widespread recognition; yet, others such as female gender (Bowsher, 1999; Meister et al., 1998), sensory deficit, and allodynia in HZ (Haanpää et al., 2000) have yet to gain universal acceptance; and controversy continues to rage around the role of antivirals in preventing the development of PHN (see reviews by Alpers and Lewis, 2000; Watson, 1998).

Furthermore, there are three distinct types of pain in PHN (see, e.g., Scadding, 1999):
1. Background pain, of fluctuating severity, including periods when the patient is painfree. This is the pain, which is often described as burning. As recovery occurs, this background pain is absent for progressively longer periods, usually before intensity begins to diminish (Bowsher, 1996).
2. Paroxysmal pains, which suddenly shoot through the affected area, often superimposed on the background pain. Paroxysmal pains do not occur in every case of PHN.
3. Allodynia—pain produced by a non-noxious stimulus in the affected area. Such pain, most frequently provoked by moving (dynamic) low-intensity mechanical
stimuli, occurs in some 90% of PHN patients (see below). It is usually the most distressing aspect of PHN and is frequently the last to disappear in the process of recovery.

It is doubtless because of paroxysms and allodynia ("triggering") that PHN is sometimes assimilated to trigeminal neuralgia (TGN). This is despite the fact that triggering in TGN is followed by a recognisable refractory period (Kugelberg and Lindblom, 1959) and therefore cannot exhibit progressive intensification on repetitive stimulation (sensitisation or windup), while allodynia in PHN displays no refractory period and frequently displays progressive intensification.

Rowbotham, Fields, and their colleagues have suggested that postherpetic neuralgia (PHN) may be subserved by several pathophysiological mechanisms (e.g., Rowbotham et al., 1998), while others have contested this hypothesis. Certainly, some of the features of PHN vary between cases and it is very reasonable to attribute this fact to possible differences in mechanism.

Tricyclic antidepressants (TCAs) are still the drugs of choice, in terms of effectiveness, in the treatment of PHN (see Sindrup and Jensen, 1999, who give an NNT of 2.3 to TCAs in PHN, as opposed to 2.5 for oxycodeone and 3.2 for gabapentin). Collins et al. (2000) give an NNT for TCAs in PHN of 2.1 (1.7–3.0) and for anticonvulsants 3.2 (2.4–5.0).

The aim of the present personal review is to correlate data, which have previously been presented separately and to add newer findings.

2. Material and methods

The case-sheets of 279 personal PHN patients who were referred to, and personally examined both at first referral and at follow-up by, the author at the Walton Centre, and all of whom took part to a greater or lesser extent in various research projects, and for whom adequate information for the purposes of this study was available, have been reviewed. The patients were seen over a period of about ten years, and all of them gave their consent, at the time, for the research projects in which they were involved. While most patients were available for study of features present at first interview, fewer were available for follow-up analysis: some because they were seen only once or twice, on account of living far away from the clinic, some because they were non-compliant with treatment, including those who stopped treatment because of side-effects. Hence, the total number of patients included in each table is not the same. The number of patients for whom the relevant data were available is clearly indicated in each table.

PHN is defined as pain persisting or recurring 3 or more months after the appearance of the shingles rash (Dworkin and Portenoy, 1996; Dworkin and Schmader, 2001; Max et al., 1988).

Most patients referred to my PHN clinic had been unsuccessfully taking drugs (usually conventional analgesics), prescribed by their family doctors. After confirmation of diagnosis and examination, PHN patients were prescribed amitriptyline (and, in a few cases, Na valproate as well-found not to make any difference and soon dropped) and advised to discontinue previously prescribed drugs.

Relief was defined as a >50% fall in visual analogue score (VAS) for pain intensity from the highest value recorded at initial consultation, before treatment with tricyclics (TCAs) was initiated.

Most patients completed the McGill Pain Questionnaire (Melzack, 1975). In the following, "burning" is scored as positive for patients who ticked any of the words in group 7 (hot, burning, scalding, and searing).

Mechanical allodynia was defined as pain produced by light stroking or brushing of the skin; cold allodynia as pain produced by touching the skin with a cold metal object. Quantitative sensory perception thresholds were determined as described by Semmes et al. (1960), Fruhstorfer et al. (1976), using the Somedic Thermotest equipment, and Chan et al. (1992); sensory deficit was clinically determined by comparing the affected area with its contralateral mirror-image area with respect to light touch with a camel-hair paintbrush, ability to distinguish between the head and point of a pin resting on the skin, and ability to discriminate the temperature difference between a cold metal instrument and the examiner's finger.

All data are derived from clinic visits by patients, who were seen over a period of some 10 years. Some were prescribed acyclovir (ACV) for their acute HZ by their GPs; this is taken account of in the Results below. The prescription of such treatment was entirely random, and depended on the doctor, some of whom gave it to all HZ patients, while most gave it to none.

3. Results

As the results are classified under such headings as allodynia, burning pain, etc., both outcome and the effects of various pain characteristics are considered together. All probabilities were calculated at 95% confidence.

1. Characteristics of postherpetic neuralgia
(a) Allodynia is an extremely common feature of PHN and is mostly of dynamic mechanical type (Table 1).
(b) Allodynia is commoner in older subjects (Table 2).
(c) Subjects with allodynia experience pain at two levels, background and the more severe brief allo-
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic mechanical (only)</td>
<td>60 (83)</td>
<td>134 (88)</td>
<td>194 (87)</td>
</tr>
<tr>
<td>Cold (only)</td>
<td>0</td>
<td>2 (1.3)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Dynamic mechanical + cold</td>
<td>1 (1.4)</td>
<td>1 (0.6)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>All allodynia</td>
<td>61 (85)</td>
<td>137 (91)</td>
<td>198 (89)</td>
</tr>
<tr>
<td>No allodynia</td>
<td>11 (15)</td>
<td>14 (9)</td>
<td>25 (11)</td>
</tr>
</tbody>
</table>

Thus, 196 of the 198 allodynic patients have dynamic mechanical allodynia.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With alodynia</td>
<td>Without alodynia</td>
</tr>
<tr>
<td>N</td>
<td>186</td>
<td>25</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>69.3 ± 10.0</td>
<td>61.8 ± 15.6</td>
</tr>
<tr>
<td>Median</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>Mann-Whitney p</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Allodynia</th>
<th>No allodynia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High (Alodynia)</td>
<td>Low (Background)</td>
</tr>
<tr>
<td>VAS score</td>
<td>122</td>
<td>90*</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>79.75 ± 21.5</td>
<td>41.9 ± 20.9</td>
</tr>
<tr>
<td>Median</td>
<td>86</td>
<td>40</td>
</tr>
<tr>
<td>VAS score</td>
<td>22</td>
<td>58.3 ± 25.9</td>
</tr>
</tbody>
</table>

Unpaired t test: Alodynia, High VAS v. No alodynia; p < 0.0001. Alodynia, Low VAS v. No alodynia; p = 0.007.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>VAS burning</th>
<th>VAS non-burning</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>62</td>
<td>94</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>88.4 ± 16.2</td>
<td>82.1 ± 18.3</td>
</tr>
<tr>
<td>Median</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Unpaired p</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

*These numbers are patients for whom both VAS scores and pain quality were known; they do not represent the proportions of PHN patients with burning and non-burning pain, which is 1.27:1.0.

dynamic pains, whereas subjects without allodynia feel only the former—which is, however, felt to be more severe than in allodynic subjects (Table 3).
(d) Those subjects whose pain is subjectively described as "burning" (56%) rate it as more intense than do subjects whose pain is not so described (Table 4).

Table 5

<table>
<thead>
<tr>
<th>Burning pain</th>
<th>Allodynia</th>
<th>No alodynia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alodynia</td>
<td>97 (84.3%)</td>
<td>18</td>
</tr>
<tr>
<td>No alodynia</td>
<td>75 (82.4%)</td>
<td>16</td>
</tr>
</tbody>
</table>

χ² test not significant; p = 0.08.

Table 6

<table>
<thead>
<tr>
<th></th>
<th>Number (%) with deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touch</td>
<td>31 (73%)</td>
</tr>
<tr>
<td>Sharpness</td>
<td>35 (82.5%)</td>
</tr>
<tr>
<td>Warmth</td>
<td>34 (80%)</td>
</tr>
<tr>
<td>Cold</td>
<td>30 (72.5%)</td>
</tr>
<tr>
<td>Hot pain</td>
<td>30 (71%)</td>
</tr>
</tbody>
</table>

(e) There is, however, no correlation between burning pain and the presence or absence of alodynia (Table 5).
(f) Sensory deficit was measured instrumentally in the non-scarred skin of 42 PHN patients (mean age 69.6 ± 9.6 years), 37 (87%) of whom had dynamic mechanical allodynia, and all of whom had deficits for more than one sensory modality (Table 6).

2. Effects of acyclovir treatment of acute shingles on subsequent postherpetic neuralgia

(a) A significantly larger proportion of PHN patients who had received ACV for their acute HZ did not exhibit burning as a feature of PHN (Table 7).
(b) The incidence of alodynia in PHN at presentation was not, however, reduced by ACV treatment of HZ; 83.9% of patients whose HZ had been treated with ACV had alodynia in PHN, as against 87.2% of those who had not received ACV.
(c) The intensity of pain in PHN at presentation was, however, slightly reduced in those patients who had received ACV for their PHN (Table 8).

Table 7

<table>
<thead>
<tr>
<th></th>
<th>With acyclovir</th>
<th>Without acyclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning</td>
<td>27 (24%)</td>
<td>84 (76%)</td>
</tr>
<tr>
<td>Not burning</td>
<td>35 (38%)</td>
<td>57 (62%)</td>
</tr>
</tbody>
</table>

χ² p = 0.03
Table 8

<table>
<thead>
<tr>
<th></th>
<th>ACV</th>
<th>No ACV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>VAS: Mean ± SD</td>
<td>76.3 ± 21.6</td>
<td>87.0 ± 15.4</td>
</tr>
<tr>
<td>Median</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

Percent reduction in pain intensity: 8.88.

Table 9

<table>
<thead>
<tr>
<th>Clinical sensory deficit</th>
<th>No clinical sensory deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACV</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>No ACV</td>
<td>47 (85%)</td>
</tr>
</tbody>
</table>

χ² p = 0.01

(d) The incidence of clinically evident sensory deficit was also reduced in PHN patients whose HZ had been treated with ACV (Table 9).

3. Outcome in PHN patients treated with tricyclic; effects of disease factors and ACV treatment of HZ

(i) Effects of interval between HZ onset and initiation of TCA treatment

The interval between HZ onset and initiation of tricyclic treatment is a critical factor (Table 10). There was no significant difference in age or initial pain intensity (VAS) in the two groups at the time of treatment initiation. The proportions relieved at various HZ–TCA intervals and the number needed to treat (NNT) is shown in Table 11.

(ii) Effects of ACV treatment of HZ

(a) The proportion of patients whose PHN was relieved by TCA was greatly increased when the original HZ had been treated with ACV (Table 12).

(b) The time from TCA treatment initiation to >50% fall in VAS score was significantly reduced by ACV treatment of original HZ (Table 13).

(iii) Effects of PHN features on outcome

(a) TCA-treated PHN was more likely to be relieved in patients whose pain was not characterized by a burning sensation (214 patients) (Table 14).

(b) TCA-treated PHN was more likely to be relieved in patients whose pain was not characterized by alldynia (144 patients) (Table 15).

(c) Comparing patients whose pain improved with TCA treatment with those in whom it did not improve, pain intensity (VAS) at presentation was slightly (8.8%), but not significantly, lower in the former group (Table 16).

(d) Rowbotham et al. (1998) have classified their PHN patients according to whether they exhibited allodynia only, alldynia plus clinical sensory deficit, or clinical sensory deficit only. Eighty-four of our patients had sufficient recorded information to allow classification in this way, together with a further six who had ongoing pain without either alldynia or clinically evident sensory deficit. Table 17 shows the results of this study in our patients, together with the effects of ACV treatment for HZ and TCA treatment for PHN.

Using Fisher's exact test, neither of the first two categories showed any significant difference in the relief rate between those who had and those who did not have their acute HZ treated with acyclovir. However, in the third category, 76% of those who had received acyclovir improved, as against 50% of those who did not, achieving near-significance (p = 0.06).

4. Discussion

A. Factors affecting characteristics of PHN:

(i) Overall, alldynia (overwhelmingly mechanical) occurs in the vast majority of PHN patients (Table 1). Older PHN patients (mean age 69.3) are significantly more likely to have alldynia than younger PHN patients (Table 2). The intensity of alldynic pain was enormously higher than the intensity of the background pain in PHN patients without alldynia (Table 3). But the background VAS score of the latter group was very significantly higher than the VAS score of the background pain in allodynic PHN patients (Table 3).

(ii) The presence or absence of alldynia does not correlate with the presence or absence of burning pain.

(iii) Burning pain is perceived as significantly more painful than non-burning pain (Table 4). Further-
Table 11
Proportion achieving >50% relief (VAS) by TCAs and number needed to treat

<table>
<thead>
<tr>
<th>Interval (mo) after shingles</th>
<th>3–6</th>
<th>7–12</th>
<th>13–24</th>
<th>25–36</th>
<th>All intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs started</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relieved</td>
<td>91</td>
<td>30</td>
<td>23</td>
<td>7</td>
<td>153</td>
</tr>
<tr>
<td>Not relieved</td>
<td>31</td>
<td>52</td>
<td>61</td>
<td>27</td>
<td>262</td>
</tr>
<tr>
<td>Total patients</td>
<td>122</td>
<td>82</td>
<td>88</td>
<td>34</td>
<td>285</td>
</tr>
<tr>
<td>% Improved</td>
<td>74.9%</td>
<td>57%</td>
<td>41%</td>
<td>26%</td>
<td>55.4%</td>
</tr>
<tr>
<td>NNT*</td>
<td>1.6</td>
<td>2.3</td>
<td>3.7</td>
<td>7.7</td>
<td>2.2</td>
</tr>
<tr>
<td>$\chi^2$ p =</td>
<td>0.03</td>
<td>0.7</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\chi^2$ p</td>
<td>3–6 mo. vs all other intervals (7–36 mo.), p &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–6 mo. vs 7–12 mo., p &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–12 mo. vs 13–24 mo., p &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–12 mo. vs 25–36 mo., p &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–24 mo. vs 25–36 mo., p = 0.2 NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Equalising numbers at all intervals, overall NNT = 2.72

* Using the total of placebo-treated PHN groups (30 relieved / total 238) reported by Sindrup and Jensen (1999) as control.

Table 12

<table>
<thead>
<tr>
<th></th>
<th>ACV</th>
<th>NO ACV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% fall in VAS score (N)</td>
<td>30 (68%)</td>
<td>55 (40%)</td>
</tr>
<tr>
<td>Pain not relieved (N)</td>
<td>14</td>
<td>18</td>
</tr>
</tbody>
</table>

$\chi^2$ p = 0.001

There was no significant difference in initial pain intensity (VAS) scores (85.7 ± 15.6 and 88.3 ± 15.1, respectively).

Table 13

<table>
<thead>
<tr>
<th></th>
<th>ACV</th>
<th>NO ACV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% fall in VAS score in &lt;6 mo (N)</td>
<td>17 (40%)</td>
<td>25 (18%)</td>
</tr>
<tr>
<td>Pain not relieved in &lt;6 mo (N)</td>
<td>28</td>
<td>112</td>
</tr>
</tbody>
</table>

$\chi^2$ p = 0.003

Table 14

<table>
<thead>
<tr>
<th></th>
<th>Burning pain</th>
<th>Pain not burning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>53 (44%)</td>
<td>68 (73%)</td>
</tr>
<tr>
<td>Not improved</td>
<td>68</td>
<td>25</td>
</tr>
</tbody>
</table>

$\chi^2$ p < 0.0001

Table 15

<table>
<thead>
<tr>
<th></th>
<th>Allodynia</th>
<th>No allodynia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>122</td>
<td>22</td>
</tr>
<tr>
<td>Pain improved &gt;50% (VAS)</td>
<td>51</td>
<td>19</td>
</tr>
<tr>
<td>Not improved</td>
<td>71</td>
<td>3</td>
</tr>
</tbody>
</table>

$\chi^2$ p < 0.0001

more, burning pain is perceived as more painful than allodynia. There is, however, no correlation between burning pain and the presence or absence of allodynia (Table 5).

(iv) Sensory deficit was present in all subjects in whom instrumental measurements were made (Table 6), but it could not be found in 23% of 90 patients examined clinically (see Table 9). This means that the deficit, although probably present, would have been so mild as not to be clinically detectable, as is the case in trigeminal neuralgia (Bowsher et al., 1997). The commonest deficits are for sharpness discrimination (tested by asking the patients to distinguish between the head and point of a pin resting on the skin) and warm-cold discrimination, tested by asking the patient to distinguish between a cold object such as a tuning fork or metal spoon and a warm (not hot) stimulus such as the examiner’s finger.

Table 16

<table>
<thead>
<tr>
<th>Pain intensity (VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Initial VAS:</td>
</tr>
<tr>
<td>Mean ± SD</td>
</tr>
</tbody>
</table>

Table 17

<table>
<thead>
<tr>
<th>Total</th>
<th>Improved</th>
<th>Not improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alldynia only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had ACV</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Did not have ACV</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Sensory deficit only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had ACV</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Did not have ACV</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Alldynia and sensory deficit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had ACV</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Did not have ACV</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>31</td>
</tr>
<tr>
<td>Ongoing pain; no alldynia, no deficit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had ACV</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Did not have ACV</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
B. Effects of acyclovir treatment of acute shingles on subsequent PHN

The incidence of burning pain in PHN is reduced by ACV treatment of antecedent HZ (Table 7), but the incidence of allodynia is unaffected. The intensity (VAS) of ongoing (background) pain in PHN at presentation is significantly reduced by ACV treatment of antecedent HZ (Table 8). The incidence of clinically evident sensory deficit in PHN is also reduced by ACV treatment of antecedent HZ (Table 9—see also Table 17).

