From the Department of Physiology and Pharmacology,
Karolinska Institutet, Stockholm, Sweden

Pain, its assessment and treatment using sensory stimulation techniques.

Methodological considerations

Iréne Lund

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ABSTRACT

Pain is a worldwide clinical problem that causes great suffering for the individual and costs for society. The assessment and evaluation of perceived pain is necessary for diagnosis, choice of treatment, and for the evaluation of treatment efficacy. The assessment of an individual's pain is a challenge since pain is a subjective, multi-dimensional experience based on the person's own self-report. The results are often varied possibly due to individual variation, but also in relation to gender and etiology. A gold standard for pain assessment is still lacking but rating scales, questionnaires, and methods derived from psychophysical concepts, such as threshold assessments are used. In the evaluation of pain and associated variables, both systematic and individual variation should be taken into account, as should pain-associated symptoms. The stress-related symptoms that can be associated with pain may possibly be measured by using a biochemical marker.

Non-pharmacological pain treatments are often used in physiotherapeutic practice, but knowledge about the optimal treatments for different pain conditions is still lacking. Gender-related, pain-alleviating effects of non-pharmacological methods are sparsely documented as are non-pharmacological interventions like acupuncture in pelvic pain in late pregnancy.

The aim of this thesis was to evaluate some of the commonly used pain rating methods and to evaluate a newly developed method in order to determine experimental and clinical pain from a physiotherapeutic perspective. Also, the aim was to find indicators, rated and biochemical, of pain-associated symptoms and reported therapeutic effects.

Assessments of electrical sensory and electrical pain thresholds were shown to be stable and reliable in healthy female subjects and female pain patients. The sensory threshold was found to be increased and the pain threshold found to have decreased for the pain patients compared with healthy subjects. Evaluation of pain intensity ratings in patients with different pain etiologies using a Visual Analogue Scale and a Verbal Rating Scale showed that the used scales may have different meanings in the different pain groups, probably can be differently interpreted and are, therefore, not interchangeable.

Gender-related responses to high frequency Transcutaneous Electrical Nerve Stimulation were found in assessed thresholds - the women's electrical pain thresholds were found to have increased while those of the men were unaffected, indicating that variability in responses to sensory stimulation may be gender-related.

Acupuncture relieves pelvic pain intensity and emotional distress in pregnant women. A relationship between the 24-hour urinary Corticotropin Releasing Factor-Like Immunoreactivity, CRF-LI, concentration and rated stress-related symptoms were found in female patients with fibromyalgia. Lowered concentrations of CRF-LI and decreased rated symptoms were seen after massage. There was great individual variation in response to the different sensory stimulation techniques, suggesting that treatments should be individually based.

Conclusion: Analysis of pain assessment should consider the non-metric properties and take the systematical as well as the individual responses into account. Threshold assessment may be an additional valuable tool for clinical evaluation given analyses separated for gender. Biochemical markers such as urinary CRF-LI concentrations may be used for measurement of stress-related symptoms in pain conditions. Therapies like TENS, acupuncture and massage may be tried for the amelioration of pain and stress but further studies are required.

THESIS SUMMARY IN SWEDISH

Svensk sammanfattning

Smärta är ett omfattande kliniskt problem som orsakar individen stort lidande och samhället stora kostnader. Bedömning och utvärdering av upplevd smärta är nödvändig för att ställa diagnos, val av behandling och för utvärdering av behandlingseffekter. Att bedöma en individs smärta är en utmaning eftersom smärta är en multidimensionell erfarenhet baserad på individens egen rapport. Variation i smärtbedömningen kan relateras till individuella faktorer men också till kön och smärtetiologi. En generell standard för smärtbedömning saknas men skattningsskalor, frågeformulär och metoder baserade på psykofysiska koncept används. Vid utvärdering av smärta och symtom associerade med smärta bör hänsyn tas både till systematiska och individuella variationer. Stressrelaterade symtom i samband med smärta kan möjligtvis detekteras med biokemiska markörer.

Icke-farmakologisk smärtbehandling används ofta inom sjukgymnastisk verksamhet. Dock saknas ännu kunskap om optimala behandlingar vid olika tillstånd. Könsrelaterade smärtlindringseffekter av icke-farmakologiska behandlingsmetoder är sparsamt dokumenterade liksom effekter av akupunktur hos gravida kvinnor med bäckensmärta.

Syftet med denna avhandling var att utvärdera några av de vanligaste smärtskattningsmetoderna och en nyligen utvecklad metod för att kunna bedöma experimentell och klinisk smärta från ett sjukgymnastiskt perspektiv. Ytterligare ett syfte var att finna indikatorer, skattade och biokemiska, för associerade symptom till smärta och även rapporterade terapeutiska effekter.

Bedömning av elektrisk sensorisk tröskel och elektrisk smärttröskel visade stabila resultat hos friska kvinnliga försökspersoner och kvinnliga patienter med smärta. I jämförelse med friska försökspersoner rapporterade smärtpatienterna höjd sensorisk tröskel och sänkt smärttröskel. Utvärdering av skattad smärtintensitet med visuell analog skala, VAS, och verbal skattningsskala, VRS, hos patienter med smärta av olika etiologi visade att de två skalorna gav olika resultat och kan därmed ha olika mening. Dessutom kan olika skalor sannolikt tolkas olika och är därför inte utbytbara.

Hos patienter med fibromyalgi påvisades en relation mellan koncentrationen av corticotropin releasing factor, CRF, i dygnsurin uppmätt med radioimmunologisk teknik och skattade stress-relaterade symptom. Könsrelaterade svar på transkutan elektrisk hudstimulering, TENS, påvisades vid tröskelbedömning hos friska försökspersoner. Kvinnorna svarade med ökning av smärttröskeln medan männens var opåverkad. Akupunktur lindrade smärtintensitet i vila, i samband med dagliga funktioner samt minskade emotionella reaktioner hos gravida kvinnor med bäcken smärta. Lägre koncentrationer av CRF i dygnsurin och minskning av skattade variabler kunde konstateras efter massage hos patienter med långvarig smärta och stress. Det fanns en påtaglig individuell variation i svaret på de olika sensoriska stimuleringsmetoderna vilket indikerar att behandlingar bör utformas individuellt. Sammanfattning: Utvärdering av smärta bör tillvarata de subjektiva variablernas icke metriska egenskaper och beakta både systematiska och individuella variationer. Tröskelbedömningar kan utgöra ett värdefullt komplement som utvärderings instrument i klinisk bedömning av smärta förutsatt att kvinnor och män analyseras separat. Biokemiska markörer som CRF-koncentration i dygnsurin, skulle kunna användas som mått på stressrelaterade symtom vid smärta. Terapier som TENS, akupunktur och massage kan prövas för att minska smärta och associerade symtom men fler studier krävs.

