Pain 136 (2008) 11–20

PAIN

www.elsevier.com/locate/pain

Research papers

Predicting outcome of TENS in chronic pain: A prospective, randomized, placebo controlled trial

Jan Oosterhof [a,b,*], Han J.A. Samwel [a,c], Theo M. de Boo [d], Oliver H.G. Wilder-Smith [a,f], Rob A.B. Oostendorp [e,g], Ben J.P. Crul [a]

[a] *Pain Expertise Centre, Department of Anesthesiology, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands*

[b] *Research Centre for Allied Health Sciences, Department of Physiotherapy, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, 6500 HB Nijmegen, The Netherlands*

[c] *Department of Medical Psychology, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, 6500 HB Nijmegen, The Netherlands*

[d] *Department of Epidemiology & Biostatistics, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, 6500 HB Nijmegen, The Netherlands*

[e] *Research Centre for Allied Health Care, Department of Quality of Care Research, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, 6500 HB Nijmegen, The Netherlands*

[f] *Pain and Nociception Research Group, Department of Anesthesiology, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, 6500 HB Nijmegen, The Netherlands*

[g] *National Institute for Allied Health Care, Amersfoort, The Netherlands*

Received 8 August 2006; received in revised form 8 April 2007; accepted 7 June 2007

Abstract

Transcutaneous electrical nerve stimulation (TENS) is an easy to use non-invasive analgesic intervention applied for diverse pain states. However, effects in man are still inconclusive, especially for chronic pain. Therefore, to explore the factors predicting result of TENS treatment in chronic pain we conducted a prospective, randomized, placebo-controlled trial ($n = 163$), comparing high frequency TENS ($n = 81$) with sham TENS ($n = 82$). Patients' satisfaction (willingness to continue treatment; yes or no) and pain intensity (VAS) were used as outcome measures. The origin of pain and cognitive coping strategies were evaluated as possible predictors for result of TENS treatment. *Results:* Fifty-eight percent of the patients in the TENS group and 42.7% of the sham-TENS group were satisfied with treatment result (chi square = 3.8, $p = 0.05$). No differences were found for pain intensity. Patients diagnosed with osteoarthritis and related disorders (especially of the vertebral column) or peripheral neuropathic pain were less satisfied with high frequency TENS (OR = 0.12 (95% CI 0.04–0.43) and 0.06 (95% CI 0.006–0.67), respectively). Injury of bone and soft tissue (especially postsurgical pain disorder) provided the best results. Treatment modality or interactions with treatment modality did not predict intensity of pain as a result of treatment. We conclude, that predicting the effect of high frequency TENS in chronic pain depends on the choice of outcome measure. Predicting patients' satisfaction with treatment result is related to the origin of pain. Predicting pain intensity reflects mechanisms of pain behavior and perceived control of pain, independent of treatment modality. Pain catastrophizing did not predict TENS treatment outcome.

© 2007 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Keywords: Transcutaneous electrical nerve stimulation; Chronic pain; Predicting outcome; Double-blind randomized controlled trial

1. Introduction

Transcutaneous electrical nerve stimulation (TENS) is an easy to use non-invasive analgesic intervention,

* Corresponding author. Address: Pain Expertise Centre, Department of Anesthesiology, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 243613811; fax: +31 243619404.
E-mail address: j.oosterhof@fysiocss.umcn.nl (J. Oosterhof).

0304-3959/$34.00 © 2007 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.pain.2007.06.009

applied for diverse pain states and introduced in the early 1970s. However, its effects are still inconclusive for chronic pain (Carroll et al., 2004), although a systematic review indicates benefit for pain in osteoarthritis of the knee (Osiri et al., 2004).

A number of causes are considered responsible for inducing or maintaining chronic pain, e.g. inflammation and nerve or spinal cord injury (Woolf, 2004). There are however significant differences in the underlying peripheral mechanisms of nociceptive and neuropathic pain. Damage of deep (muscle, joint and viscera) tissue is typically associated with peripheral inflammation, while injury of nerves often leads to neural degeneration, neuroma formation and generation of spontaneous neural inputs (Coderre et al., 1993). However, both are significantly influenced by changes in the central nervous system (i.e. central sensitization/disinhibition). Interestingly, long-lasting or intense nociceptive barrage from the periphery has been reported to give rise to persistent and self-sustaining central hyperexcitability long after all possible tissue healing has occurred (Coderre et al., 1993). In osteoarthritis however, evidence is found that central hyperexcitability is maintained by nociceptive barrage (Kosek and Ordeberg, 2000), probably by peripheral sensitization, as a result of neurogenic inflammation (Marshall et al., 1990). There is growing evidence that the pain in osteoarthritis is at least partly due to inflammation (Smith et al., 1997).

In animal models, effects of high and low frequency TENS have been extensively studied in inflammation and to a lesser extent in nerve ligation, for review see Sluka and Walsh (2003). High frequency TENS reverses primary and secondary hyperalgesia induced by carrageenan inflammation (Gopalkrishnan and Sluka, 2000; King and Sluka, 2001; Radhakrishnan and Sluka, 2003; Sluka, 2000; Sluka et al., 1998; Sluka et al., 1999), but does not diminish mechanical allodynia following chronic constriction injury of the rat sciatic nerve (Somers and Clemente, 1998). However whether these results are true for high frequency TENS in chronic pain in human research still needs to be explored. In predicting effect of TENS Lampl et al. (1998) found that patients with intractable, stabbing, pulsating, electrifying, paroxysmal and unmodulated pain – suggesting neuropathic pain (Bouhassira et al., 2004) – have less chance to achieve successful treatment outcome.

Besides mechanisms of peripheral and central hyperexcitability, psychological factors also influence chronic pain processing and treatment outcome. Cognitive coping strategies appeared to be correlated with pain intensity (Turner and Clancy, 1986) and especially self-efficacy (Kores et al., 1990) and catastrophizing (Samwel et al., 2000; Thorn et al., 2003) are found to predict outcome of treatment in chronic pain. However, effects of cognitive copings strategies on results of TENS treatment are unknown. Lampl et al. (1998) found that, marked depression, highly stressful conflict situations and ongoing litigation diminished success rate of TENS treatment.