C. Outcome in PHN patients treated with tricyclic; effects of disease factors and ACV treatment of HZ:

(i) The effect of the interval between HZ onset and the initiation of TCA treatment is perhaps the most critical and important factor in the treatment of PHN (Bhala et al., 1988; Bowsher, 1992). As can be seen in Tables 10 and 11, early treatment is significantly more effective than later, and the difference is considerably greater than can be accounted for by natural resolution.

It is unfortunately not known whether other drug treatments for PHN (e.g., ketamine, gabapentin) are similarly influenced by the HZ-PHN treatment interval, since the time after HZ onset at which treatment for PHN was instituted is not given in any of the published trials. It would be most interesting to know whether this effect is universal, or whether it is confined to TCAs, since it implies that the physiopathological process in PHN is a dynamic one. Recognition of the importance of this time interval in TCA treatment led to the effective prevention of PHN by pre-emptive treatment with low-dose TCA, immediately following the diagnosis of HZ in the elderly (Bowsher, 1997).

(ii) The present analysis confirms earlier findings (Bowsher, 1994) that ACV treatment of HZ increases the proportion of PHN patients whose pain is successfully relieved by TCAs (Table 12) and halves the time in which this relief occurs (Table 13). Others (Alpers and Lewis, 2000; Mondelli et al., 1996; Johnson, 2001; Ormrod and Goa, 2000) have concluded that the use of other antivirals for acute HZ also shortens the duration of PHN in those patients in whom it develops.

(iii) Table 14 shows that patients whose PHN is not characterised by burning are more likely to be relieved by TCAs than those complaining of burning sensation. Table 4 had already demonstrated that burning pain is rated as more intense than non-burning pain and Table 16 shows that pain intensity at presentation is significantly correlated to outcome with TCA treatment.

Overall, 58% of PHN patients with allodynia (irrespective of the interval between HZ onset and interval to TCA treatment initiation) was relieved by TCA treatment (56% of those not receiving ACV for acute HZ and 53.65% of those receiving it), while 81.25% of those with no allodynia had their pain relieved, following TCA treatment. Thus, the presence of allodynia militates against successful pain relief by TCAs, in confirmation of the findings of Max et al. (1987, 1991, 1992) and Sindrup and Jensen (1999).

(iv) Table 17 demonstrates that PHN can be subdivided into the categories proposed by Rowbotham et al. (1998), though not necessarily in every case. The numbers of patients included in Table 17 are very small and outcome measures may need to be revised when larger numbers become available. However, the figures suggest that ACV treatment of HZ improves the outcome of TCA treatment in PHN patients exhibiting both allodynia and clinically evident sensory deficit at presentation. This is surprising in view of the fact that, according to Table 15, non-allodynic patients are much more likely to be relieved by TCA if their HZ had been treated with ACV (Table 9), while the incidence of sensory deficit in PHN (with or without allodynia), but not of allodynia, is reduced by ACV treatment of HZ. Thus, we might expect the category “Sensory deficit without allodynia” to benefit more than those displaying both characteristics—but this is not apparently the case.

Judgement should perhaps be reserved as to whether the categories defined by Rowbotham et al. (1998) represent distinct pathophysiological varieties of PHN.

5. Conclusions

If shingles patients remain under the continuous care of a single practitioner, they should (if diagnosed early enough) be given an antiviral, and perhaps low-dose ami- or non-triptiline, as this has been shown to reduce the likelihood of PHN developing later (Bowsher, 1997). If the patient is still in pain 3 months after shingles onset, he/she should have pain intensity measured by the VAS scale (and at every follow-up visit) and be examined for: nature of pain—burning or not burning; presence or absence of allodynia; and presence or absence of sensory deficit. If the patient is referred to secondary care beyond 3 months post-HZ onset, careful note should be taken of the time interval between HZ onset and presentation, together with the features outlined in the preceding sentence.

In all cases, TCA or other (gabapentin, ketamine) treatment should be instituted immediately and progress assessed at regular (monthly) intervals. It should be noted that although amitriptyline is by far the cheapest drug recommended for treatment of PHN, it has a poor side-effect profile, and apparently takes much longer to
achieve 50% pain relief than does the much more expensive gabapentin (which has an excellent side-effect profile)—7 weeks in the case of gabapentin (Rice et al., 2001) and 20 in the case of amitriptyline.

By far the most practically significant feature is the effect on outcome of the interval between HZ onset and initiation of TCA treatment. It is very important to establish whether or not this relationship holds true for newer treatments. If it does, it emphasises the importance of early monitoring following diagnosis and initial treatment of HZ, as well as perhaps yielding further insights into the mechanisms of both HZ and PHN.

Acknowledgments

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References

Disuse and deconditioning in chronic low back pain: concepts and hypotheses on contributing mechanisms

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Abstract

For years enhancement of a patient’s level of physical fitness has been an important goal in rehabilitation treatment in chronic low back pain (CLBP), based on the hypothesis that physical deconditioning contributes to the chronicity of low back pain. However, whether this hypothesis in CLBP holds is not clear. In this paper, possible mechanisms that contribute to the development of physical deconditioning in CLBP, such as avoidance behaviour and suppressive behaviour, are discussed. The presence of both deconditioning-related physiological changes, such as muscle atrophy, changes in metabolism, osteoporosis and obesity as well as deconditioning related functional changes, such as a decrease in cardiovascular capacity, a decrease in muscle strength and impaired motor control in patients with CLBP are discussed. Results of studies on the level of physical activities in daily life (PAL) and the level of physical fitness in patients with CLBP compared to healthy controls were reviewed. In studies on PAL results that were either lower or comparable to healthy subjects were found. The presence of disuse (i.e., a decrease in the level of physical activities in daily life) in patients with CLBP was not confirmed. The inconclusive findings in the papers reviewed may partly be explained by different measurement methods used in research on PAL in chronic pain. The level of physical fitness of CLBP patients also appeared to be lower or comparable to the fitness level of healthy persons. A discriminating factor between fit and unfit patients with back pain may be the fact that fit persons more frequently are still employed, and as such may be involved more in physical activity. Lastly some suggestions are made for further research in the field of disuse and deconditioning in CLBP.

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Keywords: Chronic low back pain; Deconditioning; Disuse

1. Introduction

Pain in the musculoskeletal system is a major health problem in the industrialised countries. In 1991, 12.5% of the Dutch population consulted a health care professional for musculoskeletal pain problems, of which low back pain was the most prevalent problem (Tulder et al., 1995). Specific back pain occurs in no more than approximately 2% of all patients with back complaints (Spitzer et al., 1987). For the majority of low back patients the pathogenetic mechanism of low back pain is unknown. A relatively small percentage (up to 10%) of patients who have acute pain without a specific cause, eventually develops chronic pain. However, this group accounts for 75–90% of the societal costs of back pain (Nachemson, 1992). It is therefore important to find the reasons why low back pain becomes chronic in this subgroup of patients.

In recent years, physical disuse has been presented as one of the perpetuating factors for chronicity in theoretical research models on pain (Hasenbrinck et al., 1994; Vlaeyen et al., 1995a). Disuse, or a decreased level of physical activity in daily life, would lead to physical de-
conditioning or an extremely low level of physical fitness. For several decades, physical reconditioning has been proposed in clinical practice as a goal in the treatment of patients with chronic pain, resulting in a variety of rehabilitation programs based on reconditioning. However, inactivity has not only become a topic in chronic pain management, but also in general medicine. In 1993–1997, a large descriptive study on the physical activities in daily life of the Dutch population aged 20–64 years, showed that 21% of all participants led an inactive lifestyle (i.e., were active in moderate activities for less than half an hour per week, Schuit et al., 1999). This may give rise to the question whether the deconditioning problem in chronic pain exceeds its presence in the general population. The extent of the problem of deconditioning in chronic pain and its specific perpetuating role in chronicity are still unclear. Is physical deconditioning only a result of a decreased physical activity level in pain and is it reversible when pain disappears? Or has deconditioning a perpetuating role for pain itself?

In this paper literature on deconditioning and reconditioning in CLBP will be reviewed. Firstly, the available data on the concepts of deconditioning and reconditioning, as presented in literature, will be discussed. Secondly, the level of physical activity in daily life (PAL) in patients with CLBP will be reviewed. Thirdly, the available data on the level of physical fitness is discussed in patients with CLBP. And finally, future goals in research will be addressed.

2. Defining deconditioning and the deconditioning syndrome

As early as 1199 AD, Maimonides warned of the danger of physical inactivity: “Anyone who lives a sedentary life and does not exercise, even if he eats good foods and takes care of himself according to proper medical principles, all his days will be painful ones and his strength shall wane.” (from Buschbacher, 1996). In the 20th century, the term “disuse” was introduced. In 1946 Young published “The effects of use and disuse on nerve and muscle,” presenting his observations on the inactive human body (Young, 1946). He referred to disuse as the process of “not using the musculoskeletal system” in times of physical immobility. The changes of the human body that are the result of long-term immobility are often referred to as deconditioning. There is a wealth of physiology literature on deconditioning. Over time, the term “disuse” was also introduced in a different context. There, disuse refers to the inappropriate use of the musculoskeletal system that merely results in a change in the quality of movement. In the case of chronic pain, for example, muscles are not optimally co-ordinated during movement, which leads to inefficient usage of an asymmetrical gait. Main and Watson (1996) introduced the term “guarded movements” abnormalities in muscle action in CLBP patients during physical activity.

In 1984, the “disuse syndrome” is mentioned in literature for the first time. Bortz (1984) focused on the consequences of long-term inactivity and proposed to consider disuse as a syndrome, rather than a symptom. The identifying characteristics of the disuse syndrome, as quoted by Bortz, were multidimensional: cardiovascular vulnerability, obesity, musculoskeletal fragility, depression, and premature ageing. The focus was on the physical consequences of inactivity. The psychological consequences were considered to be caused mainly by social deprivation.

In Bortz’s concept of the disuse syndrome, the reason for inactive behaviour was not considered. He wrote his paper from a physiological point of view. The main theme of his paper was: What will happen to healthy persons if they are extremely inactive? In clinical practice, however, a disuse syndrome will seldom appear as a separate condition. There is nearly always a specific reason for depriving oneself from social and physical activities. The causes for such inactive behaviour can be of a somatic or a psychological nature. For most people, it is probably a health problem with a great impact on their well-being. Especially the psychological consequences of this health problem will confound those of inactivity. Evaluating aspects of the disuse syndrome in healthy persons in an experimental setting is much easier than evaluating the syndrome in patients suffering from chronic pain. In patients with chronic pain, inactivity can indeed result in psychological problems, according to Bortz’s concept. But above all, the impact of pain and the problems in coping with pain in daily life of CLBP patients seem more likely to provoke psychological distress than inactivity. It is difficult to distinguish the disuse syndrome, as presented by Bortz, from the chronic low back pain syndrome.

In contrast to Bortz’s view on the disuse syndrome, which focuses on human (in)activity in general and does not specifically address CLBP patients, Mayer and Gatchel (1988) focused in particular on the consequences of long-term inactivity in patients with musculoskeletal pain. They introduced the term “de-conditioning syndrome” for patients with pain who also suffer from both physiological and psychological loss of physical fitness (1988). Among the components of physiological deconditioning they also included muscle atrophy, decreased cardiovascular endurance, decreased neuromuscular co-ordination, and a decreased ability to perform complicated repetitive tasks. They referred to psychological deconditioning as a set of behavioural and psychological problems that occur in response to chronic pain and the patient’s attempt to cope with that pain. According to Mayer and Gatchel, psychological deconditioning included the response to both pain and inactivity. In the final stage, a deconditioning syndrome is the result of the interaction between physical and psychological deconditioning.
The discrepancy between the concepts of Bortz on the one hand and Mayer and Gatchel on the other, is most prominent in the psychological consequences of inactivity. Bortz described the psychological consequences in the syndrome as a result of inactivity, whereas Mayer and Gatchel described psychological deconditioning as a reaction to both pain and inactivity and not as solely the result of inactivity. In the concept of Mayer and Gatchel, the deconditioning syndrome in chronic pain covers almost the entire concept of the chronic pain syndrome as described by Pinsky and Crue (1984). Pinsky and Crue defined the three main aspects of the chronic pain syndrome as follows: no causality between pain and pathophysiological or pathoanatomical processes, a history of unsuccessful medical interventions, and a disturbance in the patient’s psychosocial functioning in combination with pain.

Clear definitions are a prerequisite for understanding the role of long-term physical inactivity in chronic pain. In this paper, three different constructs are proposed: “disuse,” “deconditioning,” and “disuse syndrome.” The expression “disuse” can be read as performing at a reduced level of physical activity in daily life. Disuse refers to a behavioural component leading to physical inactivity. The construct of “physical deconditioning” can best be described as a decreased level of physical fitness with an emphasis on the physical consequences of physical inactivity for the human body. And lastly, the “disuse syndrome” is defined as a result of long-term disuse, which is characterised by both physical and psychosocial effects of inactivity. In this definition, psychosocial consequences of inactivity are reactive to disuse and not reactive to pain itself. Fig. 1 represents the different constructs and their relations.

Although in the disuse syndrome, physical, and psychosocial consequences are both important, we focus on the physical consequences in CLBP in this review. In a situation of chronic pain, psychosocial consequences, as referred to in the disuse syndrome, can hardly be distinguished from psychosocial consequences in the chronic pain syndrome. It is beyond the scope of this paper to discuss psychosocial problems in CLBP. We will, however, discuss the psychosocial consequences of inactivity in a general population.

3. Models of disuse in CLBP

Why is it so difficult for patients with back pain to return to a normal level of activity after an acute attack of pain? And what explains the fact that not every patient with back pain eventually becomes inactive and that only a subgroup of patients develops disuse-related deconditioning? In recent years, explanatory models were presented on this topic (Hasenbring et al., 1994; Vlaeyen et al., 1995a). They assume that different strategies in coping with pain play a role in changes in a patient’s activity level. Two behavioural coping strategies in particular are mentioned: avoidance behaviour and suppressive behaviour.

3.1. Avoidance behaviour

According to Vlaeyen’s fear-avoidance model (as presented in Vlaeyen and Linton, 2000), a subgroup of CLBP patients is afraid of increasing their physical activity level because they fear a reactive increase of their pain or even (re)injury (presented in Fig. 2). Their high degree of fear of pain or their expectation of other adverse consequences of increasing movements may be the motivation to restrict movement (Pope et al., 1979). In the most extreme situation, the expression ‘kinesthrophobia’ is used, referring to an excessive, irrational and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury (Kori et al., 1990; Vlaeyen et al., 1995b; Crombez et al., 1998). According to this model, a state of chronic inactivity, induced by fear of (re)injury, will make it more difficult to return to a normal activity level due to physiological changes of the body system, apart from back pain problems. The physiological changes in this extreme situation of disuse may be equivalent to the deconditioning changes in the disuse syndrome mentioned above. This means that, if the fear avoidance model is applicable in the theoretical explanation for the disability in chronic pain for a subgroup of patients,
these patients have a low physical activity level in daily life and deconditioning-related changes of their body will appear.

Fear of movement may result not only in a low activity level, but also in changes in movement patterns. Main and Watson (1996) found a strong relation between fear avoidance and guarded movement. Guarded movement is the adaptation of posture in response to pain, which may give a patient short-term alleviation of pain and thus enable him or her to participate in normal activities of daily life. But after some time, adaptation of posture may result in abnormal motion and a resistant abnormal transfer of loads to other structures of the musculoskeletal system, with further restricting motion. The subject, conditioned through pain as a reaction to movement, may eventually develop a learned association between the two. Eventually this learned pain is no longer related to the initial cause of the acute pain sensation, but may have the same qualities and location. This may contribute to exaggerated illness behaviour, of which overt muscle guarding on movement is a feature. Guarded movements can in the long run contribute to the development of disuse and deconditioning.

3.2. Suppressive behaviour

Hasenbring et al. (1994) presented an avoidance-endurance model of pain chronicity. In accordance with the fear-avoidance model, she refers to a subgroup of patients with low back pain who avoid activities and develop deconditioning and chronic low back pain. But, in addition to this subgroup of patients with avoidance strategies as a coping mechanism, she also identified a second subgroup of patients who have a tendency to cope with pain using endurance strategies. These patients appear to ignore the pain and, by their suppressive behaviour, overload their muscles (overuse), which leads to muscular hyperactivity. Long-term muscular hyperactivity can eventually cause chronic low back pain. According to Hasenbring, both disuse and overuse lead to one-sided and false straining of the muscles, thus enhancing chronicization of pain.

The two different ways of coping (i.e., avoidance and suppression) in the subacute phase have different effects on the PAL of daily life. According to the theoretical models, patients who cope using avoidance strategies report a low PAL. Patients who apply endurance strategies are likely to report a physical activity level that fluctuates dramatically over time in reaction to pain. They are likely to persevere until increasing pain prevents further activity, then rest completely until the pain subsides or frustration over inactivity stimulates resumption of activity. Subsequently, they persevere again until increasing pain hinders further activity (Harding and Williams, 1998). Murphy et al. (1997) referred to this as “all or nothing” behaviour, representing the so-called “over-activity/under-activity” cycle, which has been observed in many chronic pain patients. Adequate registration of PAL over time could provide insight in the way in which a patient tries to cope with the limitations in daily life (Edwards, 1986). In the long run, however, both coping strategies will, theoretically, result in a low level of physical activity leading to a situation as presented in the disuse syndrome. Also, this low level of physical activity in daily life and its consequences should be measurable in CLBP patients.