LIST OF PUBLICATIONS

I. Lund I, Lundeberg T, Kowalski J, Sandberg L, Norrbrink Budh C, Svensson E. Evaluation of variations in sensory and pain threshold assessments by electrocutaneous stimulation. Physiotherapy Theory and Practice 2005;21:81-92.

II. Lund I. Lundeberg T, Kowalski J, Svensson E. Gender differences in electrical pain threshold responses to transcutaneous electrical nerve stimulation (TENS). Neuroscience Letters 2005;375:75–80.

III. Lund I, Lundeberg T, Lönnberg L, Svensson E. Decrease of pregnant women's pelvic pain after acupuncture: a randomized controlled single-blind study. Acta Obstetricia et Gynecologica Scandinavica 2006;85:12-19.

IV. Lund I, Lundeberg T, Kowalski J, Sandberg L, Norrbrink Budh C, Svensson E. Lack of interchangeability between visual analogue and verbal rating pain scales: a cross sectional description of pain etiology groups. BioMedCentral Medical Research Methodology 2005;5:31.

V. Lund I, Lundeberg T, Carleson J, Sönnerfors H, Uhrlin B, Svensson E. Corticotropin releasing factor in urine - a possible biochemical marker of fibromyalgia. Responses to massage and guided relaxation. In press for publication in Neuroscience Letters.

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LIST OF ABBREVIATIONS

µC	mikroColumb
CI	Confidence Interval
CPRS-A	Comprehensive Psychopathological Rating Scale – Affective
CRF-LI	Corticotropin Releasing Factor-Like Immunoreactivity
D	The measure of Disorder
EPT	Electrical Pain Threshold
EST	Electrical Sensory Threshold
kΩ	kiloOhm
MA	The coefficient of Monotonic Agreement
NHP	Nottingham Health Profile questionnaire
NRS	Numeric Rating Scales
PA	Percentage Agreement
PM	PainMatcher
RC	Relative Concentration
RIA	RadioImmunoAssay
ROC	Relative Operating Characteristic
RP	Relative Position
RV	Relative rank Variance
SD	Standard Deviation
TENS	Transcutaneous Electrical Nerve Stimulation
TFA	TriFlourAceticacid
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

INTRODUCTION

Pain in the society

Pain is a worldwide clinical problem (Harstall and Ospina, 2003). In a recent study by Gerdle and collaborators it was reported that among adults the prevalence of chronic pain was 53.9%. The prevalence of pain was associated with female gender, older age, being on sick leave and early retirement (Gerdle et al., 2004). Also, pain is associated with low self-rated health (Mantyselka, 2003) and is one of the most frequent causes of healthcare-seeking including physiotherapy (Scudds et al., 2001). Consequently pain, including its change and associated symptoms, is probably the most evaluated variable.

Definition of pain

In a biological perspective, the feeling of pain is a somatic sensation, termed nociception. Nociception is a warning signal essential for survival and intimately related to homeostasis (Craig, 2003).

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (Merskey and Bogduk, 1994). The pain sensation is described as multi-dimensional including sensory-discriminative (e.g. intensity), affective-motivational (e.g. unpleasantness), and cognitive-evaluative (e.g. thoughts, beliefs) dimensions (Melzack and Casey, 1968). All three dimensions are very likely activated more or less simultaneously (Villanueva et al., 1989; Willis and Westlund, 1997; Price et al., 2000) and are all important to include in the assessment of the patients' pain. The sensory-discriminative dimension, i.e. pain intensity or pain severity, is probably the most evaluated dimension (von Korf et al., 2000).

The duration of a pain condition is often described in terms of acute or chronic, the latter often exceeding three month, without clear definitions and borders between the two phases. The chronic phase is associated with changes in plasticity in peripheral and central neural structures (Melzack, 2001; Scholz and Woolf, 2002). Therefore, chronic pain is a clinical entity by itself (Niv and Devor, 2004) and should not be treated as being an acute condition (Lundberg et al., 2006). A long-term pain condition is also reported as associated with affective components like depression and anxiety (Riedel et al., 2002; Thieme et al., 2004; Giesecke et al., 2005).

Pain mechanism

Depending on the etiology, pain has been classified into different categories (Lundeberg and Ekholm, 2002; Wincent et al., 2003), each with its own characteristic. Woolf recently proposed a categorization of pain based on its mechanisms into: *nociceptive* - transient pain in response to a noxious stimulus; *inflammatory* - spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation; *neuropathic* - spontaneous pain and hypersensitivity to pain in association with damage to or a lesion of the nervous system; *functional* - hypersensitivity to pain resulting from abnormal central processing of normal input (Woolf, 2004).

Assessment of pain

Rating scale assessments

Pain is a highly personal and subjective experience, i.e. a complex perceptual phenomenon without certainty being equal to the physiological process of nociception. Since pain is subjective, it can only be assessed indirectly based on the patients' self-report. The perception of pain is influenced by internal and external factors (Turk, 1999; Price, 2000; Rollman et al., 2000; Ploghaus et al., 2003), and is also reported differently (de C Williams et al., 2000; Rosier et al., 2002).

The variability in pain is also influenced by gender. Women compared with men have been reported to be more sensitive to experimental painful stimuli, perceive clinical pain of higher severity and frequency, of longer duration and present in a greater number of body regions (Fillingim and Maixner, 1995; Unruh, 1996; Berkley, 1997; Wise et al., 2002). Taking all the above factors into account, evaluation or groups effects may be difficult to interpret, while individual responses are still valid, i.e. what may be true for the individual is not valid for the group. Therefore, it is important to assess the level of perceived pain and its change taking the individual variation into account in order to optimize treatment regimes (Philadelphia Panel, 2001).