Therefore, the purpose of this study is to explore the effects of the origin of pain and cognitive coping strategies and mood on predicting short-term results of high frequency TENS in the treatment of chronic pain. We expect pain in osteoarthritis and related disorders, but not peripheral neuropathic pain to be a positive predictor for results of high frequency TENS.

2. Methods

2.1. Design

To predict outcome of TENS treatment, we performed a prospective, randomized and controlled trial comparing TENS and sham TENS. A concealed block-wise randomization procedure was used, and patients, therapists and research assistants were blinded for treatment allocation.

2.2. Randomization procedure and concealment of allocation

The researcher assigned consecutive numbers to eligible patients, when they agreed to participate in this study. The research assistant, only delivering the TENS or sham TENS devices to the patients, used these numbers to determine treatment assignment, as provided by the randomization list. This list of sequential numbers, which block-wise refer to treatment allocation, was generated with the help of a computer by the Department of Epidemiology and Biostatistics. To further guarantee concealment, patients were asked to leave their treatment device with the receptionist before visiting the researcher for evaluating treatment after the treatment period.

2.3. Subjects

Patients with chronic pain participating in this study were referred to the Pain Centre of the Radboud University Medical Centre Nijmegen by their family doctor or by a medical specialist. Results of medical investigations were retrieved from the specialists before the patient was invited for the first visit to the Pain Centre. Both anesthesiologists and physiotherapists of the Pain Centre screened patients for TENS treatment.

Patients were eligible for this study if they met the inclusion criteria. Inclusion criteria were: (1) patients with chronic non-cancer pain referred to the Pain Centre, (2) duration of pain >6 months, (3) age above 18 years. Exclusion criteria were: (1) previous TENS treatment (because this could affect sham TENS credibility (Deyo et al., 1990)), (2) pain in face or head (because visible electrode placement might affect compliance, and hair could impair optimal electrode placement), (3) several different pain sites (because of the limited area TENS electrodes can serve), (4) history of a cerebral vascular accident (because possible spinothalamocortical pathway damage could affect the outcome of TENS – and possibly sham TENS treatment, too), (5) no assistance at home – e.g. relatives or friends – to help replace or connect the electrodes, thus jeopardizing optimal TENS use, (6) involvement in ongoing litigation

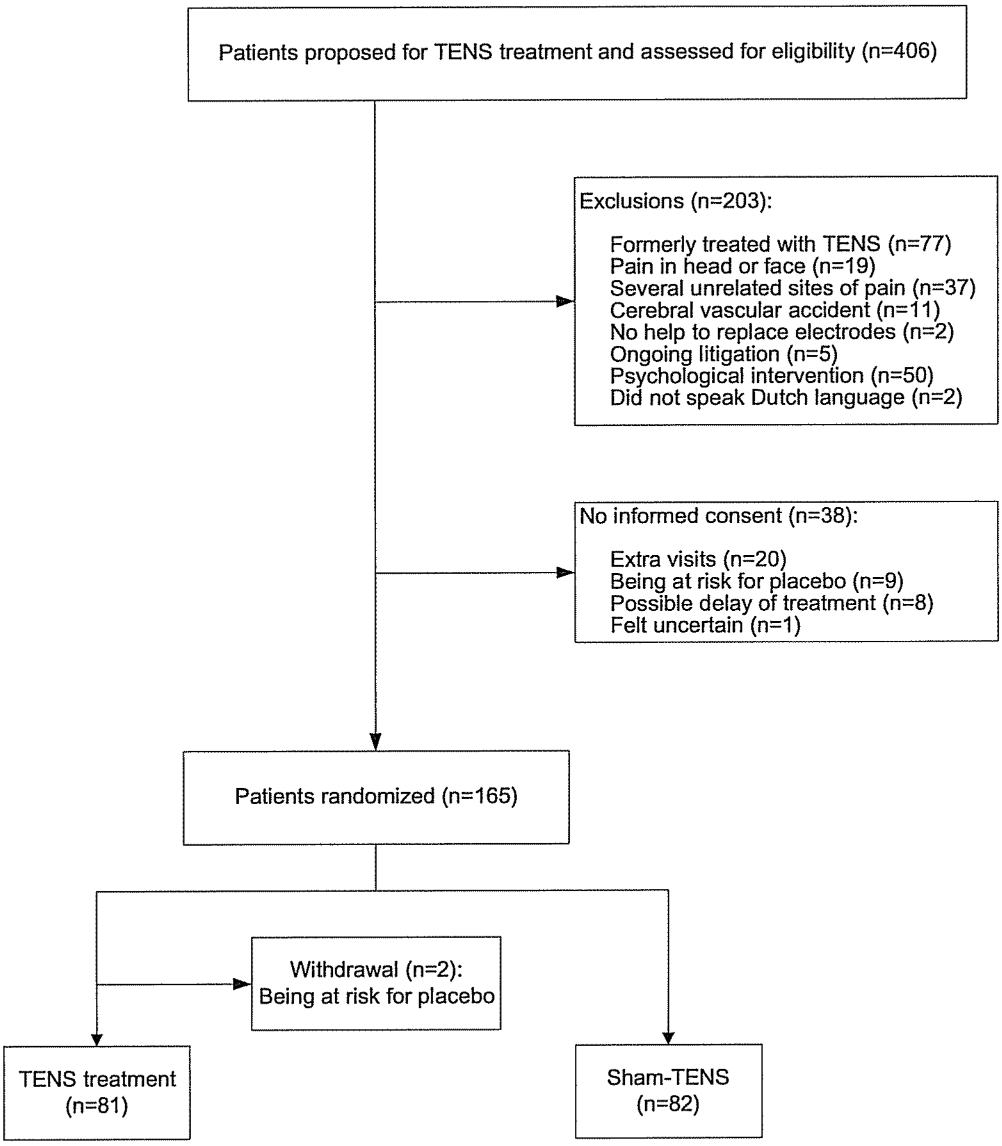

Chart 1.

because of their pain (Lampl et al., 1998) and (7) psychological intervention proposed by the Pain Centre psychologists (this would interact with TENS treatment outcome in an unpredictable way, and withholding it would be unethical). Eligible patients were included in this study after signing informed consent (Chart 1). The Central Committee on Research Involving Human Subjects approved this study.