4. Disuse in CLBP

Little information exists on the level of physical activity in daily life of CLBP patients. The results on the physical activity level (PAL) in CLBP available are inconclusive. Nielens and Plaghki (2001) found a significantly lower PAL in CLBP, which was most pronounced in occupational activities. In recent studies by Protaas (1999) and Verbunt et al. (2001), a PAL was found that was comparable with a PAL of healthy individuals. A remarkable difference concerned the percentage of persons with paid jobs in the studies. In Nielens’ study, only 20–34% of the participants had a paid job, whereas in Verbunt’s study 72% of patients had a paid job. These different levels of participation in occupational activities could explain the different results of the studies. Persons with CLBP who are still working will have at least a PAL that is sufficient to meet the physical demands of their jobs. This could result in a higher PAL, compared to the PAL in a situation in which activities are influenced by pain. It is also important to realise that different assessment methods for PAL were used in the studies. In the studies by Nielens and Protaas, the assessment of PAL was based on self-report, whereas assessment in the study by Verbunt was based on physiological measurements. To date, the validity of assessment of PAL in CLBP by self-report is
unclear. A self-report can reflect a difference between how patients function and how they believe they function, resulting in a differently reported PAL compared to the actually observed active behaviour (Fordsyce et al., 1984). The validity of self-report on PAL will be negatively influenced by this. This discrepancy in reported functioning and actual functioning has been observed before in CLBP patients. Kremer et al. (1981) compared PAL as reported by CLBP patients and as reported by their therapists simultaneously. Patients significantly underestimated their level of activity. In line with this finding, Schmidt (1986) found that CLBP patients have difficulty in judging their own performance in an experimental setting. Patients were less capable of estimating their physiological level of exertion during a performance test situation than healthy controls. In 1985, Linton found a relationship between PAL and pain intensity in global interview self-reports, but this relationship gradually disappeared when the measure of PAL became more overt and objective (Linton, 1985). This may imply that a patient’s perception of his activities is biased by other pain-related factors, which will influence the validity of his self-report. Apart from these comments with respect to content, it is surprising that only a few studies on PAL in CLBP have been performed. The information available does not allow a conclusive statement on the presence of disuse in CLBP. We need new studies on PAL in CLBP that make use of valid assessment methods.

In summary, behavioural factors such as avoidance and suppressive behaviour, are assumed to play a role in provoking disuse in CLBP. At this moment, however, insufficient evidence is available that either supports or rejects the presence or absence of disuse in CLBP. An important component of PAL appears to be work status, which therefore needs to be considered in further research. There are many assessment methods for PAL, with psychometric properties tested on healthy subjects. But the validity of these assessment methods in CLBP patients must be evaluated carefully. In the following sections, we will review various assessment methods on PAL.

4.1. Physical activity in daily life: methods for measurement

Just like in healthy persons, the registration of physical activity in CLBP patients must reflect a mean activity level over more than one day in order to represent normal daily life. The influence of extraneous factors and daily patterns, such as differences between the activities during the weekend and during the week, can be great. Greetenberg and Montoya (1992) stated that all methods measuring PAL need at least 5 or 6 days of registration to minimise intra-individual variance. Both weekdays and weekend days must be included in the period of measurement. Most methods measuring PAL have been extensively evaluated regarding validity and reproducibility in a healthy population. However, their psychometric properties in a population of CLBP patients are still unknown. In this section, we will discuss different methods for measuring PAL and evaluate their applicability in a population of chronic pain.

4.1.1. Self-report

Self-report measures, such as questionnaires or diaries, are easy to administer, require little time, and are inexpensive. This makes these measures popular in epidemiological studies featuring large sample studies. Kriska and Caspersen (1997) made a compilation of physical activity questionnaires for health-related research, in which they summarised the validity, reliability and feasibility of the questionnaires. However, as stated in the previous section, it is conceivable that psychometric properties of questionnaires on PAL are influenced by extraneous factors in a population of CLBP patients. Unfortunately, little information on this topic in CLBP is available, and a difference in discriminative validity has to be considered. With questionnaires on PAL designed for a healthy population, the lack of discriminative validity occurs especially in low physical activity levels, which may result in a so-called “floor effect” in a population of chronic pain patients. Modified questionnaires, especially designed for sedentary people, deal with this “floor effect.” In general, however, the available modified questionnaires are validated for a healthy older population and concentrate on habitual activities of this specific age group. This means that occupation-oriented questions are often absent. Nevertheless, these activities are of special interest in a population of chronic pain patients. This limits the usefulness of a modified activity questionnaire designed for older persons in CLBP. Protas (1999) suggested that questionnaires used in a population with CLBP should contain both occupational and leisure time activities, since many individuals with low back pain are still working. An example of a questionnaire that fulfils these criteria is the Baecke questionnaire (Baecke et al., 1982). Its test-retest reliability in CLBP is comparable to that in healthy controls (Jacob et al., 2001), while it is easy to administer, cheap, and takes little time to analyse.

4.1.2. Observation

A second technique to evaluate PAL is by observation. This may encompass registration of a subject’s activities by an observer or by video recording, followed by an interpretation. Observational techniques are generally considered reliable (Bussmann & Stam, 1998a), but their administration is costly and time-consuming and therefore probably only useful in daily life on a time-sample basis.
4.1.3. Movement registration

A third possibility is the registration of PAL with ambulatory systems, using motion sensors. A variety of systems exist, ranging from pedometers, designed to count steps, to three-dimensional activity monitors giving more specific data on postures and activities during movement. Most of the motion sensors are small, can register at least for one day up to four weeks, and hardly interfere with daily life. In CLBP, research has been done using accelerometry. In a previous study we compared the registration of PAL of a tri-axial accelerometer with a registration of PAL with physiological assessment (Verbunt et al., 2001). The validity of the registration of PAL during a period of 2 weeks was satisfactory with a correlation coefficient of 0.72. Bussmann et al. (1998b) reported a good validity of a tri-axial motion sensor, which is based on a combination of accelerometers, in the quantification of behaviour (e.g. duration of activities and number of movement transitions) of patients after failed back surgery. Accelerometry makes it possible to measure changes in the quantity of activities and changes in the pattern of physical activities over days. The registration of PAL with a tri-axial accelerometer seems applicable for measuring PAL in CLBP.

4.1.4. Physiological measurement

A fourth possibility is the measurement of physiological markers, which is based on the indirect measurement of physiologic responses of the body to exercise. A simple physiology-related method is a 24-h heart rate registration. Heart rate registration hardly interferes with the patient’s daily life and its costs are moderate. However, in stress reactions the registration of heart rate as a representation of physical activity can be biased by an increase of the heart rate as a reaction to stress (Raskell et al., 1993). Another disadvantage of heart rate registration is the inaccuracy in low-level physical activity (Gretebeck et al., 1991). In CLBP patients, PAL is probably limited and stress-related problems can be present in coping with pain. Heart rate registration therefore seems to be a less than ideal method to measure PAL in CLBP. Another physiological technique for PAL, based on energy expenditure, is the doubly labelled water technique (Westerterp et al., 1995). In a healthy population, this technique is generally accepted as the ‘gold standard’ for physical activity assessment in daily life (Bouten et al., 1996). It determines the average daily metabolic rate and, together with an estimate of basal energy expenditure, provides a reliable measure of energy expenditure associated with PAL during one to three weeks. However, the doubly labelled water technique is expensive and therefore only usable in small population studies.

5. Deconditioning in chronic low back pain

Disuse leads to deconditioning or a low level of physical fitness. Physical fitness is a multidimensional term, which includes a combination of physical parameters such as muscle strength, muscle endurance, muscle power, flexibility, cardiovascular capacity, motor control and body composition. As shown in Fig. 1, these parameters are negatively affected by a continuous low level of PAL. If this change in physical parameters is also present in CLBP patients, it would be an indirect sign of the presence of disuse. It seems therefore worthwhile to consider a change in physical parameters presented in the disuse model in a population of CLBP patients. In the next section, we will discuss research findings that support the physical findings in the model on CLBP. We will successively discuss reported bodily changes due to inactivity in healthy persons and observed changes in CLBP patients.

5.1. Physiological changes

5.1.1. Muscle atrophy changes in muscle composition

Inactivity causes changes in all tissues, the most obvious of which are changes in muscle characteristics, such as a decrease in muscle mass (muscle atrophy) and changes in muscle composition. In micro-gravity simulation models, postural muscles that normally counteract the effects of gravity have been reported to become atrophic to a greater extent than fast contracting locomotor muscles (St.-Pierre and Gardiner, 1987). This implies that muscles situated on the trunk and lower extremities are affected most by deconditioning. This finding was confirmed in healthy persons in several studies (Berry et al., 1993; Greenleaf, 1997). In CLBP patients, muscle atrophy was found by Gibbons et al. (1997). In patients with more frequent low back pain in the previous year, magnetic resonance imaging (MRI) studies showed a slightly smaller cross-sectional area of the paraspinous muscles and greater signal intensities, possibly due to muscle atrophy.

In healthy subjects, changes in muscle composition have been reported (Musacchia, 1988) besides a decrease in muscle mass. A human muscle contains different muscle fibres, of which fast twitch (FT) fibres and slow twitch (ST) fibres are the most prevailing. FT fibres can contract fast and are rapidly fatigued, whereas ST fibres contract slowly and are metabolically inexpensive, which means that they can therefore act much longer. In healthy subjects, cessation of normal repetitive low-level activity patterns is supposed to result in transformation of the muscle towards a faster, more fatigable type (St.-Pierre & Gardiner, 1987; Mannion, 1999). In addition to microscopic effects, long-term immobilisation can introduce macroscopic anatomic complications such as, for example, a limited range of motion or muscle
5.2.2. The role of work status in cardiovascular capacity

As can be seen in Table 1, Nielens and Plaghki (1991, 1994, 2001) reported a difference in cardiovascular capacity for men, but not for women in three studies. They assumed that a reason for this gender discrepancy could be work status. It could be more common for men to lose their jobs as a result of CLBP, leading to a loss of their occupational activities. Jobs of male individuals are probably physically more strenuous, resulting in a more explicit change in activity level after job loss compared to women. Since in healthy young men a positive relation was found between heavy physical work and a high level of physical fitness (Tammelin et al., 2002), the loss of this work-related activity level in patients will probably result in a more substantial decrease in their physical fitness level. Women, with or without a paid job, on the other hand are probably more active at home in household tasks and child care, which contributes to keeping them at an activity level that may be considered almost equivalent to that of healthy females in most cases. Again, similar to the interpretation of the activity level, work status is an important factor in interpreting the cardiovascular capacity in CLBP patients. Unfortunately information on work status is not available in all studies. Of the studies that do present the work status, it is remarkable that in most studies in which no difference in cardiovascular capacity was reported, all persons are still working. Hazard et al. (1989) compared the cardiovascular capacity of CLBP patients who were working and of patients who were not working. They found that patients with a paid job had a better cardiovascular capacity than patients without a job. This underlines the importance of occupational activities in deconditioning in CLBP.

5.2.3. Muscle strength

Immobility is reported to lead to a decrease in muscle strength and endurance, especially in the postural muscles (Dittmer and Teasell, 1993; Gogia et al., 1988). In healthy persons confined to bed for 4-5 weeks, the maximum isometric peak torque for the m. quadriceps decreased by 10.3-21% (Dudley et al., 1989; Germain et al., 1995; Gogia et al., 1988). Hultman et al. (1993) in a cross-sectional design compared endurance of the lumbar muscles in CLBP patients and healthy volunteers. The healthy group had significantly longer trunk muscle endurance times than the group with CLBP. Cassisi et al. (1993) confirmed this finding of decreased lumbar strength in CLBP. Most research on muscle strength in CLBP is focused on the lumbar muscles. In the concept of diasthesia, postural muscles, such as trunk and leg muscles, are also important. Lee et al. (1995) reported in their study a decrease in trunk strength combined with a decrease in strength of the knee extensors for CLBP patients. This finding implies that muscle weakness in CLBP is not just a local problem of the trunk, but a generalised problem, probably due to a lower PAL. Again, work status could play a role, since only 31% of the patients and 59% of the controls reported a job with a heavy physical load, while 28% of the patients and 63% of the controls regularly participated in sports activities (Lee et al., 1995).

5.2.4. Motor control

Motor control is also reported to be affected after a period of bed rest. Immobility decreases co-ordination and balance (Haines, 1974). The impairment of balance appears to be due not so much to muscle weakness, but rather to impaired neural control. Maintaining a high degree of co-ordination requires frequent performance of an activity under conditions in which the sensory perception of the motor performance can be checked for accuracy and errors may be corrected (Kottke, 1966; Dustman et al., 1984). Bed rest decreases the amount of proprioceptive stimuli, which are responsible for regulating neuromuscular performance. In CLBP, motor control can be affected too. As mentioned above, guarded movements lead to a change in movement patterns. In a laboratory setting, patients with low back pain had less trunk motion during a specific dynamic task than healthy persons (Rudy et al., 1995). The recruitment of stabilising trunk muscles during motion of the upper limbs appeared to be different in persons with and without back pain. CLBP patients showed a delayed onset of contraction of especially the abdominal muscles, which can be hypothesised to result in inefficient muscular stabilisation of the spine (Hodges and Richardson, 1996, 1999). The role of pain severity in altered motor control in CLBP must be considered. In a standardised reach task, postural control in patients with severe pain was poorer than in patients with moderate pain (Luoto et al., 1996). With impaired motor control, the problem can either be caused by pain or result from inactivity.

In the measurement of physical fitness, physical performance tests, such as strength measurement or exercise testing, are used. To decide whether patients are deconditioned, however, we need information about a patient's functional capacity rather than his or her physical performance. In sports it is assumed that physical fitness is only one factor influencing performance and that fatigue and pain thresholds must be crossed to reach optimal performance (St.-Pierre and Gardiner, 1987). The extent to which one is willing to tolerate feelings of pain or exhaustion also determines performance. In assessing physical fitness in CLBP patients, physical performance is probably modified to a larger extent by motivational and cognitive factors than in healthy persons. Watson (1999) mentioned the importance of evaluating non-physical contributing factors during performance tests in CLBP. According to Watson, physical assessment measures should be regarded as...
representing a steady psycho-physiological state. To interpret changes in outcome during repeated measurement, it is important to consider a change in these non-physical factors as well. Only then does one have the opportunity to interpret a change in physical capacity during a performance test. In CLBP, research has been done to identify non-physiological factors in performance testing. Pain-related factors such as pre-test pain level (Estlander et al., 1999; Schmidt, 1986), pain level on exertion (Keller et al., 1999), pain threshold (Pope et al., 1979) and pain expectancy (Crombez et al., 1996) were correlated to the final test result of the different cross-sectional studies. These non-physiological factors can thus influence performance assessment indicating that the validity of the test could be biased by these pain-related variables.

Over time, tests have been developed with the purpose of minimising non-physiological factors, such as Functional Capacity Evaluation (FCE). The purpose of FCE is to test a person's physical abilities to the maximum in order to produce objective documentation regarding work and activities of daily life. FCE has become part of the accepted practice in work injury prevention and rehabilitation (King et al., 1998). During a FCE, the patient has to complete a standard protocol of physical tasks while a trained observer records the performance and limitations. Practical data on the use of FCEs to determine an individual’s physical capacities have been available for over a decade, but research to justify the use of FCEs is still lacking. Although the term ‘capacity’ is included in its name, FCE is a performance test rather than a capacity test. FCE is not fully objective since an observer has to decide if a patient performed maximally or sub-maximally during the test. The influence of psychological factors is also assumed to be present in FCE but cannot be measured. In general, the interpretation of results on deconditioning requires a critical look at the assessment methods that were used.

### 5.3. Psychosocial changes

Distress, depression and anxiety—the psychosocial variables mentioned in the deconditioning model—are studied extensively in CLBP. It is beyond the scope of this paper to review the literature on distress, depression and anxiety in chronic pain. Their presence in CLBP patients is probably the result of pain rather than the result of a decreased level of physical activities, or at least a combination of both effects. It is, however, striking that in research findings on persons without pain, these variables seems to be correlated to PAL. Most research on psychosocial consequences (in persons without CLBP) in deconditioning is done in inactive people instead of in persons during immobility. Thirlaway and Benton (1992) found in 246 healthy men and women that higher levels of physical activity were associated with a better mood. Inactive, but fit people reported a poorer mood than inactive and unfit people. They concluded that the positive relation between physical activity and mental mood was less mediated by improved physical fitness but more by participation in performance of physical activity as a social event. Martinsen (1990) found that physical work capacity was reduced in depressed people. Crews and Landers (1987), in a review of 34 studies on the relation between physical fitness and stress response, found that aerobically fit people had reduced psychosocial stress responses. In a group of 100 young and healthy police officers after an aerobic training period, which improved physical fitness, Norris et al. (1990) found that self-reported stress was reduced and scores for subjective health and well-being were increased. The results of these studies suggest that inactivity is strongly associated with increased distress. Petruzello et al. (1991) conducted a meta-analysis on the anxiety-reducing effects of exercise and found that aerobic, but not anaerobic, exercise was associated with lower anxiety levels. Since deconditioning especially affects the aerobic energy capacity, anxiety may play a role. Social consequences of long-term immobility can change the person's role in society. Job loss, related economic loss and restriction of social activities may occur and may have their effects on a person's mood (Waddell, 1991).