For the self-reported pain assessments, different types of uni-dimensional rating scales like the Visual Analogue Scale, VAS (Bond and Pilowski, 1966), the numeric rating scale, NRS (Kremer et al., 1981), the Verbal Rating Scale, VRS (Keele, 1948), the Category Ratio, CR-10, scale (Borg, 1993) or multi-dimensional instruments like the McGill pain questionnaire (Melzack, 1975) are used. Pain is also a common sub-variable in multi-dimensional instruments such as the Nottingham Health Profile (Wiklund and Dimenäs, 1990). The VAS and NRS are probably the most commonly used pain assessment instruments. Although widely used, there is so far no support for a recommendation of either the VAS or NRS (McQuay, 2005). In chronic pain clinical trials the NRS has, however, previously been recommended (Dworkin et al. 2005). Due to the lack a of gold standard, there is a need to study if the individual scoring captured on one pain scale are interchangeable with the individual scoring on another pain scale.

Thresholds assessments

An alternative method for pain evaluation, derived from the psychophysical concept, is the use of threshold assessments (Hardy et al., 1940). The sensory threshold is defined as the least level of stimulation that can be detected by the subjects and the pain threshold as the least level of stimulation required producing the first perception of pain. Different modes of stimulation (Price, 1993; Riley, 1998; Gracely, 1999) are applied for the threshold assessments, commonly with ascending intensities of stimulation, the Method of Limits (Gracely, 1979, 1988; Borg, 1993; Ohrbach, 1998). The assessed threshold levels are generally dependent on the status of the nervous system, socio-cultural, and psychological factors (Turk, 1999; Price, 2000). In pain patients, the assessed electrical sensory threshold was found to be unaffected (Ashkinazi and Vershinina, 1999) or decreased (Wilder-Smith et al., 2001) and the electrical pain thresholds to be lower in comparison with healthy individuals (Alstergren and Forstrom, 2002). Further, the electrical pain thresholds were found to increase following successful treatment in patients with painful osteoarthritis (Wilder-Smith et al., 2001) indicating that a shift in pain thresholds could serve as a measure of a change in perceived pain, Fig. 1.

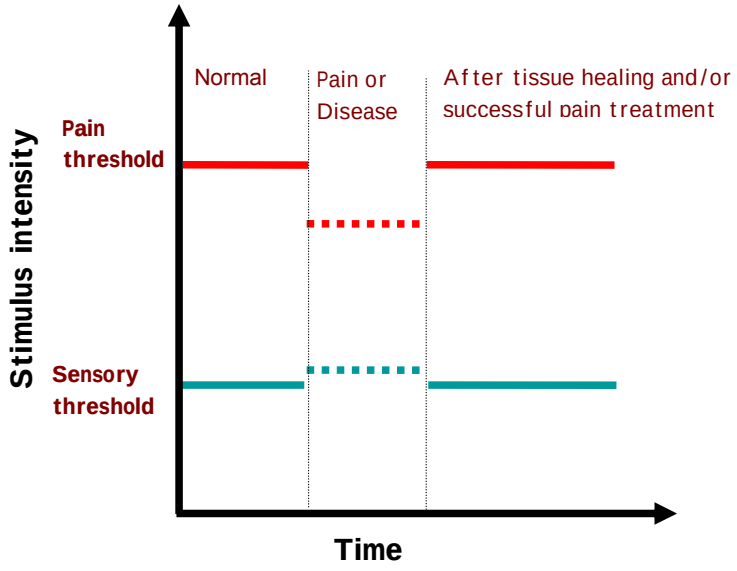

Fig. 1. Hypothesized assessments of threshold levels, sensory detection and pain, in health and pain.

Lowered pain thresholds have been reported in patients with pain within as well as outside the painful area (Malow et al., 1980; Sandrini et al., 1986; Kosek et al., 1996; Moller and Pinkerton, 1997; Wilder-Smith et al., 2001). Possibly, this reflects greater pain sensitivity (Edwards et al., 2005). Determination of thresholds is generally not part of a clinical evaluation of pain. Threshold testing has mostly been restricted to neurodiagnostic (Dotson, 1997) and experimental (Gracely, 1999) procedures. Interestingly, the assessment of supra-threshold stimulation has been implicated to possibly serve as a prognostic tool for patients at risk of developing chronic pain (Edwards, 2005).

Magnitude matching

Magnitude matching i.e. a comparison of the intensity of pain with another modality of stimulation is another method for the assessment of pain from the psychophysical concept (Borg, 1993; Price, 1993; Gracely, 1999; Lundeberg, 2001).

Properties of assessed pain

Pain data has been suggested to have linear or exponential distributions, distributions without known size and distance, or just being dichotomized into pain or no pain. (Price, 1983; Gracely, 1999; Donaldson et al., 2003) See Fig. 2a-d for example possible models of data.

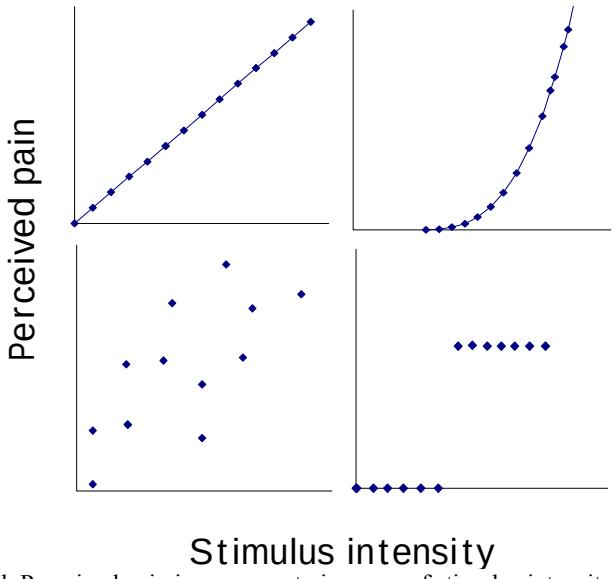

Fig. 2a-d. Perceived pain in response to increase of stimulus intensity. Possible models of responses presented as linear (a) or exponential (b) distributions producing data with known size and distance. Data of perceived pain presented as ordinal (c) or dichotomized into no pain/pain (d) without known size and distance.

In the evaluation of pain data the importance of psychometric characteristics has been acknowledged (Turk and Melzack, 2001). Support for metric properties of pain data using VAS comes from work based on direct magnitude-scaling methods by means of thermal stimulation in healthy subjects (Price, 1983; Price et al., 1994) supporting the ideas of psychophysical laws. In the area of psychophysics, general sensations like pain are studied with the goal of describing how a continuum of a sensation is represented in the mind (Ottoson, 1983). The properties of these relations have been suggested as a logarithmic model (The Weber-Fechner law) while Stevens (1970), suggested that the direct reports of subjective intensity are related to the physical intensity of stimuli by a linear relationship between the logarithm of the stimulus amplitude and the logarithm of the sensory experience.