2.4. Apparatus

For TENS and sham TENS treatment, identical devices (ELPHA II 1000, Danmeter A/S, Denmark) were used, which were specially prepared for this study. For high frequency TENS, stimulation pulse frequency was set to 80 Hz and pulse width to 50 μs. Disposable 5 cm × 6.4 cm self-adhering electrodes were used with an active area of 6.5 cm^2. Sham TENS devices showed a maximum of 10 or 20 mA on the display (current intensity below the level of perception of the patient; assessed during the visit by the physiotherapist), but no current was actually delivered to the electrodes.

2.5. General procedure

Patients eligible for the TENS treatment received written information in which they were asked to participate in the study. In the letter, it was explained that TENS seems to be effective at high and low intensities, and that treatment would be by one of these two options. There would also be a chance of receiving a sham TENS device in which the settings of pulses were neither effective nor harmful.

After inclusion, baseline measures were carried out and one week later patients visited the physiotherapist for TENS application and for instruction on both TENS treatment modalities. Electrodes were applied over the superficial cutaneous nerves in the painful segment(s) (Oosterhof et al., 2003). Once acquainted with the method of treatment, the patient left the physiotherapist and visited the research assistant whose only task was to deliver the high frequency or sham TENS device to the patient, as determined by the randomization list. "With the assignment to apply TENS treatment continuously during the day, and the written instruction how to use the device and not to change pain medication", the patient left the outpatient clinic. Ten days later, the patient returned for evaluation of the treatment effect. More details of the methods are described elsewhere (Oosterhof et al., 2006).

2.6. Outcome measures

Two outcome measures were used to predict result of TENS treatment.

The primary outcome measure was the proportion of patients satisfied with the initial treatment result and willing to continue treatment (yes or no). This outcome measure can be regarded as an index of patients' assessment of the benefits (efficay) of the treatment versus its side effects (e.g. problems in handling the device), providing a patient-based evaluation of treatment (Farrar, 2000). The secondary outcome measure was pain intensity. Pain intensity was measured using a 10-cm VAS, ranging from no pain at all to the most intense pain imaginable (Revill et al., 1976). Patients were instructed to rate their pain from that particular moment on the same time every day, for a period of 14 consecutive days, starting one week before treatment. For this purpose a pain diary was used.

2.7. Predictors

Based on medical causes of pain, patients were classified in three pain diagnoses groups: "Osteoarthritis and related disorders" (ORD) – assuming peripheral sensitization by neurogenic inflammation (Marshall et al., 1990; Smith et al., 1997) – "Peripheral neuropathic pain (PNP)" as a result of lesions of the peripheral nervous system and finally, the remainder of patients was classified as "Injury of bone and soft tissue and visceral pain disorders" (IBST) – assuming self-sustaining central hyperexcitability (Coderre et al., 1993), as there were no signs of inflammation or peripheral nerve lesions, for visceral pain disorders it is suggested that central sensitization may contribute to the pain hypersensitivity (Sarkar et al., 2000). "ORD" was specified as pain related to osteoarthritis, osteoporosis, bursitis and tendonitis – both osteoarthritis and bursitis and tendonitis share mechanisms of peripheral sensitization; the number of nerve fibers immunoreactive to substance P is increased around the vessels of the tissue related to the site of pain (Gotoh et al., 1998; Saito and Koshino, 2000), which also applies for the number of vessels in that area (Ohberg et al., 2001; Saito and Koshino, 2000). The diagnosis of PNP was established when symptoms for neuropathic pain (e.g. allodynia, hyperalgesia, hyperpathia, dysesthesia, paroxysms) were accompanied by a pain related neurological dysfunction, caused by nerve or root injury or compression and because of diabetic neuropathy.

According to Lampl et al. (1998) factors describing severity of pain adversely affect the outcome of TENS treatment. We therefore added the following pain characteristics as possible predictors: intensity of pain, duration of pain, variation in pain, and disability because of pain.

For pain intensity, the average pain level (VAS) of the baseline week was calculated. The standard deviation (SD) was used as a measure of variation of pain. Disability because of pain was measured with the Dutch version of the Pain Disability Index (PDI) (Jerome and Gross, 1991; Pollard, 1984; Tait et al., 1990) questionnaire, which is scored on a scale of 0 (no disability) to 10 (total disability). The items ask for the level of limitations in the total range of role functioning: family/home responsibilities, recreation, social activities, occupation, sexual behavior, self-care and life-supporting activities. Reliability and validity were judged as satisfactory (Gronblad et al., 1993; Tait et al., 1990). The sum of levels of the items scored was used to calculate the disability index.

For psychological factors we selected cognitive coping strategies and perceived control over pain and finally depression as possible predictors for result of TENS treatment.

Pain coping was measured with the Pain Coping Inventory (PCI) (Kraaimaat et al., 1997; Kraaimaat and Evers, 2003), which measures 3 passive cognitive and behavioral coping strategies when dealing with pain. The PCI is rated on a 4-point Likert scale (1): rarely or never to 4: very frequently). Cognitive passive coping is assessed by means of worrying (9 items). Behavioral passive coping is assessed with two scales, retreating and resting (7 and 5 items, respectively). A priori, based on face validity we expected questions 10–13 of retreating (avoid upsetting events, seeking restful environment, avoid annoying sound and avoid light; when in pain) - referring to coping with arousal due to pain- would reflect a separate factor within retreating. We therefore performed a principal component analysis with retreating, which revealed two factors, with only question 14 (Take care of food/drink) loading on a different factor. Accordingly we added the modified construct of retreating containing questions 10–13 and 32–33 (separate myself and return home soon; when in pain) as a possible separate predictor. Arousal due to pain might reflect ongoing or recurrent nociceptive pain caused by peripheral nociceptive stimulation presumably acting in addition to peripheral and central (dorsal horn) sensitization; a condition in which TENS is found to be effective, for review see (Sluka and Walsh, 2003).