In summary, there are more studies available on deconditioning than on disuse in CLBP. Most studies on deconditioning in CLBP assess the cardiovascular capacity. Again, work status seems an important variable to differentiate between levels of deconditioning. In most studies, it appeared that patients that fully participate in occupational activities have a fitness level comparable to healthy controls. It is important to realise that physical fitness is tested using a test of physical performance instead of physical capacity. In CLBP patients, pain-related non-physiological factors may influence the test to a greater extent than in healthy controls.

### 6. Conclusion and suggestions for further research

In the literature on physical activity and physical fitness in chronic pain, Bortz's disuse syndrome is cited frequently. In the studies on CLBP in which a cross-sectional comparison was made between fitness related parameters in patients and healthy controls, however, results were inconclusive. It is important to realise that disuse as described in the physiological literature is referred to in a context of immobility, whereas in chronic pain disuse is already referred to as a state of inactivity. And as we cannot judge the magnitude of the decline in fitness-related parameters in CLBP because of the cross-sectional design of most of these studies, a situation of immobility for CLBP patients probably
rarely occurs. Some complications of immobility, such as contractures and dramatic changes in metabolism, are prevented by any activity and will therefore not appear in a state of inactivity. It is therefore at least questionable if the disuse syndrome, to the extent as reported by Bortz, is applicable as a separate identity in the chronic pain syndrome.

Although disuse is not based on immobility, inactivity can still play an important role. It remains important to objectify PAL, or its change in patients with low back pain, since the assumption that physical activity decreases with the occurrence of back pain is still the basis of most reconditioning programmes. It is remarkable that in several studies presented in this review no difference could be found between patients and healthy controls in their levels of PAL or physical fitness. Work status is presented as a possible discriminating variable between fit and unfit persons with CLBP. However, this is not exclusively found in persons with back pain. In a large study of the Dutch population, involving people aged 20–64 years, 36% of the unemployed persons and 16% of the working persons had an inactive lifestyle (i.e., less than half an hour a week of moderate activities) (Schuit et al., 1999). It could be that disuse or deconditioning is more related to the moment when patients leave their paid jobs, especially in men, than to the moment when back pain appears.

In the evaluation of a decrease in PAL, the measurement of intra-individual changes over time in a longitudinal design is preferable. All studies in this review were based on a cross-sectional design, in which the level of physical activity and physical fitness of patients was compared to controls. In future research, a longitudinal design in the study of physical activity is preferred. It also seems important in future research to evaluate a change in work status and its relation to a change in physical fitness. If we evaluate physical fitness over time and possible causes of changes in activity levels, such as pain intensity over time and occupational and sport-related changes, more will be known about their relation.

In assessing physical fitness, the validity of performance tests that measure physical fitness in CLBP has to be taken into account. A multidimensional approach that includes physiological and physical factors influencing the outcome of an exercise test, is favoured in future research on chronic low back pain. A recently developed method that shows the influence of psychological factors during strength testing, is the twitch interpolation technique (Edwards, 1988; Volledestadt, 1997).

The twitch interpolation technique is based on the registration of a twitch contraction elicited by a supramaximal electrical stimulus delivered to the muscle or nerve during a maximal voluntary contraction. The force increment in response to this stimulus reflects the muscle force reserve or the difference between the maximum force that can be generated by the muscle and the maximum voluntary contraction force, in which non-physiological factors play a role. This method can be used to make the role of non-physiological factors during strength testing more transparent.

In conclusion, the presence of deconditioning and disuse in CLBP as factors contributing to chronicity in chronic pain is not confirmed by the literature presented in this review. In the evaluation of deconditioning and disuse in chronic pain, it is also important to consider the psychometric properties of the assessment methods on both PAL and physical fitness. In future research, it may be possible to confirm the assumed relation between fitness and pain as presented in theoretical models on the development of CLBP.

References


Painful and non-painful neuropathy in HIV-infected patients: an analysis of somatosensory nerve function

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Abstract

Fifteen to 50% of AIDS-patients suffer from distal predominantly sensory neuropathy (DSP), which is commonly associated with painful symptoms. In the present study, we have focused on the function of fine calibre nerve channels, in 36 consecutive HIV-1-infected patients with painful (PPN) (n = 20; 54%) and non-painful (PN) (n = 16) sensory neuropathy, assessed by clinical, quantitative thermal stimulation (QTT) (3/56), and peripheral nerve conduction examination (325/86). Control QTT data were obtained from 49 healthy subjects with a corresponding age- and sex distribution. Demographics, antiviral treatment, immunological status, and nerve conduction examination did not differ between patients with and without painful symptoms. Hypoesthesia to warmth, cold, and heat pain was observed in both neuropathy groups when compared to healthy controls. However, the perception threshold to warmth was more often impaired (p < 0.01) and the level of impairment was more pronounced (p < 0.001) in patients with painful neuropathy. Furthermore, increased pain sensitivity to cold was found only in patients with painful symptoms (p < 0.05). An abnormal outcome of any QTT parameter was found in all patients with pain, but only among 62% of patients without pain, p < 0.01, and the cumulative frequency of abnormalities in any of the four thermal percepts (warmth, cold, heat pain, and cold pain) was higher in patients with painful symptoms, p < 0.0001. This study demonstrates a more pronounced impairment of C-fibre-mediated innocuous warm perception in patients with painful neuropathy, which in the setting of impaired or absent heat pain perception suggests a more generalised loss of function in somatosensory C-fibre channels.

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1. Introduction

A variety of peripheral neuropathies may occur throughout the course of HIV-1 infection. The most common peripheral nerve disorder of late HIV-1 infection is distal predominantly sensory neuropathy (DSP). Fifteen to 50% of AIDS-patients are affected (Floeter et al., 1997; Husstedt et al., 1998; Simpson and Olney, 1992; Snider et al., 1983; Tagliati et al., 1999) and 50-60% of these patients have painful neuropathy (Cornblath and McArthur, 1988; Fuller et al., 1993; Martin et al., 1999).

The pathophysiology of DSP is still unclear. Nerve biopsy and electrodiagnostic features of HIV-1-infected patients with DSP are consistent with axonal degeneration of both thick and thin myelinated and unmyelinated fibres (Herrmann et al., 1999; Rizzuto et al., 1995; Tagliati et al., 1999). The presence of HIV-1 infected, activated monocytes and macrophages within the endoneurium of dorsal root ganglia (Brannagan et al., 1997) and peripheral nerves (Chaunu et al., 1989; Rizzuto et al., 1995) has been demonstrated. Neurotoxic substances of both viral and monocyte/macrophage origin are thought to play a role (Dalakas and Cuper, 1996). Neurotoxicity from antiretroviral drugs is another possible cause, since several of the nucleoside analogues (didanosine, zalcitabine, and stavudine) may

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induce painful sensory neuropathy (Blum et al., 1996; Fichtenbaum et al., 1995; Simpson and Tagliati, 1995).

Furthermore, alterations within the central nervous system (CNS) may also accompany the HIV-1 infection (Husstedt et al., 1998; Smith et al., 1990). Analyses of the cerebrospinal fluid of HIV-1-infected patients have shown a chronic inflammatory response within the CNS in a majority of patients (Martin et al., 1998). Vacuolar myelopathy, typically affecting the dorsal and lateral columns of the spinal cord, has been found in up to 50% of HIV-1-infected patients in post-mortem studies (Budka, 1991; Dal Pan et al., 1994).

Previous studies of HIV-1-infected patients have shown that small nerve fibre dysfunction frequently occurs in both patients with symptomatic and asymtomatic HIV-1-related neuropathy (Bouhassira et al., 1999; Winer et al., 1992), sometimes preceding clinical DSP (Winer et al., 1992). It has also been demonstrated that HIV-1-infected patients with DSP have a marked reduction of myelinated and unmyelinated epidermal small fibres (McCarthy et al., 1995). The main aim of the present study was to analyse the sensory abnormalities associated with painful (PPN) and non-painful (PN) DSP, by assessing the function of the fine calibre somatosensory system.

2. Methods

2.1. Patients

Thirty-nine consecutive HIV-1-infected patients with symptoms indicating impaired sensibility, attending the Department of Infectious Diseases, Huddinge Hospital, Stockholm, were referred to the study. Patients were included if they, after a structured clinical examination (by author C.M.), were found to have symmetrical sensory aberrations in the lower extremities with a proximo-distal gradient in at least one sensory modality (Hansson et al., 1991). Exclusion criteria were clinical signs of CNS complications, including myelopathy and/ or cognitive dysfunction. Other exclusion criteria were diseases unrelated to the HIV-1 infection, pre-disposing for polyneuropathy, including alcohol abuse. Three patients were found not to have symmetrical sensory neuropathy; one patient had mononeuropathy, one had arthralgia, and one patient had neurogenic stump pain after bilateral amputation below the knee. Six patients had had HIV-1 transmission through intravenous drug abuse, but none of these had an ongoing substance abuse (four were on long-term methadone treatment). Thirty-six patients were included, out of whom 29 were examined in full. Five were examined clinically and neurographically or by quantitative thermal testing (QTT). Two were examined only clinically. The following reasons for not completing all parts of the study were noted: four patients were admitted to hospital due to non-neurological AIDS-related complications during the study, one patient refused further cooperation, and one patient could not be reached for the nerve conduction examination.

Eighteen patients (50%) were not on antiretroviral treatment. Among the 18 patients on antiretroviral therapy, none received modern treatment including HIV-1 protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Four different antiretroviral drugs were used either in mono-therapy 12/36 (33%) or in combinations of two 7/36 (20%). The following drugs were used: zidovudine (17/36), didanosine (7/36), lamivudine (1/36), and zalcatibine (1/36).

2.2. Neurological examination

Symptoms and signs of polyneuropathy were assessed according to a structured protocol. The pain characteristics were assessed by a pain drawing, with four given symbols, each representing one or a batch of different pain descriptors. The pain drawing was supplemented by a verbal communication of pain descriptors used by the patients. Pain intensity in the affected area (worst and best) was evaluated using a 100 mm visual analogue scale (VAS). Signs of sensory impairment were assessed in all extremities by evaluating the following sensory modalities: light touch (camel-hair brush), pain/pinprick (pin), warmth (pre-heated metallic roller, \(\approx 40^\circ\)C), and cold (metallic roller at room temperature, \(\approx 20^\circ\)C). Motor function was assessed by evaluating monosynaptic muscle reflexes; (normal, diminished or absent), presence of paresis (evaluated by walking on toes, heels, and jumping on one foot) and presence of atrophy of the short toe extensors.

2.3. Nerve conduction studies

An electroneurography index (ENeG-Ix) was used (Solders et al., 1993), based on conventional neurophysiological techniques using surface electrodes and Neurostar MS 92B (Medelec, Surrey, UK) or Counterpoint (Dantec, Skovlunde, Denmark) equipment. Thirty-two patients were examined. Motor conduction velocity (MCV), distal latency (DL), compound muscle action potential (CMAP), and shortest F-response latency to 20 stimuli (F) were recorded in the median, peroneal, and tibial nerves. Sensory conduction velocity (SCV) and sensory nerve action potential amplitude (SNAP) were recorded in the distal median, radial, and sural nerves. The ENeG-Ix was expressed as the mean deviation (in SD) from normal, standardised for age and height. The reference values were obtained from normal controls consisting of 135 healthy subjects (Solders et al., 1993). Twelve parameters were included in the index, six reflecting conduction velocities (3 motor + 3
sensory, 3 upper + 3 lower extremity) and six reflecting amplitudes (3 CMAP + 3 SNAP, 3 upper + 3 lower extremity). Index values differing > 0.72 SD from normal were considered abnormal (the normal limit was calculated as > 2.5 SD/√(36)).

2.4. Quantitative thermal testing

QTT was performed on the dorsum of the right foot, within the SI dermatome, by the method of limits (Verdugo and Ochoa, 1992), using a Somedic Thermotest (Somedic Sales AB, Hörby, Sweden). Thirty-one patients were assessed. The probe, operating by the Peltier principle and originally described by Fruttschorfer et al. (1976), has a rectangular surface of 2.5 × 5.0 cm. The baseline temperature of the probe was set equal to the skin temperature (assessed with Exacon MC 8700; Scientific Instruments ApS, Roskilde, Denmark) and thermal perception thresholds were assessed by applying the Peltier element delivering, in consecutive order, five cold and five warm stimuli (randomised inter-stimulus interval 4–10 s; stimulus rate 1 °C/s) (Kosek et al., 1996). The patients were instructed to press a handheld button as soon as she/he experienced a sensation of cold or warmth thereby returning the probe to skin temperature. The temperature perception threshold was determined as the difference between the skin temperature and the mean perception level of the five consecutive stimuli of warmth (dWT) or cold (dCT). The heat and cold pain thresholds (HPT and CPT) were assessed by instructing the patient to press the handheld button as soon as the warm or cold became painful and the absolute temperature was then recorded [stimulus rate 2 °C/s (heat pain) and 3 °C/s (cold pain)]. Three consecutive measurements were performed and the heat or cold pain threshold was determined as the mean of the last two assessments. In the assessment of cold pain, only one measurement was done if the patient did not perceive pain during the first assessment (cut-off at 10 °C). To avoid tissue damage, a cut-off level of 52 °C was used for heat pain. The mean perception thresholds ±2 standard deviations (SD) for warmth, cold, and heat pain of 49 healthy, previously described controls (Martin et al., 2000), of corresponding age- and sex distribution, were used to define impaired perception thresholds among the HIV-1-infected patients. No normal threshold was determined for cold pain because of the large inter-individual variation. None of the control patients had a history of neurological disease. Means ± SD of the controls were: dWT 4.1 °C ± 2.5, dCT –1.0 °C ± 0.4, and HPT 43.6 °C ± 2.6.

2.5. Statistical analyses

Tests used for comparison of two groups included Student’s t test and Fisher’s exact test. One-way ANOVA and the χ² test were used for the comparison of three groups. Non-parametric methods were used to compare thermal pain perception thresholds due to observations below the cut-off level of 10 °C for cold pain assessments and above the cut-off level of 52 °C for heat pain assessments. The median and range were used to present data from measurements with a non-normal distribution (thermal pain perception thresholds, Fig. 2). All other parameters are presented as means ± SD. p < 0.05 was considered significant and p values between 0.05 and 0.10 are reported as trends.

3. Results

Painful neuropathy (PPN) was found in 20/36 patients (56%). No differences (Table 1) were found between patients with and without (PN) painful neuropathy with regard to age, gender, and risk factor for HIV-1 transmission or HIV-1 disease stage classification according to CDC (Centers for Disease Control, 1992). Immunological status, as measured by CD4+ levels, was similar in the two groups (PPN: 0.10 × 10⁹/L ± 0.12 versus PN: 0.11 ± 0.07). Potentially neurotoxic drugs (didanosine and zalcitabine) were used in similar frequencies in both groups. A comparison of

<table>
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<tr>
<th>Table 1</th>
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<tr>
<td>Characteristics of 36 HIV-1-infected patients with neuropathy, with (PPN) and without (PN) pain</td>
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<td></td>
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<tr>
<td>PPN</td>
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<tr>
<td>Age, mean (SD)</td>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Risk factor, n (%)</td>
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<td>Homosexual</td>
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<tr>
<td>Heterosexual</td>
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<tr>
<td>I.v. drug use</td>
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<tr>
<td>Transfusion</td>
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<tr>
<td>CDC classification, n (%)</td>
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<tr>
<td>A</td>
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<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>CD4, mean (SD)</td>
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<tr>
<td>Treatment, n (%)</td>
</tr>
<tr>
<td>Untreated</td>
</tr>
<tr>
<td>Zidovudine</td>
</tr>
<tr>
<td>Didanosine</td>
</tr>
<tr>
<td>Lamivudine</td>
</tr>
<tr>
<td>Zalcitabine</td>
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<tr>
<td>Methadone</td>
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</tbody>
</table>

CDC: HIV-1 disease stage classification according to the Centers for Disease Control (Centers for Disease Control, 1992); CD4+: levels of CD4+ cell counts in peripheral blood (<10⁹/L).
patients with and without potentially neurotoxic drugs did not reveal any demographic or immunological differences between the groups.

3.1. Clinical assessment

Symptoms and signs are described in Table 2. Pain was provoked by walking (13/20) and among these 13 patients five had pain provoked by clothes/sheets/light touch. The latter five were found to have dynamic mechanical allodynia on clinical examination. One of these five patients was wheelchair bound and one patient walked only with difficulty due to severe mechanical allodynia. Among the patients with spontaneous pain located in the distal part of the lower extremities, 16/20 (80%) had continuous pain of varying intensities. Four patients reported pain only during part of the day. Pain intensities (VAS) are presented in Table 2a. Loss of sensory function was found at similar frequencies between the two patient groups.