On the contrary, the generalizability of the psychophysical functions has been questioned by Lockhead who suggested that the scales are dynamic and that the judgement of a stimulus is not only dependent on its intensity but also on its duration, change of intensity, and the relation to its environment (Lockhead, 1992).

Implications for statistical evaluation

In psychophysics, the linear and ratio models have been suggested as preferred since they allows for a simpler calculation of sums and differences, but also for the possibility of evaluating magnitude of pain, thereby allowing for comparisons between subjects (Price, 1983; de C Williams et al., 2000). The possibilities of making statistical calculations and predictions are also given as rationale why ratio scales or scales with at least semi-ratio properties should be used (Price, 1983; Borg and Borg, 2001). However, assumptions of these models can never be perfectly met when analysing pain data of a group of individuals (Borg and Borg, 2001).

Since rated pain is a subjective variable, pain data may be regarded as to be qualitative with an ordered structure but without metric properties, such as distance and magnitude (Merbitz et al., 1989; Hand, 1996) i.e. ordinal. These rank invariant properties implicate that arithmetic operations are not appropriate since a numeric ordinal record has no arithmetical meaning but only indicates the ordered structure

(Merbitz 1989; Svensson 1993). Therefore, a change of the perceived pain can be assessed by transitional scales with the labels such as much "better, somewhat better, unchanged, somewhat worse and much worse" (Kramer and Feinstein, 1981).

The concepts of interval and ratio levels of data proposed by Stevens (1946) belong to quantitative data with complete metric properties (Siegel and Castellan, 1988) and are therefore not regarded appropriate to use in ordered categorical data.

Appropriate statistical approaches for analysis of pain data have been discussed (Maxwell, 1978; Philip, 1990; Svensson 1993; Svensson, 2001; Akhtar-Danesh, 2001). Non-parametric methods for analysis are recommended (Huskisson, 1982; Altman, 1991; Svensson, 2001) since no assumption about the data is required except for order, or that the data could be dichotomised into "no pain" or "pain". The non-metric properties of ordinal data, imply that the median, quartiles, and range are the measures for description and that change in pain assessments can be categorised as increased, (+), unchanged, (0), or decreased, (-), Fig. 3.

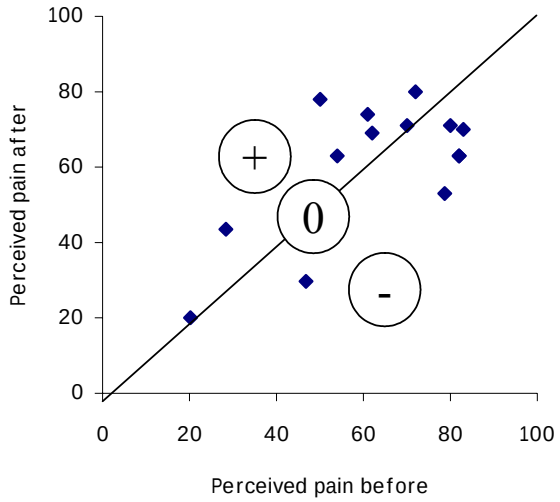

Fig. 3 Individual data of rated pain demonstrated in a scatter plot. Changes from ratings before to after intervention are shown as increased (+), unchanged (0) or decrease (-).

According to the psychometric paradigm, others (Maxwell, 1978; Price, 1983; Dexter and Chestnut, 1995) have recommended parametric methods with or without compensation of the data for normality. Precautions are, however, suggested in using parametric tests, especially when many patients (>16%) rank their pain at one of the extremes of the rating scale (Dexter and Chestnut, 1994). Furthermore, the use of parametric methods is restricted by the requirements of quantitative and normally distributed data or being transformed to better fit a normal distribution if these assumptions are not met.

As a result of statistical research, new methods taking into account the non-metric, ordered, categorical properties of data from scale assessments has been developed (Svensson, 1993). The methods for paired categorical data are suitable for analyses of systematic and individual changes, but also for inter- and intra-observer agreement as well as inter-scale comparisons. The advantage of using statistical methods that do not require metric or other distributional properties of data are that the results are reliable and valid without restrictions and can also be used for small samples.

Biochemical markers of pain associated symptoms

In long-term pain conditions, associated symptoms of physiological and psychological distress are reported (Riedel, 2005) and seen, for example as stress-

related symptoms like depression (Giesecke et al., 2005) and anxiety (Thieme et al., 2004). From a physiological point of view, an aberrant function of the sympathetic nervous system (Petzke and Clauw, 2000), the hypothalamic-pituitary-adrenal (HPA) axis (Neck, 1999), or its negative feedback loop (Demitrack and Crofford, 1998; Neeck and Riedel, 2002) have been discussed as plausible causes of the stress-related symptoms, in pain conditions like fibromyalgia. Corticotropin releasing factor, CRF, synthesized in the hypothalamic paraventricular nuclei is reported as a key physiological mediator of different endocrine, autonomic, and behavioral responses to stress (Arborelius et al., 1999; Baraniuk et al., 2004; Barden, 2004). Elevated plasma and cerebrospinal fluid (CSF) concentrations of CRF have been found in patients with fibromyalgia (Riedel et al., 2002) and patients with post-traumatic stress disorder (Bremner, 1997). Hyperactive CRF neurons have, therefore, been suggested playing a role in the nociceptive and psychological mechanisms in fibromyalgia (Crofford, 1998; Neeck and Riedel 1999; Neeck, 2002; Riedel et al., 2002). The central autonomic control of stress is complex and not easily assessed by a single test, for which reason a variety of techniques have been tried out (Petzke and Clauw, 2000). CRF concentration is usually measured in CSF, which is a procedure that may be stressful by itself. To reduce the stress-related sampling procedures, but also to diminish the influence of diurnal variation, analysis of CRF concentration in 24-hour urinary samples could be an alternative.

Endogenous pain modulation

Endogenous pain modulation, operating in the central nervous system (CNS), both inhibitory and facilitatory, have been described (Basbaum and Fields, 1984; Rainville, 2002; Le Bars, 2002; Han, 2004) and a number of different neurotransmitters like opioids, and monoamines have been suggested to play a key role (Millan, 2002; Bodnar and Klein, 2004; Fields, 2005;).