Pain cognition was measured with the Pain Cognition List (PCL) (Vlaeyen et al., 1990). This instrument represents a measure for the verbal-cognitive response system of chronic pain and consists of fifty items, each of which is assigned to one of five factors (pain impact, catastrophizing, outcome efficacy, acquiescence and reliance on health care). Items are scored on a 5-point scale (1: highly disagree to 5: totally agree). In our study the scales for catastrophizing and negative self-efficacy were used to predict outcome.

Perceived control over pain was measured by answering the following question: "Can you decrease the severity of your pain by performing activities; distracting from pain; relaxation exercises; reducing activities or resting; or none of these possibilities?" Patients were assigned to one of three groups. Group number one comprised of patients perceiving no control; group number two consisted of patients only perceiving control by decreasing activities or resting and group number three were patients perceiving control by activities, distraction or relaxation exercises.

Depression was measured with the Dutch version of the Beck Depression Inventory (BDI) (Bouman and Kok, 1987). Validity was judged as satisfactory (Beck et al., 1988).

2.8. Statistical methods

All analyses were done on the intention-to-treat population, defined as all randomized patients that started with treatment (also called modified intention-to-treat population). Level of significance used was 0.05. Apart from the primary parameters, all analyses were exploratory in nature. The primary outcome parameter was the proportion of patients satisfied with treatment result and willing to continue (sham) TENS treatment (yes or no). The difference between the two treatment groups was tested with the chi square test. The second outcome parameter was the difference in the time course of the VAS-score during the first treatment week and the mean of the VAS-score in the baseline week. These were analyzed using a mixed repeated measures model.

To investigate the possible predictive role of given parameters on the result outcome (patients' satisfaction), the following procedure was used. Using as criterion the highest likelihood score statistic within a logistic model, the best subset of 1, 2, 3, ... parameters at a time was determined. For each of these best subsets, Akaike's Information Criterion (AIC) was computed, a measure of the goodness of fit, corrected for the number of predictors. As final predictor set, that subset was chosen for which AIC was smallest (starting with the best subset with 1 predictor), before increasing again.

To investigate the possible predictive role of given parameters on the VAS score on day 14 the following procedure was used. Using as criterion the highest R^2 within a multiple linear regression model, the best subset of one, 2, 3, ... parameters at a time was determined. As final predictor set, that subset was chosen for which R^2, compared with the subset with one predictor less, still increased with at least 0.01 (starting with the best subset with 1 predictor).

3. Results

3.1. Subjects

Two hundred and three patients were included in this study. One hundred and sixty-five patients signed informed consent and 38 patients refused. Two of the included patients withdrew before the actual treatment took place; they were both assigned to the TENS group. Pain diagnoses, pain characteristics and psychological assessment revealed no differences between TENS and sham TENS groups (see Table 1), neither did demographic data nor other pain characteristics, as reported previously (Oosterhof et al., 2006). The results of the

Table 1
Baseline prognostic variables; pain and psychological characteristics

	TENS ($n = 81$)	Sham-TENS ($n = 82$)	TOTAL ($n = 163$)
Pain diagnoses[a], n (%)			
Peripheral neuropathic pain	16 (20)	25 (30)	41 (25)
Osteoarthritis and related disorders	31 (38)	26 (32)	57 (35)
Injury of bone and soft tissue and visceral pain	34 (42)	31 (38)	65 (40)
Intensity of pain, mean ± SE mm			
Average pain in baseline week (VAS)[b]	62.2 ± 2.1	61.5 ± 2.0	61.9 ± 1.4
Variation of pain, mean ± SE mm			
SD of pain intensity in baseline week	11.4 ± 0.8	11.1 ± 0.7	11.2 ± 0.6
Perceived control of pain, n (%)			
By decreasing activities or resting	43 (53)	42 (51)	85 (52)
By performing activities or distraction	16 (20)	20 (24)	36 (22)
None	22 (27)	20 (24)	42 (26)
Pain disability (PDI)[c]			
Sum score, mean ± SE mm	28.0 ± 1.8	28.8 ± 2.0	28.4 ± 1.34
PCI[d], mean ± SE mm			
Resting (5–20)	12.8 ± 0.4 ($n = 77$)	12.4 ± 0.4 ($n = 77$)	12.6 ± 0.3 ($n = 154$)
Retreating (7–28)	11.2 ± 0.5 ($n = 77$)	11.9 ± 0.5 ($n = 77$)	11.6 ± 0.3 ($n = 154$)
Worrying (9–36)	17.6 ± 0.7 ($n = 77$)	17.3 ± 0.6 ($n = 77$)	17.4 ± 0.5 ($n = 154$)
PCL[e], mean ± SE mm			
Negative self efficacy (17–85)	43.4 ± 1.2 ($n = 78$)	44.5 ± 1.4 ($n = 77$)	43.9 ± 0.9 ($n = 155$)
Catastrophizing (17–85)	43.6 ± 1.7 ($n = 78$)	44.2 ± 1.7 ($n = 77$)	43.9 ± 1.2 ($n = 155$)
BDI[f], mean ± SE mm			
Depression-score (0–63)	10.2 ± 0.8 ($n = 77$)	10.5 ± 0.8 ($n = 77$)	10.3 ± 0.6 ($n = 154$)

[a] See Table 2 for more details.
[b] Visual analogue scale (0–100).
[c] Pain Disability Index (0–70).
[d] Pain Coping Inventory.
[e] Pain Cognition List.
[f] Beck Depression Inventory.