3.2. Nerve conduction studies

The function of thick calibre peripheral nerves was assessed by the ENeG-Ix. In the PPN and PN groups, all but one and two patients, respectively, had abnormal values at similar levels; the mean ENeG-Ix of patients with pain \((n = 17)\) was \(-1.98 \pm 0.77\) and in patients without pain it was \((n = 15)\) \(-1.56 \pm 1.1\), \(p = 0.23\) (Table 1c). The corresponding amplitude index was \(-1.95 \pm 1.09\) versus \(-1.49 \pm 1.20\), \(p = 0.29\), and the index of conduction velocity was \(-1.84 \pm 1.14\) versus \(-1.19 \pm 0.94\), \(p = 0.11\). The mean sensory ENeG-Ix (6 parameters) was \(-1.66 \pm 0.82\) versus \(-1.24 \pm 1.01\), \(p = 0.20\) (Table 1c). The mean sensory ENeG-Ix of the suralis nerve (2 parameters), corresponding to the site

<table>
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<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>Symptoms (a), signs (b), and nerve conduction studies (c) of 36 HIV-1-infected patients with neuropathy, with (PPN) and without (PN) pain</td>
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<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td><strong>PPN</strong> (n = 20)</td>
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<tr>
<td>-------------------------------------------</td>
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<tr>
<td><strong>Pain descriptors and intensity</strong></td>
</tr>
<tr>
<td>Pins-and-needles</td>
</tr>
<tr>
<td>Burning</td>
</tr>
<tr>
<td>Aching</td>
</tr>
<tr>
<td>Frequent cold pain</td>
</tr>
<tr>
<td>Stabbing/shooting</td>
</tr>
<tr>
<td>Pain provoked by walking</td>
</tr>
<tr>
<td>by clothes/sheets</td>
</tr>
<tr>
<td>VAS worst, median (range)</td>
</tr>
<tr>
<td>VAS best, median (range)</td>
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<tr>
<td><strong>Other sensory symptoms</strong></td>
</tr>
<tr>
<td>Numbness</td>
</tr>
<tr>
<td>Paraesthesia</td>
</tr>
<tr>
<td><strong>Weakness</strong></td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>(b) Signs, n (%)</strong></td>
</tr>
<tr>
<td><strong>Motor impairment</strong></td>
</tr>
<tr>
<td>Diminished ankle reflexes</td>
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<tr>
<td>Pareisis</td>
</tr>
<tr>
<td>Atrophy</td>
</tr>
<tr>
<td><strong>Sensory impairment</strong></td>
</tr>
<tr>
<td>Touch</td>
</tr>
<tr>
<td>Dysesthesia</td>
</tr>
<tr>
<td>Dynamic mechanical allodynia</td>
</tr>
<tr>
<td>Pinprick</td>
</tr>
<tr>
<td>Warmth</td>
</tr>
<tr>
<td>Cold</td>
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<tr>
<td><strong>(c) Nerve conduction (mean ± SD)</strong></td>
</tr>
<tr>
<td>ENeG-Ix</td>
</tr>
<tr>
<td>Amplitude-Ix</td>
</tr>
<tr>
<td>Conduction velocity-Ix</td>
</tr>
<tr>
<td>Sensory-Ix</td>
</tr>
</tbody>
</table>

ENeG-Ix, electromyography index; SD, standard deviations; n.s., not significant; N.A., not applicable.
where QTT was performed, was $-2.04 \pm 1.80$ in patients with pain versus $-1.60 \pm 1.94$ in patients without pain, $p = 0.52$.

The electrophysiological abnormalities were consistent with a predominantly axonal sensory-motor polyneuropathy. The ENeG index of patients with and without potentially neurotoxic drugs revealed a tendency towards more advanced neuropathy in 23 patients without neurotoxic treatment: $-2.0 \pm 0.7$; versus eight patients receiving potentially neurotoxic drugs: $-1.3 \pm 0.9$, $p = 0.08$.

3.3. Quantitative thermal testing

3.3.1. Perception thresholds for warmth and cold

The mean warm perception threshold (dWT) of patients with pain ($n = 18$) was higher than among patients without pain ($n = 13$); mean $dWT$ 13.4°C $\pm$ 3.1 versus 8.4°C $\pm$ 3.3, $p < 0.001$. Both groups differed from that of the controls; $dWT$ 4.1°C $\pm$ 2.5, $p < 0.0001$, respectively (Fig. 1). Patients treated with potentially neurotoxic drugs ($n = 8$) had similar perception thresholds as those who were not ($n = 23$); $dWT$ 10.7°C $\pm$ 3.9 versus 11.5°C $\pm$ 4.1, $p = 0.66$.

The mean cold perception threshold (dCT) did not differ between patients with and without pain; PPN: mean $dCT$ $-4.9 \pm 3.8$ versus PN: $-29 \pm 2.9$, $p = 0.12$, but both groups had higher thresholds than the controls; $dCT$ $-1.0 \pm 0.4$, $p < 0.0001$, respectively (Fig. 1). The eight patients treated with neurotoxic drugs had similar perception thresholds as those 23 who were not; dCT $-3.4°C \pm 3.4$ versus $-4.3°C \pm 3.6$, $p = 0.54$.

No significant differences in mean skin temperatures were found between the groups: PPN 30.7°C $\pm$ 1.6, PN 29.7°C $\pm$ 2.6, and controls 29.9°C $\pm$ 2.0.

3.3.2. Heat and cold pain perception thresholds

The heat pain thresholds did not differ between patients with ($n = 18$) and without ($n = 13$) pain; median HPT 48.5°C (range 44–52°C) versus 47.0 (range 43–52°C), but both groups had elevated HPT compared to controls; 43.6°C (range 37.7–50.9°C), $p < 0.0001$, respectively (Fig. 2).

The pain sensitivity to cold was increased in patients with pain, median 16.1°C (range $<10$–26°C), both compared to patients without pain; median $<10°C$ (range $<10$–30.5°C), $p < 0.05$, and compared to controls; median $<10°C$ (range $<10$–26.8°C), $p < 0.05$.

3.3.3. Individual pattern and frequency of altered perception thresholds for warmth, cold, and heat pain

Table 3a displays the frequency of individual patterns of sensory aberrations. Six patterns of dysfunction were observed in 2631 patients. The patterns were characterised by different combinations of hypoaesthesia (to warmth, cold, and heat pain). None of the patients had increased sensitivity to heat pain. Although no single pattern of abnormality differed significantly in frequency between patients with and without pain, there was a general trend towards higher frequencies of abnormality in patients with pain. This was reflected by the tendency towards higher frequency of warm and/or cold hypoaesthesia found in the PPN group: 13/18 (72%) versus PN: 5/13 (38%), $p = 0.08$, as well as the positive corre-

![Fig. 1. Mean warm (dWT) and cold (dCT) perception thresholds of 31 HIV-1-infected patients with neuropathy and 49 healthy controls (HC). The perception thresholds to warmth and cold are presented as degrees above (warmth) and below (cold) skin temperature. Eighteen patients had painful neuropathy (PPN) and 13 had neuropathy without pain (PN). Standard deviations and p values are indicated.](image1)

![Fig. 2. Heat pain (HPT) thresholds of 31 HIV-1-infected patients with neuropathy and 49 healthy controls (HC). Eighteen patients had painful neuropathy (PPN) and 13 had neuropathy without pain (PN). Means (○) and medians (―) are indicated within the 25–75 inter-quartile box and a vertical line denotes outliers. p Values are indicated. A dashed line denotes the cut-off level of HPT (52°C).](image2)
Table 3
Pattern (a) and cumulative frequency (b) of impaired perception thresholds to temperature and thermal pain in 31 HIV-1-infected patients with neuropathy, with (PPN) and without (PN) pain

<table>
<thead>
<tr>
<th>(a) Patterns of impairment</th>
<th>PPN n = 18</th>
<th>PN n = 13</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure warm hypoesthesia</td>
<td>2/18 (11)</td>
<td>0/13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Warm hypoesthesia + cold hypoesthesia</td>
<td>5/18 (28)</td>
<td>3/13 (23)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Warm hypoesthesia + cold hypoesthesia + heat hyperalgesia</td>
<td>8/18 (44)</td>
<td>2/13 (15)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Warm hypoesthesia + heat hyperalgesia</td>
<td>1/18 (6)</td>
<td>0/13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cold hypoesthesia + heat hyperalgesia</td>
<td>0/18</td>
<td>2/13 (15)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cold hypoesthesia</td>
<td>2/18 (11)</td>
<td>1/13 (8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Normal</td>
<td>0/18</td>
<td>5/13 (38)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

(b) Frequency of impairment
Perception thresholds
| Warm hypoesthesia | 16/18 (89) | 5/13 (38) | 0.006 |
| Cold hypoesthesia  | 14/18 (78) | 7/13 (54) | n.s.  |

Pain thresholds
| Heat pain hyperalgesia | 9/18 (50) | 4/13 (31) | n.s.  |
| Cold pain > 10°C | 12/18 (67) | 3/13 (23) | 0.03  |
| Cumulative frequency  | 51/72 (71%) | 19/52 (37%) | <0.0001 |

n.s. not significant.

lation found between warm and cold perception thresholds in patients with pain, $r = 0.59$; $p < 0.01$, but not in patients without pain, $r = 0.32$; $p = 0.28$. An abnormal outcome of at least one QTT parameter was found in all patients with pain, but only among 8/13 (62%) patients without pain, $p < 0.01$. The remaining five patients all had impaired nerve conduction studies.

The frequency of impairment of a single sensory modality was compared between patients with and without pain (Table 3b). The frequency of impaired perception thresholds to warmth, but not cold or heat pain, was higher in patients with than without pain, $p < 0.01$. The frequency of cold pain reported above 10°C was increased in patients with PPN compared to both patients without pain, $p < 0.05$ and to controls, $p < 0.05$. Both patients with and without pain reported a high frequency of impaired thermal and nociceptive perception thresholds compared to controls; warmth: $p < 0.0001/p < 0.01$, cold: $p < 0.0001/p < 0.001$, and heat pain: $p < 0.0001/p < 0.01$.

To analyse the overall impairment of the fine calibre somatosensory system, the cumulative frequency of abnormalities (for warmth, cold, heat pain, and cold pain) was calculated, which confirmed further the differences between the two patient groups; PPN: 51/72 (71%) versus PN 19/52 (36%), $p < 0.0001$.

4. Discussion

HIV-1-related distal predominantly sensory neuropathy (DSP) is frequently accompanied by painful symptoms (Cornblath and McArthur, 1988; Dalakas and Fezeshkpour, 1988; Fuller et al., 1993; Martin et al., 1999). The majority of previous studies on DSP have used conventional electrodiagnostic techniques, which analyse the function of thick myelinated peripheral nerve fibres (Barohn et al., 1996; Cornblath and McArthur, 1988; Fuller et al., 1993; Husstedt et al., 1998; Tagliati et al., 1999). The thermal and nociceptive somatosensory systems can be examined by quantitative psychophysical techniques (Verduo and Ochoa, 1992). In the periphery, thin myelinated A-δ fibres innervate cold receptors and unmyelinated C-fibres innervate warm receptors. A subgroup of both fibre types innervate nociceptors (Adriaensen et al., 1983; Hallin et al., 1982). A few recent studies have demonstrated that the thermal and nociceptive somatosensory system is compromised in the majority of patients with DSP (Bouhassira et al., 1999; Winer et al., 1992).

In the present study, 36 patients with neuropathy, 20 with painful symptoms, were assessed clinically, by nerve conduction studies (32/36) and by quantitative thermal testing (QTT) (31/36) to analyse the somatosensory function, with emphasis on fine calibre nerve channels. The two patient groups, with and without painful symptoms, were similar with regard to immunological and demographic status. Nerve conduction data demonstrated large nerve fibre dysfunction consistent with a predominantly axonal sensory-motor polyneuropathy in both groups. Approximately half of the patients received antiretroviral treatment (nucleoside analogues only) and one-fifth (eight patients) were treated with potentially neurotoxic drugs (didanosine and zalcitabine). None of the patients had received modern, highly active antiretroviral therapy. Treated patients were distributed evenly between the groups with painful and non-painful neuropathy, and no differences were found between treated
and untreated patients, as well as between patients with and without potentially neurotoxic drugs, with regard to the pattern of outcome abnormality using clinical, neurophysiological or QTT examinations.

Abnormality of fine calibre somatosensory channels was common in both patient groups compared to healthy controls, but the cumulative frequency of abnormalities in any of the four thermal percepts was higher in patients with painful neuropathy. QTT revealed a pattern of hypoesthesia of thermal nociceptive (heat pain hypoalgesia) and non-nociceptive channels (hypoesthesia to warmth and cold) in both patient groups. In patients with painful neuropathy, hypoesthesia to warmth was more pronounced compared to patients with non-painful neuropathy. Patterns of hypoesthesia have been observed in several different neuropathic pain states. In three earlier studies of painful diabetic neuropathy, the results of two resembled those of the present findings (Heimans et al., 1986; Ziegler et al., 1988). In these studies, hypoesthesia to temperature (difference limen) was more pronounced among patients with painful symptoms compared to both diabetic patients without pain and healthy controls. Also, in central neurogenic pain states, such as post-stroke pain (Boivie et al., 1989) and central pain in multiple sclerosis (Österberg et al., 1994), the predominant finding was hypoesthesia to temperature (difference limen) and heat pain in the affected part of the body compared to the unaffected side. However, in a study of patients with spinal cord injury, no difference was found with regard to nociceptive and non-nociceptive thermal perception thresholds between painful and non-painful sides of denervated skin (Eide et al., 1996). Contrary to the findings of increased perception thresholds to temperature and heat pain, some neuropathic pain states demonstrate lowered thresholds to heat pain, i.e., allodynia to heat, usually combined with normal perception thresholds to warmth and cold. This has been demonstrated in patients with the allodynic form (tactile allodynia) of post-herpetic neuralgia (PHN) (Rowbotham and Fields, 1996) and in a subgroup of patients with post-traumatic neuralgia (Kolzenburg et al., 1994), findings that have been interpreted as suggestive of peripheral sensitisation, including spontaneous activity. In the present study, none of the patients demonstrated lowered heat pain thresholds, and thus, lack of support for peripheral sensitisation of C-nociceptors.

Hypoesthesia to warmth demonstrated the most pronounced difference between patients with and without pain, pointing to a more pronounced dysfunction of this C-fibre channel. However, the heat pain thresholds, which also are C-fibre dependent (Yarnitsky and Ochoa, 1991), were equally increased (hypoalgesia) in the two patient groups. The lack of difference in heat pain thresholds between the patient groups may be explained by the relatively low degree of spatial summation in the periphery needed for the sensation of heat pain (Yarnitsky and Ochoa, 1991). A difference in function of this C-nociceptor channel therefore has to be substantial in order to be detectable. On the other hand, the sensation of warmth is highly dependent on spatial summation in the periphery (Yarnitsky and Ochoa, 1991). A previous study has shown that the small calibre innervation density of the epidermis is reduced in HIV-1-infected patients with sensory neuropathy (McCarthy et al., 1995). Furthermore, a recent study including eight HIV-1-infected patients has demonstrated a negative correlation between epidermal small nerve fibre density and clinical severity (with regard to regional distribution of neuropathy) in patients with painful sensory neuropathy (Holland et al., 1997). In a study of the allodynic form of PHN, a positive correlation was found between cutaneous fine calibre innervation density and both thermal, nociceptive and non-nociceptive, sensory perception, and severity of dynamic mechanical allodynia, suggesting an important role of small calibre nociceptive afferents for peripherally generated neuropathic pain (Rowbotham et al., 1996).

Patients with PPN were found to have increased pain sensitivity to cold stimuli compared to both patients without pain and healthy controls. The frequency of cold pain reported above the cut-off level of 10°C, as well as the level of cold pain perception, was significantly increased (less cooling required) among patients with painful symptoms. Increased pain sensitivity to cold has previously been observed during experimental compression block of myelinated nerves (Wahren et al., 1989). Also, in patients with fibromyalgia pain, increased pain sensitivity to cold was reported (Kosek et al., 1996). In both studies, the increased sensitivity was interpreted as a possible change in central processing, which in the case of compression block was thought to be mediated via release of inhibition, normally sustained by input from myelinated nerves. In the present study, however, the function of thick (EneG-Ix) and thin (dCT) myelinated nerves was equally compromised in both patient groups. The present data will thus not enable an interpretation with regard to central or peripheral mechanisms of the increased pain sensitivity to cold.

Abnormality of fine calibre somatosensory function has been previously described in HIV-1-infected patients (Bouhassira et al., 1999; Martin et al., 2000; Winer et al., 1992). One recent study demonstrated, as its main finding, selective static mechanical allodynia and hyperalgesia in patients with painful symptoms (Bouhassira et al., 1999). The authors proposed a modality specific peripheral sensitisation since, in agreement with our findings, no thermal hyper-phenomenon was found; hypoesthesia to warmth and cold, and heat hypoalgesia was the general pattern, but contrary to our findings no significant difference was found between patients with painful and non-painful neuropathy in any.
of the thermal parameters. Patient selection may differ between the two studies; in the study of Bouhassira et al., none of the patients received antiretroviral treatment, as opposed to half of the patients in the present study. Furthermore, in the present study patients with painful symptoms seemed to be more immunocompromised (0.10 versus 0.13 CD4+ cell count). However, the VAS scores of pain intensity appear to be in the same order of magnitude and the frequency of dynamic mechanical allodynia was similar (presently 5/20 versus 3/15). Methodological differences may also influence the results. Bouhassira et al. have used a common formula of the QTT with a fixed baseline probe temperature of 30°C, as opposed to skin temperature, which was used as baseline in the present study. This difference may be of importance, since extreme skin temperatures are more common in late stage HIV-1-infected patients due to conditions such as fever and/or cachexia.

Thermal sensibility thresholds reflect the status of the thermal somatosensory system, from the receptor to the cerebral cortex. In the present study, all patients were diagnosed with sensory neuropathy and none of the patients had overt signs of central neurological dysfunction. Still, the possibility that peripheral neuropathy may mask signs of CNS pathology has to be considered. In HIV-1 related myelopathy, there is a well-established discrepancy between the lack of clinical signs and pathologic findings at autopsy, which may be present in up to 50% of the patients, typically affecting the posterior and lateral columns of the thoracic cord. Furthermore, a progressive deterioration of both peripheral and central sensory pathways, corresponding to a decline in immunological status, has been reported in a longitudinal study (Husstedt et al., 1998). Taken together, it is not possible to rule out that HIV-1 related affection of central sensory pathways may partly contribute to the present findings, although all patients but three had neuropathological evidence of impaired peripheral thick caliber nerve function.