In order to activate the endogenous pain inhibitory mechanisms, different modes of sensory stimulation are used. The pain inhibitory control is attributed to an induced activity starting in the peripheral receptors and primary afferent nerves leading to an inhibited propagation of pain-impulses in the dorsal horn at the spinal cord level, first described by Melzack and Wall (1965) as the gate control theory. The activity in afferent nerves also leads to inhibitory effects elicited from higher centers in the CNS (Andersson and Lundeberg, 1995; Han, 2002; Lundeberg and Barlas, 2005). The induced effects of sensory stimulation are often reported as an increase of pain thresholds and a decreased of rated pain (Widerstrom et al., 1992; Chesterson et al., 2002; He et al., 2004).

Some of the most common used methods in physiotherapy are transcutaneous electrical nerve stimulation (TENS), acupuncture and massage. All methods are regarded as old, often very appreciated, and with a long tradition for the use of pain alleviation. The questions of evidence for treatment efficacy are discussed in the medical community. In a recent report the Swedish Council on Technology Assessment in Health Care (2006) concluded that there is evidence for the usefulness of TENS and acupuncture in different chronic pain states. On the other hand, there was for the moment not sufficient evidence for the use of massage.

AIMS

A general goal was to evaluate commonly used pain rating methods and to evaluate a newly developed method assessing threshold levels in order to determine experimental and clinical pain from a physiotherapeutic perspective. Also, the aim was to find indicators, rated and biological, of pain-associated symptoms and reported therapeutic effects.

Study I The aim of this study was to evaluate the reliability of electrical sensory threshold, EST, and electrical pain threshold assessments, EPT, in healthy subjects and pain patients in terms of systematic and individual variability between and within days. In addition, healthy subjects were compared with pain patients regarding assessed EST and EPT levels.

Study II The aim of this study was to evaluate the systematic and individual changes in electrical sensory and pain thresholds, EST and EPT, following transcutaneous electrical nerve stimulation, TENS, in healthy women and men.

Study III The aim of this study was to evaluate the effects on both group and individual levels of two alternative modes of acupuncture stimulation (superficial and deep) on perceived pelvic pain in late pregnancy, also taking into account daily activities and emotional reactions.

Study IV The aim of this study was to evaluate the quality of the intra-individual assessments of self-reported pain intensity using a continuous Visual Analogue Scale, VAS 0–100, and a discrete five-category Verbal Rating Scale, VRS. The evaluation included inter-scale concordance, implying to which extent the assessment on one scale can be replaced by the assessment on the other, without change of the result. The intra-individual assessment stability of both scales was evaluated by test-retest reliability. The patients were separately described in groups of pain etiology.

Study V The aim of this study was to examine in patients with fibromyalgia, the concentrations of 24-hour urinary corticotropin releasing factor-like immunoreactivity, CRF-LI, and its possible relationship with rated indicators of stress-related symptoms like depression and anxiety as well as associated variables like emotional reactions. A secondary aim was to evaluate the changes in the assessed above-mentioned variables in response to treatment of massage or guided relaxation.

MATERIAL AND METHODS

Ethics

The ethics committee of Karolinska University Hospital approved the studies I, II, IV and V while the ethics committee of the Uppsala University approved study III.

Subjects and study designs

Table 1 summarizes the information about number of subjects, design, variables, and outcome instruments used in the different studies. This information is also specified below.

Study I

In this prospective study, 48 healthy female subjects, (mean age 22.5; SD 2.6 years) were asked to test their perceived electrical sensory threshold, EST, and electrical pain threshold, EPT, using the PainMatcher instrument. After drop-out, 35 individuals (mean age 22.2; SD 2.5 years) were included in the analysis. Evaluation of the test-retest variability in EST and EPT assessments were made between days in two consecutive days. During the two days four daily assessments were performed with a 30-minute rest between each to avoid possible carry-over effects.

Also 36 female patients (mean age 41.1; SD 12.5 years) with pain present in different body areas, of different etiologies, and with duration of pain ranging from 0 to more than 12 months were asked to assess their thresholds twice within 30 minutes on the same day. The assessments were made on the same day in order to possibly minimize the influence of different variation factors. The study was restricted to women primarily to avoid gender-related effects.

Study II

This study was performed as an prospective study and 29 healthy women (mean age 27.7; SD 6.8 years) and 29 healthy men (mean age 27.8; SD 6.9 years) participated to assess their electrical sensory threshold, EST, and electrical pain threshold, EPT, by the PainMatcher instrument in response to 20 minutes of transcutaneous electrical nerve stimulation, TENS, applied in the same segmental area for the neurological innervation as the assessment of the thresholds. Assessments were made four times with ten minutes between every occasion - before TENS, TENS ten minutes, after 20 minutes of TENS and ten minutes after ended TENS.

Study III

In this randomized clinical controlled study, 70 pregnant women with pelvic pain (mean age 29.1; SD 4.4 years) were enrolled and randomized into treatment with two different modes of acupunctural stimulation: superficial and deep. After drop outs, the number of women treated with acupuncture included in the analysis were - superficial, n= 22 (mean age 29.9; SD 3.0), and deep, n=25, (mean age 29.0; SD 5.5 years). The superficial mode is here defined as when thin acupuncture needles were inserted over classical acupuncture points and then left un-stimulated. The deep mode is defined as needles inserted in classical acupuncture points to the recommended depth and repeatedly manually stimulated during the treatment. The women were offered ten treatments that each lasted for 30 minutes. Used acupuncture points are shown in Table 2.

For the evaluation of change in rated pain intensity at rest and activity, the Visual Analogue Scale, VAS, was used. Pain and associated affective variables of the pain condition, emotional reactions and loss of energy were assessed according to the Nottingham Health Profile questionnaire.

Study IV

This study was performed as a cross-sectional study in the sense that the pain intensity assessments of three pain etiology groups (chronic/idiopathic, nociceptive, and neuropathic) were described separately. The 80 recruited patients, (mean age 42.8; SD 12.7 years) were diagnosed as chronic/idiopathic, n=30 (mean age 42.8; SD 10.6 years); nociceptive, n=31 (mean age 40.0; SD 14.2 years); neuropathic, n=19 (mean age 47.3; SD 12.7 years). The female proportions were 13, 15 and eight in the three groups respectively. The patients current pain intensity were assessed twice using a continuous Visual Analogue Scale, VAS, (0-100) and a discrete five category Verbal Rating Scale, VRS, in random order. The assessments were completed 30 minutes prior to the patients' appointment with their physicians.