Table 2
Type of pain diagnoses and rate of patients satisfied with treatment result for TENS and sham TENS

	Treatment (n)	Rate of patients satisfied with treatment result
Peripheral neuropathic pain ($n = 41$)		
Nerve injury	TENS (0)	–
	Sham (2)	0
Dorsal root injury	TENS (0)	–
	Sham (1)	0
Nerve compression	TENS (5)	3/5
	Sham (8)	5/8
Dorsal root compression	TENS (10)	6/10
	Sham (14)	7/14
Diabetic neuropathy	TENS (1)	1/1
	Sham (0)	–
Osteoarthritis and related disorders ($n = 57$)		
Osteoarthritis (vertebral column)	TENS (21)	6/21
	Sham (21)	7/21
Osteoporosis of the spine	TENS (3)	2/3
	Sham (1)	0
Osteoarthritis (hip, knee, ankle)	TENS (2)	2/2
	Sham (2)	1/2
Bursitis and tendonitis	TENS (5)	2/5
	Sham (2)	0
Injury of bone and soft tissue and visceral pain ($n = 65$)		
Soft tissue lesions	TENS (5)	4/5
	Sham (5)	2/5
Bone fractures	TENS (7)	4/7
	Sham (2)	1/2
Whiplash injury	TENS (4)	3/4
	Sham (4)	3/4
Postsurgical pain[a]	TENS (13)	10/13
	Sham (12)	4/12
Visceral pain	TENS (5)	4/5
	Sham (8)	5/8

[a] Indicates significant difference between TENS and sham TENS; $p = 0.047$, Fisher's exact test.

classification of pain diagnoses groups are shown in Table 2. Because some booklets were not returned or lost, data of the PCL from three patients, and data of the PCI and BDI from four patients in the TENS group and five patients of the sham TENS group (PCL, PCI and BDI) were missing.

3.2. Outcome

The proportions of patients satisfied with treatment result differed significantly for high frequency TENS compared to sham TENS (58.0% and 42.7%, respectively, *chi square* = 3.8, $p = 0.05$). However, no significant differences in pain intensity were found for patients treated with TENS or sham TENS ($p = 0.53$).

3.3. Predicting patients' satisfaction with treatment result (willingness to continue treatment)

Descriptive data of the predictors are presented in Table 3, arranged by type of pain diagnoses and including success rate (patients satisfied with treatment result) of TENS and sham TENS.

As can be seen by the odds ratios in Table 4, both for the ORD-group as for the PNP-group, the chance that patients were satisfied and willing to continue treatment was less for high frequency TENS. However, for patients with higher sum scores of the modified retreating scale of the PCI the chance for continuing treatment was greater for high frequency TENS. As regards patients of the PNP-group, longer duration of pain increased the (diminished) chance for willingness to continue high frequency TENS. Independent of treatment modality, greater variation of pain intensity during the baseline week resulted in a greater chance in continuing treatment.

3.4. Predicting pain (VAS)

Results of predicting pain intensity are shown in Table 5. Treatment modality or interactions with treatment modality did not predict intensity of pain as a result of treatment. Pain intensity (adjusted for baseline values) was predicted by resting (PCI subscale) scores (negative), and pain disability (PDI) scores (positive).

Table 3
Proportions of patients satisfied with treatment result for TENS and sham TENS[a] and mean scores (SD) of predictors arranged by type of pain diagnoses

	Peripheral neuropathic pain ($n = 41$)		Osteoarthritis and related disorders ($n = 57$)		Injury of bone and soft tissue and visceral pain ($n = 65$)	
	TENS	Sham	TENS	Sham	TENS	Sham
Satisfied patients, % (rate)	62.5 (10/16)	48.0 (12/25)	38.7 (12/31)	30.8 (8/26)	73.5 (25/34)	48.4 (15/31)*
PCI[b], retreating[c] (6–24)	10.4 (4.5)	9.1 (2.9)	10.0 (3.2)	11.9 (4.8)	8.9 (3.7)	9.4 (2.9)
Duration of pain (years)	6.7 (5.2)	6.7 (6.0)	5.6 (7.8)	9.1 (11.7)	6.4 (6.6)	4.4 (3.7)
Variation of pain intensity[d]	9.7 (6.3)	11.3 (6.6)	11.9 (7.7)	10.7 (6.9)	11.7 (8.0)	11.1 (6.4)

[a] Not corrected for the effects of retreating, duration of pain or variation of pain intensity.
[b] Pain Coping Inventory.
[c] Modified retreating subscale (see text).
[d] SD of VAS scores in baseline week.
* Indicates significant difference ($X^2 = 4.33$, $p = 0.037$) between TENS and sham TENS.

Table 4
Logistic regression report predicting willingness to continue treatment

Variable	ORs (95% CI)	p-value
Treatment * ORD[a]	0.12 (0.04–0.43)	0.001
Treatment * PCI[b] retreating[c]	1.18 (1.07–1.31)	0.001
Treatment * PNP[d]	0.06 (0.006–0.67)	0.022
Treatment * duration * PNP[d]	1.40 (0.94–2.08)	0.099
Variation of pain intensity[e]	1.05 (1.0–1.10)	0.066

Treatment: TENS = 1, sham TENS = 0. Percentage concordant: 69.5%.
[a] Osteoarthritis and related disorders.
[b] Pain Coping Inventory.
[c] Modified retreating subscale (see text).
[d] Peripheral neuropathic pain.
[e] SD of VAS scores in baseline week. ORs: odds ratios; 95% CI: 95% confidence intervals.

Perceiving reduction of pain by decreasing activities and resting, or with performing activities, relaxation exercises and distraction from pain, were positive predictors of pain intensity.

4. Discussion

The results of our study show that predicting the effect of high frequency TENS depends on the choice of outcome measure. The chance that patients were satisfied with high frequency TENS treatment was reduced, both for pain related to osteoarthritis and related disorders as for peripheral neuropathic pain, whereas for patients, who retreat more because of arousal when in pain (modified retreating scale of the PCI), the chance was increased. Only for chronic pain because of bone or soft tissue injury the proportion of patients satisfied with treatment result was significantly higher for high frequency TENS compared to sham TENS (Table 3).