This study demonstrates that HIV-1 infected patients with sensory neuropathy have a pronounced dysfunction of fine calibre somatosensory channels. The main finding was a more pronounced hypoesthesia to innocuous warmth in patients with painful neuropathy, which in the setting of reduced or absent heat pain perception may suggest a more generalised loss of function in somatosensory C-fibre channels in patients with painful symptoms.

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References


Implicit attitude towards pictures of back-stressing activities in pain-free subjects and patients with low back pain: an affective priming study

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Abstract

In this paper, it is investigated whether an implicit evaluative-negative attitude towards back-stressing activities exists in pain-free subjects and in chronic low back pain patients. Using an affective priming task, it was investigated whether pictures of threatening back-stressing movements (primes) facilitate (respectively, slow down) the categorisation of subsequent evaluative-negative (evaluative-positive) words (targets). In study 1 using 20 pain-free subjects, the affective priming effect indicated evidence for an implicit negative attitude towards pictures of back-stressing activities. In study 2 using 30 low back pain patients, a reverse priming effect was found. In line with previous research, it is argued that this reverse priming effect is owing to the evaluative extremity of the primes: patients recognize the possibility that extreme primes will interfere with the categorisation of the targets and overcompensate for this possible effect. The implications for the prevention of negative attitudes towards back-stressing activities in non-clinical and clinical samples are discussed.

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1. Introduction

Several biomedical factors have been proposed to explain why only a minority of individuals with acute pain develops chronic pain problems. It is, however, clear that biomedical variables alone cannot fully account for the development of chronic pain, suffering and disability. Waddell et al. (1984) calculated that only approximately half of total disability in patients complaining of chronic back pain can be attributed to physical impairment. Furthermore, psychosocial variables have already been identified as important and unique predictors of chronic pain, suffering, and disability (Linton, 2000). Depression has been shown to predict disability better than pain intensity and duration (Rudy et al., 1988), and has also been found to predict disability one year after a new occurrence of low back pain (Burton et al., 1995). Also, dissatisfaction with employment is found to be prospectively associated with reporting a new episode of low back pain (Papageorgiou et al., 1997; van Poppel et al., 1998), return-to-work in employees with 3–4 months sick leave due to low back pain (Van der Giezen et al., 2000), and persistent disabling low back pain in patients consulting a general practitioner (Thomas et al., 1999).

Another important predictor of chronic pain problems is pain-related fear, which is broadly defined as the fear of pain and the fear of activities associated with pain such as physical activity and (re)injury. Pain-related fear has been consistently found to be predictive of pain and disability in both cross-sectional and prospective studies.
(Linton, 2000; Vlaeyen and Linton, 2000). The importance of pain-related fear is further highlighted in theoretical accounts explaining the transition of acute to chronic pain problems (for a review see Vlaeyen and Linton, 2000). Patients with high fear of pain are at risk for the development of an exaggerated pain perception and chronic pain problems due to excessive avoidance of activities presumed to worsen pain and injury (Lethem et al., 1983; Philips, 1987; Vlaeyen et al., 1995).

There is a large consensus that an evaluative-negative attitude towards pain is of key importance in the emergence of the tendency to escape/avoid (Crombez et al., 1997; Lang, 1993). People in general have negative attitudes towards pain and discomfort, but back pain patients may have learned by their negative experiences to extend this attitude towards back straining activities. Indeed, experimental psychological research has demonstrated that attitudes are flexible and can change by contingent experiences (Cacioppo et al., 1992; Hermans et al., 2002). As pain patients experience several negative consequences following back-stressing movements, an initial neutral attitude towards movements and activities can change and become negatively valenced. Once acquired, negative attitudes are resistant to extinguish (Vansteenwegen et al., 1998) and become automatically activated (Hermans et al., 2002).

The above-described characteristics of a negative attitude towards back-stressing movements have similarities with implicit attitudes as discussed in social psychology. Fazio (1990) stressed the importance of implicit attitudes in the emergence of behaviour in naturalistic environments. He criticised previous attitude models which state that in most circumstances our behaviour is directed by our conscious, explicit attitudes, in which pros and cons of behavioural options are rationally weighed (see Ajzen and Fishbein, 1980). On the contrary, he postulated that in most circumstances, attitudes become automatically activated and influence behaviour in a spontaneous way. Applied to chronic pain, avoidance behaviour is not the result of a rational and conscious weighing of all risks associated with back-stressing movements. Rather, it is the result of an automatic and implicit appraisal of the movements as threatening for the back.

This distinction between explicit and implicit attitudes is not only of theoretical but also of clinical interest. Common sense considers providing information to back pain patients as necessary and sufficient to alter attitudes towards activity and to recover. However, to the extent that attitudes towards back-stressing movements are implicit, providing explicit information may have only limited impact. Even more, a discrepancy between explicit and implicit attitudes can arise as patients may learn rationally that there is nothing threatening, but feel it completely different.

Experimental procedures have been developed to measure implicit attitudes and their automatic activation. A frequently used paradigm is the affective priming paradigm (Fazio et al., 1986). In a standard affective priming task (e.g., Hermans et al., 1994), a series of positive or negative target stimuli (e.g., words) is presented, which have to be evaluated as quickly as possible as either 'positive' or 'negative'. Each target is preceded by a prime stimulus (e.g., a picture), which can be positive, negative, or neutral, and which has to be ignored by the participant. Results show that the time to evaluate the target stimuli is moderated by the valence of the primes. The time needed to evaluate the target stimuli as either 'positive' or 'negative' is significantly shorter when prime and target share the same valence (positive-positive or negative-negative; affectively congruent) as compared to when prime and target are of opposite valence (positive-negative or negative-positive; affectively incongruent) (Bartholow et al., 1992; Fazio, 1986; Hermans et al., 1994). The generality of this affective priming effect is now well-established (Bartholow et al., 1992, 1996; Fazio, 1986; Hermans et al., 1994). Research has shown that this process of stimulus evaluation is an automatic process (Hermans et al., 2000); it is a fast process and occurs while simultaneously performing other, attentionally demanding tasks. In line with this idea, congruency effects have been observed at very short intervals between prime onset and target onset (e.g., Stimulus Onset Asynchrony [SOA] of 300 ms). This finding is interpreted as a strong indication for automaticity as such short intervals are considered too brief to recruit conscious and controlled response strategies (Neely, 1977).

The main aim of this study was to investigate whether pictures of back-stressing movements activate an evaluative-negative attitude in pain-free subjects and in chronic back pain patients. This research question was addressed by using the affective priming paradigm. The results of two studies are reported here. In study 1 participants were pain-free subjects. In study 2 participants were patients with chronic low back pain. In both studies a priming procedure with standard affective pictures (e.g., happy baby, cemetery) and a priming procedure with pictures of movements were employed. In study 1 we expected an affective priming effect for the standard affective priming task. No specific hypotheses were formulated for the task with pictures of movements as primes. Finally, to the extent that the priming effects were fully automatic, affective priming effects were expected at a short interval between prime onset and target onset of 300 ms. In study 2 we also expected an effect in the standard affective affective priming task. Furthermore, as it is reasonable to assume that back pain patients have a negative attitude towards back straining activities, an affective priming effect was expected with pictures of threatening back straining movements. Finally, to the extent that the priming effects were fully automatic, affective priming effects were expected at the
short interval between prime onset and target onset of 300 ms.

2. Study 1

2.1. Methods

Participants. Participants were 20 members of Ghent University, who volunteered to participate in the study (13 females and 7 males). No participants reported pain at the time of testing. Also, they were not in treatment for a pain problem. The mean age was 28.3 years (SD = 6.81). Eighteen participants were researchers of the Faculty of Psychology and Educational Sciences, and two were researchers of the Faculty of Medicine and Health Sciences. All participants were unaware of the research hypotheses. Participants gave informed consent. This study was approved by the Ethics Committee of the Faculty of Psychology and Educational Sciences of Ghent University.

Materials. Targets were 6 positive adjectives (e.g., "love", "friend") and 6 negative adjectives (e.g., "war", "AIDS") selected from Hermans and De Houwer (1994). According to their norms, positive and negative targets differed significantly on the affective dimension, $t(10) = 44.07$, $p < .0005$ ($M_{\text{positive}} = 6.59$; $M_{\text{negative}} = 1.40$) on a 7-point scale.

Primes for the standard priming task were 20 pictures chosen from the International Affective Picture Set (IAPS; Lang et al., 1995). Ten were positive pictures (e.g., "woman with baby"); "people on a beach") and 10 were negative pictures (e.g., "hospital patient", "cemetery"). Criteria for selection were extreme positive or negative valence, and low arousal. For the "back-stressing movements" priming task, 20 pictures were chosen from the Photograph Series of Daily Activities (PHODA; Kugler et al., 1999). Ten pictures were thought to be depicting low-threatening movements (e.g., "driving a car", "hanging up a coat") and 10 pictures depicting high-threatening movements (e.g., "raising a heavy beam", "digging in the garden").

The presentation of experimental stimuli and data collection was controlled by the INQUISIT Millisecond software package (Inquisit 1.28, 1998) on an S710 Compaq Deskpro computer with a 72 Hz screen. The pictures had a mean height of 21 cm and a mean width of 14.7 cm. Words were presented in the middle of the screen, and had a constant height of 0.5 cm and a mean width of 2 cm. Subjects were seated at approximately 50 cm from the screen.

Procedure. The study consisted of two phases. In the prime selection phase, participants were handed out colour prints of the 20 IAPS pictures and were required to rate these pictures by putting them on a 150 cm scale, which ranged from very negative over neutral to very positive. The experimenter stressed that they should rely on their first, spontaneous impression. Participants were instructed to have a quick look at each of the pictures before rating them. Next, participants were handed out colour prints of the 20 back-related movements and were instructed to rate these pictures by putting them on a 150 cm scale ranging from "extremely high threatening for the back" to "extremely low threatening for the back". From each set, four pictures with the highest scores and four pictures with the lowest scores were selected as primes.

Next, in the experiment phase, it was explained that the task concerned the speed at which people are able to categorize stimulus words. It was told that adjectives would be presented on the computer screen and that the task consisted of evaluating the target words as quickly as possible as positive or negative. Participants responded to the positive targets by pressing the "5" key (coloured green) with the right index finger. Participants responded to negative targets by pressing the "Q" key (coloured red) with the left index finger. Participants were further informed that each target word would be preceded by a picture (the prime) on the computer screen, which they were instructed to ignore, as their only function was to make the task more difficult. The target disappeared as soon as the participant pressed the key. The intertrial interval was 1750 ms. Participants practised the task with 15 trials using standard affective pictures as primes: to increase accuracy, feedback was provided after each practice trial. Also the percentage of errors and the mean response time was displayed on the screen after the practice phase.

In each participant, two separate affective priming tasks were consecutively run: an affective priming task with standard affective pictures as primes and an affective priming task with pictures of back movements as primes. The order was counterbalanced. Half of the participants began with the first task (standard pictures) and the other half with the second task (pictures of movements). Both priming tasks consisted of 72 trials, subdivided in three blocks of 24 trials. Each block had a different stimulus onset asynchrony (SOA, the time between the onset of the picture prime and the onset of the target word): SOA 300, SOA 500, and SOA 1000 ms. Each block consisted of 12 affectively congruent pairs (positive-positive, negative-negative) and of 12 affectively incongruent pairs (positive-negative, negative-positive). For each participant,
the computer randomly selected the order in which SOAs were presented.

2.2. Results

As in previous research (De Houwer and Hermans, 1994; Hermans et al., 1994, 2001), data with response latencies shorter than 250 ms or longer than 1500 ms were excluded to reduce the influence of outlier responses (0.07%). Also, data from trials on which an incorrect response was given (e.g., positive instead of negative) were discarded from the analyses. The number of errors across participants was 2.01%. For each participant, response latencies were calculated for each of the 12 cells of the design, for the standard pictures priming task as well as for the “movements” priming task.

**Standard priming task.** A 3 (SOA: 300 ms vs. 500 ms vs. 1000 ms) × 2 (affective congruency: congruent vs. incongruent) × 2 (target: positive vs. negative) repeated-measure ANOVA was performed upon the mean latencies for the standard priming task. All variables were within-subject. ANOVA revealed the predicted SOA × congruency interaction, $F(2, 18) = 4.80; p < .05; MSE = 1565$. As Fig. 1 displays, at SOA 300 ms participants were faster in categorising the targets during congruent pairs than during incongruent pairs. At SOA 500 ms and at SOA 1000 ms the congruency effect seemed to disappear. A priori F-tests confirmed this view. At SOA 300 ms ($F(1, 19) = 13.90; p < .001$), the congruency effect was significant, but not at SOA 500 ms ($F(1, 19) = 2.71$) and at SOA 1000 ms ($F(1, 19) = 1.20$). There was also a significant main effect of target, $F(1, 19) = 11.01; p < .005; MSE = 3946$, indicating faster responses to positive targets (mean = 513 ms) than to negative targets (mean = 540 ms). Furthermore, a significant main effect of SOA was found, $F(2, 38) = 3.75; p < .05; MSE = 5186$, indicating slower responses to short SOAs. All other effects were non-significant (congruency, $F(1, 19) = 3.73; MSE = 1008$, SOA × target, $F(2, 38) = .20; MSE = 1475$, congruency × target, $F(1, 19) = .41; MSE = 1584$, SOA × congruency × target, $F(2, 38) = 1.30; MSE = 2025$).

**“Back stressing movements” priming task.** A similar 3 (SOA: 300 ms vs. 500 ms vs. 1000 ms) × 2 (affective congruency: congruent vs. incongruent) × 2 (target: positive vs. negative) repeated-measure ANOVA upon the mean latencies for the “back-stressing movements” priming task revealed a significant main effect of congruency, $F(1, 19) = 6.35; p < .05; MSE = 1586$ (see Fig. 2). There was no significant interaction between SOA and congruency, $F(2, 38) = .37; MSE = 2872$. Other

![Fig. 2. Mean reaction time for congruent (low threat-positive/high threat-negative) and incongruent (low threat-negative/high threat-positive) pairs for pain-free subjects on the “back-stressing movements” priming task.](image-url)

![Fig. 1. Mean reaction time for congruent (positive-positive/negative-negative) and incongruent (positive-negative/negative-positive) pairs for pain-free subjects on the standard priming task, as a function of the time between the onset of the picture prime and the onset of the target word (SOA).](image-url)
significant effects were the main effect of SOA, $F(2, 18) = 9.41; p < .005$; $MSE = 3462$. and of target, $F(1, 19) = 41.42; p < .0005$; $MSE = 1010$. All other effects failed to reach significance [congruency x target, $F(1, 19) = .79; MSE = 615$. SOA x target, $F(2, 38) = .13; MSE = 1403$. and SOA x congruency x target, $F(2, 38) = .62; MSE = 1180$].

2.3. Discussion

Study 1 clearly replicates the standard affective priming effect (Barth et al., 1992, 1996; Fazio et al., 1986; Hermans et al., 1994). Participants were faster in categorising targets as positive or negative when these were preceded by affectively congruent primes. The finding that the effect is present at SOA 300 ms is in line with the idea that the affective priming effect is a fast and automatic process: controlled or strategic processes are presumed to need more time to be recruited (Neeley, 1977).

Of interest, but also to our surprise, we found an affective priming effect when pictures of back-stressing movements were used as primes. This effect was not moderated by SOA. Overall, pain-free participants were faster to evaluate affectively congruent pairs (high threatening movement-negative target/low threatening movement-positive target) than affectively incongruent pairs (high threatening movement-positive target/low threatening movement-negative target).

In the next study, both priming tasks will be run in low back pain patients. Taking into account the results of study 1, we expected a replication of the affective priming effect in both priming tasks. In addition, as we presumed that the negative attitudes towards back-stressing activities would be more pronounced in back pain patients, we expected that the evaluative-negative attitudes would be more rapidly evoked, thus appearing at the shortest SOAs. Finally, as it might be expected that patients differ in their negative attitude towards back straining activities (Crombez et al., 1999), we wanted to explore the influence of individual difference variables, such as catastrophic thinking about pain and pain-related fear, on the priming effect.

3. Study 2

3.1. Methods

Participants. Thirty patients between 18 and 65 years of age with non-specific chronic or recurrent low back pain were recruited from the Department of Physical Medicine and Rehabilitation at the University Hospital in Ghent, Belgium. All participants were white Caucasians. The mean age was 43.30 years ($SD = 9.56$). The majority of participants were female (63.3%) and 76.8% was married or cohabiting. Almost half of the patients (43.3%) finished a higher education. The average duration since time of pain onset was 97.07 months ($SD = 109.04$; range = 4 months–39 years), and 23.3% of the patients had undergone at least one spinal surgery. Sixteen patients (53.3%) were not in paid employment. All patients gave informed consent. The study was approved by the Ethics Committee of the Ghent University Hospital.

Procedure. Material and procedure were almost identical to the first study. After the affective priming tasks, patients received a number of questionnaires to assess following constructs: Fear of (re)injury due to movement was assessed by the Dutch version of the Tampa Scale for Kinesiophobia (TSK; Kori et al., 1990; Vlaeyen et al., 1995), which consists of 17 items measured on a 4-point scale with scoring alternatives ranging from ‘strongly agree’ to ‘strongly disagree’ (e.g., ‘I wouldn’t have this much pain if there weren’t something potentially dangerous going on in my body’). The TSK is reliable ($z = 0.78$) and valid (Goubert et al., 2000). Significant correlations were found with measures of pain intensity, catastrophizing, impact of pain on daily life activities, and generalised fear.