Study V

The relation between the concentrations of corticotropin releasing factor-like immunoreactivity, CRF-LI, in 24-hour urine samples and rated depression and anxiety was evaluated in 19 women with diagnosed fibromyalgia (mean age 50.7; SD 9.7 years) in this study. After base-line assessments, the women were randomized into treatments of massage and guided relaxation. The patients were given 12 treatments, each lasting for 30 minutes. The change in response to treatments regarding the urinary CRF-LI concentrations, ratings of depression, anxiety as well as pain and emotional reactions were evaluated.

Table 1. An overview of used study design, variables and, outcome instruments.

Study	Design	Variable	Instruments
I	Prospective; test retest	EST EPT	Electrocutaneous stimulation (PainMatcher)
II	Prospective; change	EST EPT	Electrocutaneous stimulation (PainMatcher)
III	RCT; change within / between groups	Current pain intensity Variables associated with pain	VAS NHP
IV	Cross sectional; concordance, test retest	Current pain intensity	VAS, VRS
V	Prospective, RCT; change within groups	Biochemical stress markers Variables associated with pain Blood pressure Heart rate	CRF-LI of urine sample C PRS-A, NHP

CPRS-A= Comprehensive Psychopathological Rating Scale – Affective; CRF-LI=Corticotropin releasing factor-like immunoreactivity; NHP=Nottingham Health Profile; RCT=Randomized Controlled Clinical Trial; VAS=Visual Analogue Scale; VRS= Verbal Rating Scale.

Outcome variables and assessment instruments

Threshold assessments

Electrocutaneous stimulation applied to the thumb and index-finger of one hand was used to assess the electrical sensory threshold, EST, defined as the least stimulation perceived at all, and the electrical pain threshold, EPT, defined as the least stimulation required producing the first perception of pain *(Study I, II)*. The perceived intensity of the stimulation was continuously increasing and the given information were that a paresthesia-like sensation would appear in the fingers when the EST was reached, and a distinct sensation of pain, separated from perceived unpleasantness, at the EPT.

The electrical stimulation device used for threshold assessments, PainMatcher (Cefar Medical AB, Lund, Sweden), fig.4, is a microprocessor that distributes constant current, 15 mA, in mono-phasic rectangular pulses at random velocity with a frequency of 10 Hz to the electrodes. To create an electrically closed circuit the electrodes of the instrument are pressed with the thumb and second finger of one hand. The electrode placed under the index finger is the negatively charged electrode, the cathode. The contact area of the electrode (~6 cm^2) and, hence, the resulting current density, is ensured by a certain minimum finger pressure against the electrodes. The stimulator is designed to compensate for skin resistance variations, in case of e.g. sweating or anxiety, up to 13 kΩ in order to produce a constant current. Perceived intensity is raised by an increased pulse duration ranging from a minimum of 4 μs to a maximum of 396 μs in increments of 4 μs and a total of 99 steps. One measurement series from minimum to maximum intensity takes less than one minute. The electrical charge per pulse is extremely low, 5.9 μC. When reaching the thresholds, EST and EPT respectively, the fingers are released from the electrodes and an open circuit is detected. The increase in the constant current generation is interrupted and a value between 0 and 99 (directly related to the pulse width) is then displayed on the LCD screen and automatically saved in the memory. The assessment procedure is based on individual responses with no visualized predetermined lower or upper limits, which blinds the subjects as well as the examiner to the assessment outcome.

Fig. 4. The threshold assessment instrument with permission from Cefar Medical AB.

The Visual Analogue Scale, VAS

The continuous, horizontal, Visual Analogue Scale, VAS, (0-100) with the anchor points, "no pain" and "worst possible pain", respectively was used to assess pain intensity *(Study III, IV)*. In *Study III* VAS was used for ratings both at rest and during functional movements. The patients were asked to rate their actual pain intensity by marking a level on the scale corresponding to their experienced pain intensity level.

The VAS recordings provide 101 possible categories based on the positions on the 100 mm long line relative the anchor “no pain”.
”How intense do you perceive your actual pain?”

The Verbal Rating Scale, VRS

The discrete, five-category, Verbal Rating Scale, VRS, with the eligible alternatives - no pain (0), mild (1), moderate (2), severe (3), worst possible pain (4) – was used to assess pain intensity *(Study IV)*. The patients were asked to rate their actual pain intensity by marking a level on the scale corresponding to their experienced pain intensity level. The assessed category was recorded as 0 through 4.

”How intense do you perceive your actual pain?

○ No pain

○ Mild pain

○ Moderate pain

○ Severe pain

○ Worst possible pain

Variables according to the Nottingham Health Profile, NHP

The Swedish version of the Nottingham Health Profile, NHP, questionnaire (Wiklund and Dimenas, 1990) was used for the assessment of pain and variables associated with the pain – emotional reactions *(Study III, V)* and loss of energy *(Study III)*. Its included variables are assessed by agreement, yes or no, to statements concerning complaints. Eight statements assessed the variable pain, nine statements assessed the variable emotional reaction, and three statements assessed the variable loss of energy. The numbers of agreed statements are operationally defined as the levels of perceived pain, emotional reactions and loss of energy. Hence the level of e.g. pain is scored from 0 (no indication of pain) to 8 (all indicators of pain were chosen).

Variables according to the Comprehensive Psychopathological Rating Scale – Affective, CPRS-A

The questionnaire Comprehensive Psychopathological Rating Scale – Affective, CPRS-A (Svanborg, 1994), modified for patients with pain at the Karolinska University Hospital is designed to assess symptoms of depression and anxiety associated with pain and was used in *Study V*. The CPRS-A contains 22 items and the seven response alternatives to each question are graded from 0 to 3 (in steps of 0.5). The higher response value, the higher level of distress is indicated.