However, contrary to patient's satisfaction with treatment result, pain intensity as result of treatment was not explained by treatment modality. Furthermore, pain catastrophizing and depressive mood did not predict treatment outcome.

As hypothesized – based on results of animal research (Somers and Clemente, 1998) – we found that peripheral neuropathic pain was a negative predictor for results of high frequency TENS. A possible explanation is that high frequency TENS as applied in the present study decreases nociceptive input in the dorsal horn by means of selectively stimulating large diameter afferent neuron fibers (Melzack and Wall, 1965), resulting in activating inhibitory interneurons in lamina II. This A-fiber mediated inhibition is diminished in rats with sectioned nerves (Woolf and Wall, 1982), probably by apoptosis of inhibitory interneurons as a result of peripheral nerve injury (Scholz et al., 2005). Only for this group we found that with increasing duration of the existing pain, the chance of patients to be satisfied with treatment result augmented; whether this results from adaptive changes in the nervous system in the course of time, or that these patients are satisfied with less gain, needs further investigation.

We expected pain in osteoarthritis and related disorders to be a positive predictor for high frequency TENS treatment, but instead, it appeared a negative predictor. In a review Osiri et al. (2004) conclude that high frequency TENS is shown to be effective in pain control over sham TENS in the treatment of osteoarthritis of the knee. However in our study, – as can be deduced by the data from Table 2 – a proportion of 73% of the patients in this group suffered from severe osteoarthritis of the vertebral column, with only 6/21 (29%) and 7/21 (33%) of the patients satisfied with high frequency TENS and sham TENS treatment, respectively. Accordingly, in a comparable group of patients with chronic low back pain Moore and Shurman (1997) found poor results from high frequency TENS treatment, as well. A possible explanation is that inflammation near to the dorsal root and even a minor lesion of articular structures of the vertebral column is found to induce changes in neurotrophic factors in the dorsal root neurons (Hou et al., 2003; Kayama et al., 1996; Obata et al., 2002). These neuropathic changes might impair the working mechanisms of high frequency TENS, however this needs verification.

Patients, who retreat because of arousal when in pain, benefit from TENS treatment (modified retreating scale, PCI). As mentioned before, we assume higher scores reflect higher levels of nociceptive pain, in which TENS

Table 5
Multiple linear regression report predicting VAS score on day 14 (after one week of treatment)

Variable	Regression coefficient	Standard error	t-value	Probability level
Mean baseline pain intensity, VAS[a]	0.80	0.09	8.62	<0.001
PCI, resting[b]	−2.24	0.56	−3.99	<0.001
PDI[c], total sum score	0.50	0.15	3.22	<0.002
Perceiving pain reduction by resting	11.31	3.83	2.95	<0.004
Perceiving pain reduction by activities	10.31	4.67	2.21	0.028

Model: $F(5.146) = 26.19$. $p < 0.001$. $R^2 = 0.47$.
[a] Visual analogue scale.
[b] Subscale "resting" of Pain Coping Inventory.
[c] Pain Disability Index.

is found to be effective, for review see (Sluka and Walsh, 2003). However, this modified scale needs further validation.

Independent of treatment modality, baseline variation in pain intensity influences patients' satisfaction in treatment result, with increased pain variation resulting in greater chance of success of treatment. This is in accordance with the results of Lampl et al. (1998), who found that TENS in unmodulated pain is less effective. We assume that higher rates in fluctuation of pain intensity reflect a greater availability of inhibitory controls. Furthermore, participating in a study will heighten the sensitivity and vigilance of the patients, thereby increasing the detection of beneficial improvements (Kaptchuk, 2001), especially when pain intensity fluctuates, improvements are more likely to be noticed by the patients and attributed to treatment effect.

Only for chronic pain because of injury of bone and soft tissue (including a minor group of visceral pain disorders), the proportion of patients satisfied with treatment result was significantly higher for high frequency TENS compared to sham TENS (Table 3). This cannot easily be explained by the influence of the other predictors of patients' satisfaction, as can be seen by the data in Table 3.

4.1. Predicting pain (VAS)

For predicting pain intensity (VAS), as a result of high frequency TENS or sham TENS application, treatment modality does not show any interference. So, in the present study intensity of pain seems not to be influenced differently by either TENS or sham TENS treatment. After treatment, patients who were more disabled because of pain and those perceiving control of pain (by resting, performing activities and distraction from pain) have higher pain intensity scores than less disabled patients and those not perceiving control. Presumably, those patients already experiencing control of their pain seem to tolerate more pain during either TENS or Sham TENS treatment or benefit less from either treatment modality. Furthermore, patients who seek more rest because of their pain manifest less pain, as a result of either Sham TENS or TENS treatment.

4.2. Predictors found in other studies

Other factors predicting less effect of TENS treatment, described in the study of Lampl et al., were marked depression, and pain qualities as stabbing, pulsating, paroxysmal and electrifying pain. Marked depression, as predictor, was not found in the present study, which could be due to the low depression score, explained by the exclusion of patients indicated for psychological treatment. Whereas for the various pain qualities, this agrees with our findings as these symptoms are more common in patients with neuropathic pain than those with non-neuropathic pain (Bouhassira et al., 2005).

In a previous study in our centre, catastrophizing proved to be a factor explaining pain reduction by radiofrequency lesioning of the cervical spinal dorsal ganglion (Samwel et al., 2000). Catastrophizing did not explain pain or patients' satisfaction with treatment result in the present study, although the study was performed with the same measure (PCL) and only slightly different scores in both studies (mean and (SD): 45.5 (13.9) and 43.9 (14.9)). A possible explanation could be that both TENS and sham TENS stimulated a perception of pain control because patients handled their (sham) TENS devices themselves, thus diminishing the feeling of helplessness about pain, which is a major characteristic of catastrophizing (Sullivan et al., 2001).