To measure pain catastrophizing, the Dutch version of the Pain Catastrophizing Scale was used (PCS; Sullivan et al., 1995; Van Damme et al., 2002). This is a 13-item scale developed for both non-clinical and clinical populations. Participants reflect on past painful experiences and indicate the degree to which they experienced thoughts and feelings during pain on a 5-point scale (e.g., ‘I can’t seem to keep it out of my mind’, ‘I feel I can’t stand it any more’). The Dutch version has a good reliability and validity in a student population (Crombez et al., 1998) and in a clinical population (Crombez et al., 1999; Van Damme et al., 2000).

State Anxiety was measured by the Dutch version of the state form of the State-Trait Anxiety Inventory (STAI-state; recent version: Spielberger et al., 1983; Van der Ploeg et al., 1980). The questionnaire consists of 20 items (e.g., ‘I am confused’). Patients are asked to rate on a 4-point scale how one feels on this moment. The Dutch version has proven reliable (Hermans, 1994; Van der Ploeg et al., 1980) and valid (Van der Ploeg et al., 1980).

Finally, the Dutch version of the Multidimensional Pain Inventory—Part 1 (MPI-DV; Kerns et al., 1985; Lousberg et al., 1999) was administered. Part 1 of the

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4 Priming were idiosyncratically selected. The most frequently selected pictures were the following: evaluative-positive standard pictures (2540: woman with baby, 15.8% and 2340: man with kids, 17.5%); evaluative-negative standard pictures (9040: starving baby, 20.0% and 2800: sobbing baby, 17.5%); low-threatening movements (94: walking, 18.3%: standing, 14.2% and 25: hanging up a coat, 14.2%); high-threatening movements (19: raising a heavy beam, 21.7%: 2: digging in garden, 21.7% and 20: lifting a crate of beer, 17.9%).
MPI-DV consists of five scales: pain severity (3 items), interference with daily life due to pain (11 items), perceived life control (4 items), affective distress (3 items), and social support (3 items). The Dutch version of the MPI has shown to have good reliability and validity (Lousberg et al., 1999).

3.2. Results

Self-reports. In comparison with the MPI-DV results of a patient group entering a cognitive-behavioural rehabilitation program (Lousberg et al., 1999), the severity of the pain complaints in this patient sample is moderate to average. The mean score of the pain severity scale was 3.24 (SD = 1.39; mean of comparison group = 4.50; \( t(30) = -4.93, p < .0005 \)), mean score of the interference scale was 3.74 (SD = 1.52; mean of comparison group = 4.52; \( t(30) = -2.80, p < .005 \)), mean score of the affective distress scale was 2.87 (SD = .90; mean of comparison group = 3.24; \( t(34) = -2.17, p < .025 \)), mean score of the life control scale was 3.92 (SD = 1.23; mean of comparison group = 3.12; \( t(32) = 3.49, p < .005 \)), and the mean score of the social support scale was 4.53 (SD = 1.44; mean of comparison group = 4.78; \( t(31) = -9.4, p < .01 \)).

Furthermore, the means of the TSK-DV (M = 43.02, SD = 9.22, percentile 7) and the PCS-DV (M = 24.87, SD = 11.94, percentile 7) in this patient sample indicated a high degree of fear of movement/reinjury and catastrophic pain-related thoughts compared to norms for Dutch-speaking chronic low back pain patients (Gouwerts et al., 2000; Van Damme et al., 2000).

Affective priming. As in previous research (De Houwer and Hermans, 1994; Hermans et al., 1994, 2001), all reaction times below 250 ms and over 1500 ms (.51%) were discarded from the analysis. Also, all trials on which an incorrect response was given (e.g., positive instead of negative) were discarded from the analysis (.76% of all trials). As in study 1, mean response latencies were computed for the standard priming task as well as for the “back-stressing movements” priming task.

Standard priming task. A 3 (SOA: 300 vs. 500 vs. 1000 ms) × 2 (affective congruency: congruent vs. incongruent) × 2 (target: positive vs. negative) repeated-measure ANOVA was performed on the mean latencies for the standard priming task. All variables were within-subject. Although the findings were in line of our expectations no significant main effect of incongruency was found, \( F(1,29) = .15; \text{MSE} = 3554; \text{M} = 641.75, \text{SD} = 18.91; M_{\text{congruent}} = 639.25, \text{SD} = 19.69 \). The relevant SOA × congruence interaction effect also failed to reach significance, \( F(2,58) = 1.24; \text{MSE} = 3551 \). Only a main effect of target was observed, \( F(1,29) = 9.46, p < .005; \text{MSE} = 9418 \). Response latencies for positive targets were significantly shorter than response latencies for negative targets. Finally, also the congruency × target interaction (\( F(1,29) = 1.75; \text{MSE} = 2262 \)) and the SOA × congruency × target interaction (\( F(2,58) = 1.56; \text{MSE} = 2757 \)) failed to reach significance.

“Back-stressing movements” priming task. A similar 3 × 2 × 2 repeated-measure ANOVA upon the mean latencies for the “back-stressing movements” priming task revealed a significant main effect of congruency, \( F(1,29) = 4.49, p < .05; \text{MSE} = 3345 \). However, as can be seen in Fig. 3, the effect was opposite to that of study 1. For chronic low back pain patients, mean latencies for affectively congruent trials were longer than for affectively incongruent trials. Thus, patients were faster to evaluate a positive word when it was preceded by a picture of a high-threatening movement than when it was preceded by a picture of a low-threatening movement. Similar response latencies to a negative word were shorter when it was preceded by a picture of a low-threatening movement than when it was preceded by a picture of a high-threatening movement. The SOA × congruency interaction effect failed to reach significance, \( F(2,58) = .10; \text{MSE} = 3013 \). There were also significant main effects of SOA, \( F(2,58) = 10.37, \epsilon = .81; NDf (1.62, 46.86); p < .0005; M_\text{SOA} = 1241^6 \) and target, \( F(1,29) = 20.41, p < .0005; M_\text{target} = 6600 \). Again, response latencies were shorter for positive primes than for negative primes. The other effects failed to reach significance: [congruency × target, \( F(1,29) = 1.69; \text{MSE} = 4147 \); SOA × congruency × target, \( F(2,58) = .09; \text{MSE} = 2587 \)].

Fig. 3. Mean reaction time for congruent (low threat-positive/high threat-negative) and incongruent (low threat-negative/high threat-positive) pairs for chronic low back pain patients on the “back-stressing movements” priming task.

\(^5\) Merging the data of study 1 and 2, a 2 (group: pain-free participants vs. chronic low back pain patients) × 3 (SOA: 300 vs. 500 vs. 1000 ms) × 2 (affective congruency: congruent vs. incongruent) × 2 (target: positive vs. negative) repeated-measure ANOVA was performed upon the mean latencies for the ‘movements priming task’, with group as between-subject variable. A significant congruency × group interaction was found, \( F(1,48) = 9.10, p < .005; \text{MSE} = 2649 \).

\(^6\) Greenhouse-Geisser corrections (with adjusted degrees of freedom) were performed and stated whenever the sphericity assumption was violated (Mauchly’s Test of Sphericity, \( p < .05 \)).
The influence of individual difference variables. To further explore the role of individual difference variables, we calculated a measure of the degree of the affective priming effect by subtracting the response latencies on the congruent condition (high-threatening movements as primes followed by a negative target word) from the response latencies on the incongruent condition (high-threatening movements as primes followed by a positive target word). We correlated this index with pain catastrophizing, fear of pain/movement/(re)injury and state anxiety. The correlation between the measure of affective priming and fear of movement/(re)injury was consistent with the reverse priming effect, but failed to reach significance \((r = -.24, \text{ ns})\). Also, the correlations between pain catastrophizing, respectively, state anxiety and affective priming were non-significant (respectively, \(r = -.006, r = .24\)). As in previous studies, a significant correlation was observed between the TSK-DV and the PCS \((r = .70, p < .0005)\).

3.3. Discussion

The results of study 2 can be readily summarised. There was no affective priming in the task with standard pictures. As yet, we have no full explanation for this result, but a possibility is the reduced statistical power owing to a large error variance in clinical samples. There was, however, an effect in the task with pictures of back-stressing movements as primes. The latter effect consisted of reverse priming. In contrast to our expectation, mean response latencies on affectively incongruent trials were shorter than on affectively congruent trials. This reverse priming effect was not moderated by SOA.

The results of the “back-stressing movements” priming task were unexpected. A reverse priming effect was found. It is highly implausible that the pictures of high-threatening movements were perceived as positive as they were idiosyncratically selected. In previous research, a reverse priming effect using a standard affective priming task has first been published by Glaser and colleagues (Glaser, 2001; Glaser and Banaji, 1999). In a series of experiments in normal subjects, they demonstrated the robustness of the reverse priming effect in the context of extreme attitudes towards race words, race-neutral words and race-neutral food words (Glaser and Banaji, 1999). They explained the reverse priming by suggesting that participants recognized the possibility that evaluative-extreme primes interfere with the categorisation of the target words. According to them, as participants are motivated to respond accurately they will attempt to correct for that possible interference effect resulting in an overcompensation (as do many corrections in psychological phenomena, see Helson, 1948). This correction is also considered automatic (Glaser, 2001; Glaser and Banaji, 1999). The above-described overcompensation process may offer a possible explanation for the reverse priming effect found in the “back-stressing movements” priming task in chronic low back pain patients. Probably back-stressing activities are perceived as extremely negative in patients with chronic low back pain. Since these extreme primes threaten to bias the response to the target word, patients may be highly motivated to respond accurately. In line with this idea is the observation that chronic low back pain patients seem to make fewer errors in the priming task with back-stressing movements in comparison with the pain-free subjects.

4. General discussion

Of particular importance in both studies was the affective priming task with back-stressing movements. Unexpectedly, we found an affective priming effect in pain-free subjects. This finding is of interest for several reasons. First, primes in our study consist of pictures of movements instead of pictures of objects or stimuli. Therefore this is the first demonstration of affective priming with pictures of movements as prime. It is not unreasonable to assume that these movement primes are more complex and therefore may require more time to process and to influence target categorisation. This might explain why the affective priming effect is not moderated by SOA. Second, a negative implicit attitude towards high threatening back movements is found in pain-free subjects. This was an unexpected finding as we assumed that a negative attitude towards back-stressing activities develops as a consequence of the experience of chronic pain. There are several possible explanations for our findings. First, a negative attitude may not be specific for patients suffering from chronic pain, but may also develop as a result of acute or recurrent pain. A large proportion of the general population has already experienced a back pain episode in their life (Papageorgiou et al., 1995; Von Korff et al., 1993). Therefore, the experience of acute or recurrent pain may be sufficient for the acquisition of a negative implicit attitude towards back-stressing movements. A second explanation could be the existence of cultural beliefs about back pain, in particular beliefs about the dangerousness of performing back-stressing movements. Indeed, research has shown that myths about back pain and back-
stressing movements are prevalent among Western societies (Deyo, 1998). Examples are: “If your back hurts, you should take it easy until the pain goes away”, “Bed rest is the mainstay of therapy”.

In contrast to study 1, we found a reverse priming effect in chronic low back pain patients. A possible explanation could be the evaluative extremity of the picture primes. The attitude towards back-stressing movements may be extremely negative in chronic low back pain patients, and, being aware of the risk of interference, patients may be highly motivated to respond accurately. However, in their attempt to respond accurately they may overcompensate when asked to categorise target words (Glaser, 2001; Glaser and Banaji, 1999). Either way, the primes have a clear effect on the categorisation of the words. The results are not conclusive regarding the speed of the priming process: the effect is not moderated by SOA.

Research about implicit attitudes is a new, but promising, research area. Our results point out some implications and new avenues of research. First, the affective priming effect found in pain-free subjects suggests that most people have a negative attitude towards back-stressing activities. This highlights the importance of health education about back pain and coping with back pain in persons without pain. It is highly feasible that this campaign has to start early in life, as research has shown that once learned attitudes are difficult to change (Bouton, 2000). The second implication concerns interventions in chronic low back pain patients. Common sense assumes that giving information is a necessary and sufficient condition to alter negative attitudes towards back-stressing activities. If strong negative attitudes already exist, it is doubtful whether the provision of explicit information has an effect on the implicit level. This needs to be further investigated. The affective priming paradigm appears to be a useful paradigm to study the impact of explicit information upon implicit attitudes. Next to information, the actual experience that back-stressing movements are a dynamic and gradual process (Crombez et al., in press; Goubert et al., 2002). Finally, as negative attitudes towards back-stressing activities are widespread, also many health care workers hold such negative attitude (Rainville et al., 2000). Using a questionnaire survey, Rainville et al. (2000) found that most physicians believe that chronic back pain necessitates some avoidance of activities and justifies some level of disability. For this reason, they frequently recommend avoidance of painful activities or greater restrictions. With the increase of clinical guidelines and its dissemination, an increase in explicit knowledge is to be expected among health care providers. However, it still has to be investigated whether this has an impact upon the implicit level and upon daily practice. In line with the view of Fazio (1990), it might be expected that implicit attitudes are more important than explicit attitudes in influencing the advice and recommendations to patients in daily clinical practice as health care providers have often no full opportunity to rationally weigh all arguments in their busy practice. In such situations implicit attitudes are automatically activated and direct behaviour and communication. In this way, health care providers reinforce the implicit negative attitudes of their patients.

There are some limitations to our investigation. First, we did not obtain numerical self-report ratings of the picture primes. Therefore, we have no converging evidence that chronic low back pain patients rate back-stressing movements as more negative than pain-free subjects. Second, as this study is the first to our knowledge that investigated implicit attitudes in pain patients, further research is needed to replicate and to extend our findings. In particular, more and less extensive (back-straining) primes (on the basis of idiosyncratic selection) could be used to test the hypothesis that the reverse priming effect is attributable to evaluative extremity. Third, more research into this area of implicit attitudes towards back-stressing movements is required using other paradigms, such as the implicit association task (Greenwald et al., 1998; Greenwald and Banaji, 1995). Fourth, although the effects for the standard priming task were in the expected direction in chronic low back pain patients, the results were non-significant. One of the reasons for the lack of statistical significance could be the great variability of the response latencies in the patient group. Therefore, replication is needed with a greater patient group.

References


The treatment of complex regional pain syndrome (CRPS) involving upper extremity with continuous sensory analgesia

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Abstract

Continuous sensory analgesia of brachial plexus (CSA BP) was only occasionally reported to have been used in the treatment of CRPS. In the past four years, we have treated 21 patients with a working diagnosis of CRPS. The treatment was instituted one to six months after inciting injury. All patients were admitted to hospital. In the first two days, the therapy consisted of elevation, cryotherapy, and active exercises. Five patients responded well to this initial physiotherapy (5/21). In 16 cases, no evident improvement was observed and CSA BP was introduced. At follow-up (3–36 months), the results were: 13/16 (81%) had at least good results (excellent 2, good without any sequelae 5, good with sequelae of initial injury 6, and poor 3).

The results were judged as follows: excellent (completely normal hand); good (only temporary pain up to 2 on a 0–10 numeric rating scale; no signs of dysfunction of sympathetic nervous system; ROM of wrist over 50% of normal hand; ROM of fingers excellent or good; and the strength of hand grasp and key pinch over 50% of normal hand measured with dynamometer) and if any of the former criteria was missing, the result was defined as poor.

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Keywords: CRPS; Upper extremity; Continuous sensory analgesia; Results

1. Introduction

Despite great efforts all over the world, CRPS I/RSD/ Sudeck is still an enigma. Its pathophysiology is unknown, diagnostic criteria are still debatable, and the results of treatment are poor (Gaier et al., 2001).

For years, a continuous brachial plexus anesthesia/analgesia (CSA BP) has been our method of choice in the treatment of serious hand injuries, especially crush injuries with vascular damage. It combines the advantages of pain relief and sympatholysis. The catheter was inserted into the perineural sheath of the brachial plexus by axillary or vertical infraclavicular approach. Sensory blockade was established by intermittent injections of bupivacaine in a concentration that did not affect motor function of the hand. Our intentions were twofold: (a) early and painless active exercises and (b) to diminish the possibility of vasoconstriction and threatening thrombosis of sutured vessels. Since the treatment of CRPS has a similar goal, we have conducted the pilot study from 1996 to 1998, trying to determine the possible role of CSA in the treatment of CRPS. These first and promising results have been presented and published as preliminary report (Margaric and Pirc, 1998). Since then, all patients with a working diagnosis of CRPS have been included in this study.

2. Methods

2.1. Selection of patients

Our hospital covers the northwest part of Slovenia with around 110,000 inhabitants. Based on the organization of health care, almost all patients in this area are referred to our hospital and, subsequently, almost all hand injuries and diseases are treated at our department. Being the division of general surgery department (in-
cluding trauma and orthopedic surgery), our concept of treatment was soon accepted by all surgeons and thereafter by general practitioners and physiotherapists. So, all patients suspected of having CRPS were sooner or later referred to us.

2.2. Diagnostic criteria

Working diagnosis of CRPS was applied only to patients who have fulfilled IASP criteria (Janig, 1996; Merskey and Bogduk, 1994) and where dominant signs/symptoms were continuous with unexplained pain at rest and aggravated during attempted activities, altered skin color and temperature, edema, and reduced range of movements (Bruehl et al., 1999; Harden et al., 1999; Hord and Mueed, 2001).

2.3. Treatment protocol

All patients were hospitalized and the initial working diagnosis was checked again. For the first two days, elevation, cryotherapy (application of cold as an ice massage), and active stress loading program (Watson and Carlson, 1987) were introduced. On the third day, the reaction to this initial treatment was checked. If the response was good, we continued the same treatment for a few days. If this initial treatment was unsuccessful, brachial plexus catheter was inserted and a continuous sensory analgesia started. Brachial plexus block was established with a bolus of 15 ml of 0.25% bupivacaine, and then, depending on the degree of motor blockade, the concentration and volume of the anesthetic were reduced. A continuous analgesia was provided by intermittent injections of 10–15 ml of 0.25–0.125% bupivacaine every 6 h. The aim was to achieve good sensory analgesia without motor blockade. Since the motor function was unaffected, an active and painless exercise program was possible.