Corticotropin Releasing Factor-Like Immunoreactivity, CRF-LI, RadioImmunoAssay, RIA

For the assessment of a possible biochemical marker of stress-related symptoms associated with pain *(Study V)*, the urine samples were collected in plastic boxes,

containing 6 M hydrochloric acid, during 24 hours. The individual total urine volume was mixed, measured, and a sample of 50 mL was stored at -70°C. Prior to analysis the urine sample was filtrated and additionally acidified with 50µL of 10% TFA. Before application of the urine sample, the cartridges used for the purifying process (Sep-Pak® C18, Water Assoc. Inc., Milford, MA, USA), were prepared with 10 mL of methanol containing 0.1% of TFA, and followed by 10 mL H2O with 0.1% TFA. After application of urine sample, the cartridges were rinsed with 2 mL of H2O with 0.1% TFA and the sample was eluted by 4 mL of methanol with 0.1% of TFA. Finally, the samples were vacuum-dried and stored at +4°C. At analysis, each vacuum-dried sample was dissolved in 1 mL phosphate buffer (0.05 M, 1.0% BSA, pH 7.4) and a standard curve was prepared. For the RIA analysis RAB-019-06 CRF antiserum (Phoenix Pharmaceuticals Inc, USA) were used. One hundred µL of antiserum was incubated with 100 µL of standard solution or the purified sample in +4°C for 48 hours. One hundred µL of [^{125}I] tracer solution, (Eurodiagnostica, Malmö, Sweden), was then added to the sample and incubated at +4°C for 24 hours. For separation of the bound from the unbound fraction in the sample, 500 µL of a second antibody, Decanting Suspension 3 (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) was added and incubated for 30 minutes in room temperature. By adding 1.0 mL water to each sample this reaction was stopped. After centrifugation in 15 minutes at +4°C (2800 x g), the supernatant was poured off and the activity of the isotope [^{125} I] in the precipitate was measured for three minutes/sample in a gamma counter (Wizard 1470, Wallac, Turku, Finland). The detection limits for CRF in each test sample were 3.9 pmol/L and 1000 pmol/L. The cross reactivity was 100% to CRF (human, rat); 0% to ACTH (human), 0% to LH-RH, 0% to PACAP-38 (human, rat, ovine), 0% to [Arg8]-Vasopressin, 0% to Urocortin (human), 0% to Urocortin (rat), 0% to BNP-45 (rat). All samples in the analysis were made in duplicate and the 24-hour CRF-LI concentration was calculated for each individual relative the eluted and the total urine volume.

Treatment - Sensory stimulation

Transcutaneous Electrical Nerve Stimulation, TENS

High frequency, 80 Hz, Transcutaneous Electrical Nerve Stimulation, TENS, was used *(Study II)* with distributed current in asymmetrical biphasic pulses, 100% compensated, pulse duration of 180µs and available amplitude of 0–60 mA (Cefar Primo stimulator, Cefar Medical AB, Lund, Sweden). Carbon electrodes, ~12 cm^2 coated with conducting gel, were fixed to the skin at the medial dorsal side of one forearm, i.e. the same side as for threshold assessments, and connected to the TENS unit. The negative electrode (cathode) was positioned 5 cm distal to the elbow joint and the positive electrode (anode) 5 cm proximal to the wrist joint, i.e. intra-segmental (dermatome C6–8) for the neurological innervation to the electrical threshold assessments. The current amplitude of the TENS was increased until a sensation just below unpleasantness was felt and without muscle contraction, representing approximately two to three times the perceived sensory detection level induced by TENS (~7–15 mA). The subjects were instructed to maintain this level and to adjust the intensity level in case of adaptation, perceived as a decrease, during the TENS period. When assessing thresholds during stimulation, the current of the TENS unit was temporarily cut off.

Acupuncture

For the acupuncture treatments *(Study III)*, ten classical acupuncture points were selected for stimulation and chosen depending on the site of pain (BL 27, 28, 29, 31, 32, 54, KI 11, CV 3) in combination with peripheral points (SP 6, LR 2, LI 4), intra- or extra-segmentally related to the neurological innervations of the painful area, Table 2. Usually three to four of the BL points were used and applied bilaterally. Two types of sterilized steel acupuncture needles were used for acupunctural stimulation: 15 mm length/0.20 mm diameter (Seirin) and 30 mm length/0.30 mm diameter (Marco Polo, Schwa Medico).

Table 2. Acupuncture points used for the treatment of pelvic pain in pregnant women.

Points	Localization	Segmental innervations Peripheral nerve (spinal segment)	Penetrated tissue, deep stimulation modality
BL 27	The level of 1st sacral foramina, 1.5 cun lateral to the dorsal body midline	S: N. lumbalis (L3) M: Nn. thoracodorsalis, thoracicus, lumbalis (C6-8, Th9-12, L1-3)	Fascia thoracolumbalis, m. erector spine
BL28	The level of 2nd sacral foramina, 1.5 cun lateral to the dorsal body midline	"	"
BL 29	The level of 3rd sacral foramina, 1.5 cun lateral to the dorsal body midline	"	"
BL 31	The level of 1st sacral foramina, between BL 27 and the dorsal body midline	"	"
BL 32	The level of 2nd sacral foramina, between BL 28 and the dorsal body midline	"	"
BL 54	The level of hiatus sacralis, 3 cun lateral to the dorsal body midline	S: N. sacralis (S1-3) M: N. gluteus inferior (L5-S2)	M. gluteus maximus
KI 11	2 cun caudal to the umbilicus, 0.5 cun lateral to the ventral body midline	Nn. thoracicus, subcostalis (Th6-12)	Vagina m. recti abdominalis, m. rectus abdominis
CV 3	In the ventral body midline, 4 cun caudal to the umbilicus	N. iliohypogastricus (L1)	Connective tissue
SP 6	3 cun proximal to the most prominent point of the medial malleolus	S: N. saphenus (L3-4) M: N. tibialis (L4-S2)	Mm. flexor digitorum longus, tibialis posterior
LR 2	Between the 1st and the 2nd metatarsal bone	N. peroneus profundus (L4-5, S1-2)	Connective tissue
LI 4	At the middle, radial side of the 2nd metacarpal bone in the highest point of m. interosseus dorsalis with the thumb adducted	S: N. radialis (C6-8) M: Nn. medianus, ulnaris (C8, Th1)	Mm. interossues dorsalis I, lumbricalis II, adductor pollicis

Abbreviation of acupuncture channels names - BL=Bladder; KI=Kidney; CV=Conception Vessel; SP=Spleen; LR=Liver; LI=Large Intestine. For localization of acupuncture points both anatomical landmarks and when needed, a proportional measurement, cun based on the patients size, were used. Abbreviation in segmental innervations - S=Skin; M=Muscular.

Massage

The massage treatment *(Study V)* was applied to different body areas (feet, legs, hands, arms and face) and consisted of the standardized massage techniques stroking (effleurage), kneading (petrissage), friction and shakings - all performed in a slow rate of approximately 1Hz. The hand pressure was always adjusted according to the patients' preference. Massage lotion (CCN, Stockholm, Sweden) or massage oil (Rolf Kullgren AB, Stockholm, Sweden) was used to diminish friction in the skin-to-skin contact during massage treatment.