4.3. Predicting pain versus predicting patients' satisfaction

Most striking is the fact that predictors for pain intensity differ from those who predict patients' satisfaction with treatment result, both in nature as in interaction with treatment modality. Although closely related, these two outcome measures differ because patients' satisfaction comprises the considerations of the relevancy of the experienced improvements for the patient (e.g. for the pain that was most annoying, threatening, disturbing or disabling), whereas the VAS score reflects a measure of pain intensity perceived at a fixed time of the day. As described before (Oosterhof et al., 2006) the satisfied patients exhibited on average a 28.5% pain reduction, which signifies a clinical important relief of pain (Farrar et al., 2001). Patients' satisfaction might, therefore, predict clinical important relief of pain.

4.4. Strong and weak points of the study

High frequency TENS was applied in a standardized way and a main outcome measure was patients' satisfaction with result of treatment, which would have warranted the relevance for daily practice. Furthermore compliance (registered operation time of the device) was not different for the TENS or sham TENS group, and there was only a weak correlation between the actual and perceived treatment application (i.e. TENS or sham TENS), as reported previously (Oosterhof et al., 2006).

The main purpose of this study was to explore the effects of the origin of pain on the result of high frequency TENS in chronic pain. However the classification of the origin of pain may have flaws. Especially, the difference between the PNP group and the injury group (IBST) may be arguable, as a large proportion of the patients in the latter group developed chronic pain after surgery (see Table 2), and it is assumed that neuropathic pain is the most common type of post surgical pain (Kehlet et al., 2006). Although there were no signs of sensory loss, we cannot fully exclude the existence of neuropathic pain in this group, as there is no gold standard for defining neuropathic pain (Rasmussen et al., 2004). However it would mean that the effect of high frequency TENS on PNP is not definite, because contrary to the PNP group, in the postsurgical pain group high frequency TENS performed significantly better than sham TENS (see, Tables 3 and 2, respectively). Interestingly, TENS is found to reduce postoperative analgesic consumption (Bjordal et al., 2003). However, there is a need for the development of a mechanism-based classification of pain, as proclaimed by (Woolf et al., 1998; Woolf and Decosterd, 1999).

We conclude that predicting the effect of high frequency TENS in chronic pain depends on the choice of outcome measure. Predicting patients' satisfaction with treatment result is related to the origin of pain: both, peripheral neuropathic pain and osteoarthritis, especially of the vertebral column, negatively predict treatment outcome; whereas injury of bone and soft tissue (especially postsurgical pain disorder) is a positive predictor. Predicting changes in pain intensity following treatment reflects mechanisms of pain behavior and perceived control of pain, independent of treatment modality. Pain catastrophizing did not predict TENS treatment outcome.

Acknowledgements

This study was funded by The Netherlands Organization for Health Research and Development Grant 940-31-053. We further wish to thank Wim Lemmens from the Department of Epidemiology and Biostatistics and Ria te Winkel-Slotboom from the Department of Medical Psychology, both for help in handling the data.

References

Beck AT, Steer RA, Carbin MG. Pschometric properties of the beck depression inventory: twenty-five years of evaluation. Clin Psychol Rev 1988;8:77–100.

Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. Eur J Pain 2003;7:181–8.

Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29–36.

Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the neuropathic pain symptom inventory. Pain 2004;108:248–57.

Bouman TK, Kok AR. Homogeneity of Beck's Depression Inventory (BDI): applying rasch analysis in conceptual exploration. Acta Psychiatrica Scandinavica 1987;76:568–73.

Carroll D, Moore RA, McQuay HJ, Fairman F, Tramer M, Leijon G. Transcutaneous electrical nerve stimulation (TENS) for chronic pain (Cochrane Review). In: The Cochrane Library Issue 3;2004:Chichester

Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993;52:259–85.

Deyo RA, Walsh NE, Schoenfeld LS, Ramamurthy S. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. Am J Phys Med Rehabil 1990;69:6–10.

Farrar JT. What is clinically meaningful: outcome measures in pain clinical trials. Clin J Pain 2000;16:S106–12.

Farrar JT, Young Jr JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–58.

Gopalkrishnan P, Sluka KA. Effect of varying frequency, intensity, and pulse duration of transcutaneous electrical nerve stimulation on primary hyperalgesia in inflamed rats. Arch Phys Med Rehabil 2000;81:984–90.

Gotoh M, Hamada K, Yamakawa H, Inoue A, Fukuda H. Increased substance P in subacromial bursa and shoulder pain in rotator cuff diseases. J Orthop Res 1998;16:618–21.

Gronblad M, Hupli M, Wennerstrand P, Jarvinen E, Lukinmaa A, Kouri JP, Karaharju EO. Intercorrelation and test-retest reliability of the Pain Disability Index (PDI) and the Oswestry Disability Questionnaire (ODQ) and their correlation with pain intensity in low back pain patients. Clin J Pain 1993;9:189–95.

Hou SX, Tang JG, Chen HS, Chen J. Chronic inflammation and compression of the dorsal root contribute to sciatica induced by the intervertebral disc herniation in rats. Pain 2003;105:255–64.

Jerome A, Gross RT. Pain disability index: construct and discriminant validity. Arch Phys Med Rehabil 1991;72:920–2.

Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? J Clin Epidemiol 2001;54:541–9.

Kayama S, Konno S, Olmarker K, Yabuki S, Kikuchi S. Incision of the anulus fibrosus induces nerve root morphologic, vascular, and functional changes. An experimental study. Spine 1996;21:2539–43.

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618–25.

King EW, Sluka KA. The effect of varying frequency and intensity of transcutaneous electrical nerve stimulation on secondary mechanical hyperalgesia in an animal model of inflammation. J Pain 2001;2:128–33.

Kores RC, Murphy WD, Rosenthal TL, Elias DB, et al. Predicting outcome of chronic pain treatment via a modified self-efficacy scale. Beha. Res. Therapy 1990;28:165–9.