On the seventh day, the analgesia was withdrawn but the axillary catheter was left "in situ" and the program of elevation and active exercises was carried on. In this period, some painful conditions were noted and immediately treated. If, on the 10th day, there was a significant relief of pain and improvement of active round of movement (ROM) then the catheter was removed and a few days later the patient was discharged. At home, elevation, cryotherapy, and active exercises without pain were recommended. Patients were instructed to contact us if they notice any worsening; the first control was scheduled one to three months later.

2.4. Outcome variables

2.4.1. Pain

Pain was divided into local and diffuse. It was measured by using 0–10 numeric rating scale. Diffuse pain was described as pain at rest, pain during or after normal daily activities or as pain after unusually heavy work, a local one as myofascial trigger points, pain caused by evident pathological background or as complications/sequelae of initial injury.

2.4.2. Functional measurements

Activities: Patients were asked if they have any problems at work, during normal daily activities, during hobbies, or if they have changed the working place because of CRPS.

Mobility:

- **Fingers**: Range of movements (ROMs) was measured in degrees and graded as:
  - (a) Excellent.
  - (b) Very good: lack of extension up to 15°, when fingers are flexed the distance from pulp to distal palmar crease has to be equal to or less than 1 cm.
  - (c) Good: lack of extension equal to or less than 30°, with flexed fingers that can touch the palm.
  - (d) Poor: lack of extension or flexion greater than under paragraph c.

- **Wrist**: Measured values were those of extension, flexion, radial and ulnar deviation, and pronation and supination. They were measured in degrees and expressed as percentage of movement of the unaffected part. Results were divided in to:
  - (a) Excellent.
  - (b) Good: compared with the unaffected part the total ROM was 50% or higher.
  - (c) Poor: ROM <50%.

- **Strength**: Grip and pinch strength were measured with dynamometer:
  - (a) Excellent.
  - (b) Good: results equal to or higher than 50% of the unaffected part.
  - (c) Poor: strength <50% of opposite hand.

2.4.3. Final results were presented as

I. Excellent: completely normal hand.

II. Good (all the following criteria must be fulfilled):

1. Only temporary pain up to 2 on the 0–10 numeric rating scale.

2. No signs of dysfunction of the sympathetic nervous system.

3. ROM of wrist estimated at least as good.

4. ROM of fingers marked as good or better.

5. Good strength of grasp and key pinch.

III. Good with sequelae.

Patients with sequelae/complications of initial injury or those with worsening of a preexisting condition (osteoarthritis, nerve compression, etc.). In similar situations when all signs of CRPS have disappeared the final result was determined by using the criteria accepted for assessing the results of treatment of initial injury.
IV. Poor.
If any criterion described above was missing, the result was defined as poor.

3. Results

From 1996 to 2000, we have treated 21 patients with established diagnosis of CRPS of upper extremity. There were four men and 17 women, the mean age was 58 years (arithmetical mean value $x = 58$, $SD = 12.14$). The diagnosis of CRPS was confirmed and the treatment was introduced in one to six months after injury ($x = 3.7$). Mean hospitalization stay was $x = 13.16$ days (range 3–30). One of us (MK) saw all patients 3–36 months after treatment ($x = 13.8$, $SD = 7.73$ months). Later, all were contacted by phone one to three years afterwards: they stated that their current status was similar to or better than that on their last visit.

3.1. Epidemiology and demography

Since community covered by our hospital is relatively close, we can calculate that the incidence of CRPS affecting upper extremity is 5–6 per 100,000 inhabitants per year. Our data show female preponderance similar to other reports, but our population was older, with 14 cases over 50 and 6 of them over 70 years (Allen et al., 1999; Galer et al., 2001).

Most of our patients were either retired or housewives, or injured out of work, and therefore “on-the-job” injuries, and legal or worker compensation issues have not influenced the outcome.

3.2. Inciting injury

At the upper extremity, the most common inciting injuries were the fractures of wrist (11/21). Ten of them were treated by closed reduction and immobilization. In the second place were fractures of metacarpals and phalanges (3/21), and carpal tunnel release (3/21).

3.3. Myofascial trigger points

Myofascial trigger points were found proximally to anesthetic areas in nine (9/21) patients. They have responded well to the local injection of steroids. This proximal myofascial pain could be an important factor in vicious cycle of disease and must therefore not be overlooked (Allen et al., 1999; Galer et al., 2001; Rashiq and Galer, 1999).

3.4. Operative procedures during and after treatment of CRPS

In five patients, painful conditions were treated surgically. Two were operated during initial CSA (carpal tunnel release in a case where electrodiagnosis done few months before inciting injury has demonstrated severe entrapment neuropathy and removal of screw) and three few months afterwards (arthrodeses of two proximal interphalangeal joints, removal of plate and screws, and carpal tunnel release). These procedures have not worsened the present illness nor influenced the outcome.

3.5. Results of the treatment

Initial physiotherapy (elevation, cryotherapy, and active exercises) caused rapid improvement in five (5/21) hospitalized cases. Two (2/5) had prompt and full recovery, while three of them (3/5) were dismissed as good results with sequelae of inciting injury. CRPS of upper extremity was refractory to this initial “conservative” treatment in 16 out of the 21 cases and CSA BP was introduced. At follow-up, 13/16 (81%) have had good to excellent result (excellent 2, good without sequelae 5, good with sequelae 6, and poor 3). Six patients were qualified as good with sequelae. Three of them have sustained crush injuries that have led to osteoarthritides, arthrodeses and pain after heavy work, and diminished mobility and strength. In one patient, fracture of distal humerus caused lesion of the ulnar nerve, hence final measurements were influenced by nerve dysfunction.

Two of the three poor results were in one patient. She had symptoms on both hands; both after carpal tunnel release, both were treated with CSA. A year after the last treatment, she died of malignant disease. The second patient was an unemployed woman, without formal education. She lost her job after the initial injury. Two years after the treatment she has pain only after heavy work (up to 4), wrist mobility up to 49%, good ROM of fingers, and only 30% of strength in the unaffected hand.

4. Discussion

4.1. Diagnostic criteria

IASP diagnostic criteria for CRPS seem to be too loose. It was documented that immobilization alone can cause all signs of CRPS (Butler et al., 2000). Similar signs were noted in some posttraumatic conditions with spontaneous remission (Birklein et al., 2001). In some of our patients, full remission was observed after hospitalization and initial physiotherapy. In the second group, the CSA was necessary to control the symptoms. Therefore, we temporarily use the term complex posttraumatic reaction (CRPS-CPR) for patients where hospitalization was necessary for rapid and full recovery. It seems that hospitalisation is necessary to pull them out of their surroundings and to demonstrate to the patient himself and his neighborhood that the illness is serious. Released from everyday duties, they can fi-
nally start with elevation, cryotherapy, and active exercises. In this group, signs of CRPS have quickly disappeared uncovering initial cause or its sequelae.

4.2. Surgical procedures

Surgery on the extremity affected with complex regional pain syndrome is generally avoided. In our study, five patients were operated in acute stage or few months later. All were done in brachial plexus anesthesia, followed by CSA. There was no worsening or recurrence.

Authors believe that CSA interrupts the "circulus vicious" of pain and that all painful conditions should be treated immediately; therefore, we do not hesitate to operate in the acute stage.

4.3. Outcome measurements

Describing the results of treatment, almost all authors use similar terminology: diminished pain and improved mobility. Since there are no exact and comparable criteria in the literature, we were forced to suggest those we have used in the assessment of the results of specific injuries. Furthermore, we suggest that only the completely normal hand can be accepted as an excellent result. Extremity with minimal impairment can be described as a very good outcome. The largest, and most heterogenous groups, are those classified as good results. The first wish of any patient is pain relief; normal function is desired but not necessary (Galer et al., 2001). Therefore, only a complete relief of diffuse continuous pain can be assumed as a good result. For a good result, the function of the involved hand must reach at least 50% of a normal hand.

There are no reports in the literature on local pain and functional impairment as complications or sequelae of initial injury. These problems must be properly diagnosed and treated. From our point of view when comparing results, the residual local pain and complications attributed to initial injury must be excluded or neglected. Therefore, we distinguish two subgroups of good results: good without and good with complications or sequelae of initial injury.

4.4. CSA BP

Brachial plexus block as a method of treatment of CRPS is only occasionally mentioned and even then it was successfully used in few patients (Klein and Klein, 1991; Murray and Atkinson, 1995; Ribbers et al., 1997; Wang et al., 2001). Intermittent or continuous block of sympathetic nervous system was successfully used in few occasions (Gibbons et al., 1992; Linson et al., 1983). We have used CSA BP routinely in all patients that have not responded to initial "conservative" approach. In this report, CSA BP was instituted in first months after injury, that is, in the early stage of the disease, yet, the published case reports suggest that it can be successfully used in later stages too.

We are aware that CSA is sensory and sympathetic blockade. Our prime goal was not to find the difference between them but to eliminate the painful condition.

4.5. The duration of CSA BP

All our recommendations are based on our trial and errors. The sensory block of brachial plexus was maintained for 6-7 days. Then, the analgesia was stopped, but the catheter was left in place in case the patient would need some more analgesia in the following days. Patients were asked to measure their pain using a numeric scale and to report any point of permanent pain, or if intermittent pain was greater than 2 on a 0-10 numeric scale.

Aggressive active exercises can displace the catheter. In one patient, axillary catheter got dislodged the second day and as it was not replaced immediately all the symptoms returned. It seems to be important that the analgesia is not interrupted.

5. Conclusion

CSA BP was used in the treatment of early stage of CRPS of upper extremity in 16 cases that have fulfilled all diagnostic criteria. The result was excellent in two, good in 11, and poor in three. In all cases, continuous pain and allodynia disappeared in a few days and the mobility was significantly improved. There were no recurrences of the disease.

References


Comparison of the effect of video glasses and nitrous oxide analgesia on the perceived intensity of pain and unpleasantness evoked by dental scaling

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Abstract

The aim of this study was to evaluate whether distraction induced by video glasses had an effect on the perceived intensity of pain and unpleasantness during dental scaling compared with the effect of nitrous oxide (N\textsubscript{2}O) analgesia. The pain stimulus was dental scaling (removal of dental calculus) with an ultrasonic scaler. As a standardised, non-dental painful stimulus, Von Frey filaments were used. A total of 26 patients with superficial chronic periodontitis were enrolled in this randomised, controlled clinical study. The effect of video glasses was compared with N\textsubscript{2}O in one session and the effect of video glasses versus a control situation in another. The patients rated the intensity of pain and unpleasantness evoked by dental scaling and Von Frey filament stimulation on 100-mm visual analogue scales (VAS). For dental scaling, there was no effect of video glasses on the perceived pain (p = 0.85) or unpleasantness (p = 0.73) nor of N\textsubscript{2}O (p = 0.63 and p = 0.51, respectively) compared with the control situation. Similarly, no significant difference was found between VAS scores in the video glasses and N\textsubscript{2}O session (p = 0.48, p = 0.53). A significant effect of video glasses and N\textsubscript{2}O (p < 0.008) was found on the perceived pain intensity produced by Von Frey filament stimulation compared with the control situation, but no significant difference was seen between these methods (p = 0.07). Post-treatment interviews of the patients revealed that 81% of the patients in the video and 65% in the N\textsubscript{2}O session stated that the method had some beneficial effect on their overall experience of the treatment situation. In conclusion, administration of video glasses or N\textsubscript{2}O did not affect the perceived intensity of pain and unpleasantness evoked by dental scaling.

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Keywords: Nitrous oxide; Video glasses; Distraction; Pain; Dental scaling

1. Introduction

It is well-known that distraction can influence the perceived unpleasantness and intensity of painful stimuli. Systematic studies on modulation of pain and unpleasantness have documented an effect of showing movies and have demonstrated that humour, repulsive scenes as well as tragedy can increase pain tolerance (Weaver and Zilhmann, 1994; Weisenberg et al., 1995, 1998). In a number of clinical situations, such as abdominal discomfort during flexible sigmoidoscopy (Lembo et al., 1998), burn care pain (Hoffman et al., 2000a,b), and anxiety among children undergoing genital examinations (Berenson et al., 1998), the use of video glasses has proved beneficial. In connection with dental procedures, the use of video-games and video-comedy programmes has been shown to distract patients and provide a hypoalgesic effect (Seyrek et al., 1984).

In accordance, recent experimental studies on the modulation of pain and unpleasantness induced by the cold pressor test have documented a positive effect of distraction by the use of video glasses (Bentsen et al., 1999, 2000). Regarding nitrous oxide (N\textsubscript{2}O), it has been shown to have an hypoalgesic effect on cold pressor pain (Pierce et al., 1995) and to increase the threshold of tolerable pain and touch sensation in the face (Siil et al., 1999). There are, however, a limited number of clinically
controlled studies on the hypoalgesic effect of N₂O (Sprehn et al., 1994).

In a recent clinical study on dental pain (Bentsen et al., 2001), no significant effect of video glasses was found on the perceived pain and unpleasantness when the painful stimulus was the preparation of a tooth cavity for a dental filling. Since pain evoked by drilling in a tooth may be described as sharp, sudden, and intense by the patient, the present study pertained to focus on a different dental pain stimulus, dental scaling. N₂O analgesia during dental scaling is still commonly used in dental practice and has previously been shown to raise the pain threshold and tolerance when the stimulus was electric pulp stimulation (Dworkin et al., 1983).

Thus, the aim of this study was to evaluate whether distraction induced by video transmitted through video glasses has an effect on the perceived intensity of pain and unpleasantness evoked by dental scaling compared with N₂O and a control situation. The specific null hypothesis to be tested was: H₀—there is no difference between the effect of video glasses, N₂O, and a control situation on the perceived intensity of pain and unpleasantness.

2. Materials and methods

2.1. Patients

Patients with a diagnosis of superficial chronic periodontitis (pocket depths 4–5 mm), who were treated regularly with tooth scaling at the School for Dental Hygienists, Aarhus, Denmark, were offered to participate in the study. The patients were very familiar with the clinic and the treatment procedure as they all had been attending the School for Dental Hygienists for more than two years. The patients had not been previously offered N₂O analgesia and were not familiar with video glasses. To estimate the sample size, a former experimental study by the authors on the effect of video glasses was taken into consideration (Bentsen et al., 1999). The variance was in that study 250 and when 10 in the present study was set as the minimal relevant clinical effect measured on a 100-mm visual analogue scale (VAS), it could be calculated that the minimum sample size had to be 20 (α = 0.05 and β = 0.20). To compensate for a possible drop-out, a total of 26 patients (12 female and 14 male) with a mean age of 55 years (range 29–92 years) were enrolled in this randomised, controlled study. All patients gave their informed consent in accordance with the Helsinki Declaration.

2.2. Methods

Two methods with a possible hypoalgesic effect on dental pain, video glasses, and N₂O were administered. The video equipment consisted of a video recorder (NV-HD 660 Panasonic) connected to a pair of video glasses (I-Glasses, Virtual i-O, Seattle, USA), which were used to transmit the video signal to the patient. The pair of video glasses have dimensions that enable the dentist to work almost freely in the oral cavity, and due to the minimal weight (8 ounces/240 gr), they are comfortable for the patient to wear. The patients could choose freely between three music videos: The Beatles’ “Help,” a music video for relaxation (Phoenix film, Denmark), and an opera film with “The three tenors.” These videos had been assessed, prior to the study by the authors to have a neutral, non-offensive content, since it was not the purpose of this study to evaluate distraction in relation to the nature of the videos. The N₂O analgesia was administered with the AnalgesiAn and a 50% N₂O oxygen mixture was used as a standard. The N₂O was administered through a mask covering only the nose connected with a scavenging unit that removed any excess gas. Initially, only oxygen was given and gradually N₂O was added until a continuous flow of 4 L of oxygen per minute and 4 L of N₂O was reached. The patients were instructed to breathe through the nose and after approximately 4 min the scaling began. After the scaling was finished, the analgesia was terminated with breathing pure oxygen for 2 min.

In two clinical sessions with at least a one-week interval, the patients’ root surfaces were scaled with an ultrasonic scaler (Hygienist, Denmark). Two of the patients’ four jaw quadrants were randomly assigned to be scaled at either the first or second session. Both sessions had two randomised treatment sequences, one with video glasses and N₂O analgesia, and the other with video glasses and control (no distraction). In this way, the patients all had two treatment sequences with video glasses.

A non-dental, painful skin stimulus, Von Frey filament (Voerman et al., 1999), which is a standardised method used in similar studies (Siba et al., 1999) with good reproducibility (Bell-Krotoskij and Tomancik, 1987), was incorporated in this study as a control to the dental stimulus. The patients were stimulated five times in a row on the upper lip with the Von Frey filament (Semmes-Weinstein Monofilament, Stoelting, IL, USA) before and during the treatment. At baseline, a particular monofilament size (point load) was chosen, which was reported by the patient to produce a perceived pain of approximately 50 on a 100-mm VAS (Monofilament number: median 5.88, range 4.56–6.10). The same filament was then used during the sessions to measure the patient’s general level of sensitivity. The difference between the VAS score during treatment and the baseline VAS score was defined as a measure for the general effect of the distraction methods.

To evaluate the patient’s general anxiety level at the two clinical sessions, Corah’s dental anxiety scale (Corah et al., 1978) was completed at each session just be-