Kosek E, Ordeberg G. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. Eur J Pain 2000;4:229–38.

Kraaimaat FW, Bakker A, Evers AWM. Pijncoping-strategieen bij chronische pijnpatienten: De ontwikkeling van de Pijn-Coping-Inventarisatielijst (PCI). Pain coping strategies in chronic pain patients: the development of the pain coping inventory (PCI). Gedragstherapie 1997;30:185–201.

Kraaimaat FW, Evers AW. Pain-coping strategies in chronic pain patients: psychometric characteristics of the pain-coping inventory (PCI). Int J Behav Med 2003;10:343–63.

Lampl C, Kreczi T, Klingler D. Transcutaneous electrical nerve stimulation in the treatment of chronic pain: predictive factors and evaluation of the method. Clin J Pain 1998;14:134–42.

Marshall KW, Chiu B, Inman RD. Substance P and arthritis: analysis of plasma and synovial fluid levels. Arthritis Rheum 1990;33:87–90.

Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.

Moore SR, Shurman J. Combined neuromuscular electrical stimulation and transcutaneous electrical nerve stimulation for treatment of chronic back pain: a double-blind, repeated measures comparison. Arch Phys Med Rehabil 1997;78:55–60.

Obata K, Tsujino H, Yamanaka H, Yi D, Fukuoka T, Hashimoto N, Yonenobu K, Yoshikawa H, Noguchi K. Expression of neurotrophic factors in the dorsal root ganglion in a rat model of lumbar disc herniation. Pain 2002;99:121–32.

Ohberg L, Lorentzon R, Alfredson H. Neovascularisation in achilles tendons with painful tendinosis but not in normal tendons: an ultrasonographic investigation. Knee Surg Sports Traumatol Arthrosc 2001;9:233–8.

Oosterhof J, Anderegg Q, Kersten H, Crul BJ, TENS-protocol Pijncentrum UMC St Radboud, In: TENS bij chronische pijn. Handleiding voor fysiotherapeuten., Uitgeverij Coutinho, Bussum, 2003, pp. 31–43.

Oosterhof J, De Boo TM, Oostendorp RAB, Wilder-Smith OHG, Crul BJP. Outcome of transcutaneous electrical nerve stimulation in chronic pain: short-term results of a double-blind, randomised, placebo controlled trial. J Headache Pain 2006;7:196–205.

Osiri M, Welch V, Brosseau L, Shea B, McGowan J, Tugwell P, Wells G. Transcutaneous electrical nerve stimulation for knee osteoarthritis (Cochrane Review). Chichester, UK: John Wiley & Sons, Ltd; 2004.

Pollard CA. Preliminary validity study of the pain disability index. Percept Mot Skills 1984;59:974.

Radhakrishnan R, Sluka KA. Spinal muscarinic receptors are activated during low or high frequency TENS-induced antihyperalgesia in rats. Neuropharmacology 2003;45:1111–9.

Rasmussen PV, Sindrup SH, Jensen TS, Bach FW. Symptoms and signs in patients with suspected neuropathic pain. Pain 2004;110:461–9.

Revill SI, Robinson JO, Rosen M, Hogg MI. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976;31:1191–8.

Saito T, Koshino T. Distribution of neuropeptides in synovium of the knee with osteoarthritis. Clin Orthop Relat Res 2000:172–1782.

Samwel H, Slappendel R, Crul BJ, Voerman VF. Psychological predictors of the effectiveness of radiofrequency lesioning of the cervical spinal dorsal ganglion (RF-DRG). Eur J Pain 2000;4:149–55.

Sarkar S, Aziz Q, Woolf CJ, Hobson AR, Thompson DG. Contribution of central sensitisation to the development of non-cardiac chest pain. Lancet 2000;356:1154–9.

Scholz J, Broom DC, Youn DH, Mills CD, Kohno T, Suter MR, Moore KA, Decosterd I, Coggeshall RE, Woolf CJ. Blocking caspase activity prevents transsynaptic neuronal apoptosis and the loss of inhibition in lamina II of the dorsal horn after peripheral nerve injury. J Neurosci 2005;25:7317–23.

Sluka KA. Systemic morphine in combination with TENS produces an increased antihyperalgesia in rats with acute inflammation. J Pain 2000;1:204–11.

Sluka KA, Bailey K, Bogush J, Olson R, Ricketts A. Treatment with either high or low frequency TENS reduces the secondary hyperalgesia observed after injection of kaolin and carrageenan into the knee joint. Pain 1998;77:97–102.

Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. J Pharmacol Exp Ther 1999;289:840–6.

Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. J Pain 2003;4:109–21.

Smith MD, Triantafillou S, Parker A, Youssef PP, Coleman M. Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. J Rheumatol 1997;24:365–71.

Somers DL, Clemente FR. High-frequency transcutaneous electrical nerve stimulation alters thermal but not mechanical allodynia following chronic constriction injury of the rat sciatic nerve. Arch Phys Med Rehabil 1998;79:1370–6.

Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 2001;17:52–64.

Tait RC, Chibnall JT, Krause S. The pain disability index: psychometric properties. Pain 1990;40:171–82.

Thorn BE, Ward LC, Sullivan MJ, Boothby JL. Communal coping model of catastrophizing: conceptual model building. Pain 2003;106:1–2.

Turner JA, Clancy S. Strategies for coping with chronic low back pain: relationship to pain and disability. Pain 1986;24:355–64.

Vlaeyen JW, Geurts SM, Kole-Snijders AM, Schuerman JA, Groenman NH, van-Eek H. What do chronic pain patients think of their pain? Towards a pain cognition questionnaire. Br J Clin Psychol 1990;29:383–94.

Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441–51.

Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? Pain 1998;77:227–9.

Woolf CJ, Decosterd I. Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. Pain 1999;Suppl 6:S141–7.

Woolf CJ, Wall PD. Chronic peripheral nerve section diminishes the primary afferent A-fibre mediated inhibition of rat dorsal horn neurones. Brain Res 1982;242:77–85.