Guided relaxation

In the relaxation therapy *(Study V)* the patients were personally guided into progressive relaxation according to Jacobsen, 1978.

Statistical methods

General aspects

Different types of questions and data are statistically treated in this thesis. Quantitative data have been described by the mean and standard deviation, (SD), when assumption of normal distribution was likely, else by the median and range. Ordered categorical data was described by the median and range, see Table 3.

The research questions regarding intra- and inter-observer agreement, test-retest stability, and change in qualitative variables were solved by evaluation of paired data and statistical methods developed for paired ordinal data was applied (Svensson, 1993; Svensson, 1998), see Table 3.

Distributions of paired discrete ordered categorical data were presented by square contingency tables. The paired continuous data from assessments on the Visual Analogue Scale, VAS, and assessments of the electrical pain threshold were shown in scatter plots. The main diagonal of unchanged values in the contingency table is oriented from the lower-left to the upper-right corner, which corresponds to direction of the main diagonal in the scatter plots. In the contingency tables the marginal frequency distributions of the total number of subjects were also shown, see fig. 5a.

The percentage agreement, PA, i.e. the percentage of subjects that agreed to the same assessment value in the paired data, was used to describe the intra-observer agreement (test -retest) (*Study I, IV*).

The applied rank-invariant statistical method by Svensson for evaluation of systematic disagreement/change and individual disagreement/variation

A presence of disagreement in pairs of observations has mainly two different sources of explanation: a systematic, referring to the group, and an occasional disagreement referring to the individual. The systematic disagreement in intra- and inter-observer agreement means bias and is a sign of a common group change in studies of change in ordinal data. The occasional disagreement concerns the level of disagreement that could not be explained by bias or a common group change, respectively. The statistical measures of the systematic and occasional components of disagreement are shortly described here.

The two sets of marginal frequency distributions of the raw data reveal the systematic part of disagreement (Svensson, 1993). The level of bias based on the distribution of marginal frequencies was graphically illustrated by plotting the two sets of cumulative frequencies of the observed assessment values against each other beginning at the point (0, 0) yielding a type of relative operating characteristic, ROC, curve (*Study I-III*). As mentioned, in case of bias, the two marginal frequency distributions differ, and so do the two sets of cumulative frequencies, meaning that the ROC curve will deviate from a straight line, see fig. 5b.

Two measures of systematic disagreement were calculated; the relative position, RP, (*Study I-V)* and the relative concentration, RC, *(Study V)* with possible values ranging from -1 to 1.The value of RP estimates the difference between the probability of the scale assessments on one occasion being shifted towards higher categories relative to the other occasion and the probability of the assessments on one occasion being shifted towards lower categories relative to the other. A negative RP value indicates that the assessments are systematically shifted to lower level of the second occasion relative the first and is shown as a deviating curve above the main diagonal in the ROC curve. The contrary holds for a positive RP value. RP = 0 means lack of systematic disagreement between the two assessments. The value of RC estimates the

difference between the probability of the pain assessments on one occasion being concentrated relative to the other occasion and vice versa.

The joint distribution of paired data in the contingency table or in the scatter plot contains information about an additional individual variability that is unexplained by the systematic disagreement, seen as the different marginal frequencies.

Apart from the systematic disagreements a measure of individual disagreement/variation was calculated, denoted relative rank variance (RV) (*Study I-III, V)*. In order to calculate the additional individual disagreement the pairs of data were transformed into pairs of rank values where the ranks are tied on the cells of the table. The square of the rank differences is the basis of the calculation of the relative rank variance, RV. The higher the values of RV, the more dispersed are the observations. Possible values of RV range from RV=0, lack of individual variations, to RV=1 which means a variability of the same magnitude as from uniformly distributed pairs over the contingency table (Svensson, 1993; Svensson, 1998).

A clinical implication of the value of RP is essential for the systematic response in evaluation of assessment quality (disagreement) and in the evaluation of change (e.g. treatments effects). The value of RV indicates information that is related to the individual, e.g. the need for individually designed treatment strategies and evaluation, and additional to the systematic.

5a

Pain level before treatment

Pain level after treatment	0	1	2	3	4	Tot	CF	CP
4						0	100	1.00
3				3	2	5	100	1.00
2			16	19	6	41	95	0.95
1	1	4	23	12	5	45	54	0.54
0		2	6	1		9	9	0.09
Tot	1	6	45	35	13	**100**		
CF	1	7	52	87	100			
CP	0.01	0.07	0.52	0.87	1.00			

5b

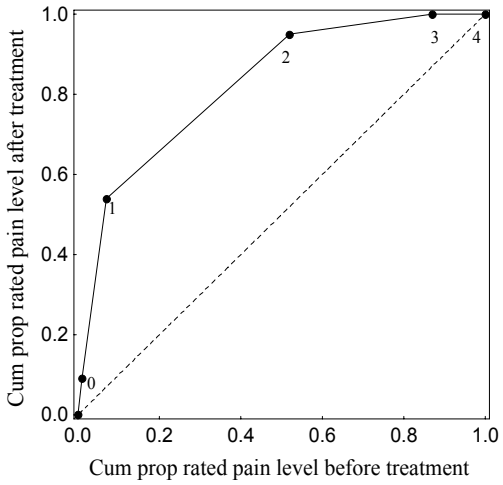

Fig. 5a-b. Contingency table and ROC curve from paired categorical data of pain ratings, 0-4, before and after treatment.

5a Joint distribution of paired data in contingency table. Tot = Total distribution of marginal frequencies; CF=Cumulative frequency; CP= Cumulative Proportion of cumulative relative frequencies.

5b ROC curve demonstrating the cumulative proportions (cum prop) of the paired data. It appears from the ROC curve that the category 1 in the five point scale contains 54% of the patients after treatment and category 2, 95% compared with 7% and 52% before the treatment respectively. This indicates that the rated pain level of the group changed systematically towards lower levels after treatment

Evaluation of inter-scale comparisons according to Svensson

The inter-scale comparisons were evaluated by means of another statistical method by Svensson, 2000a, 2000b. In *Study IV* the data set consists of paired data from assessment of different scale (VAS, VRS). The evaluation of interchangeability between scales with different numbers of response categories requires lack of overlapping of the records on one scale relative the other, i.e. a high level of order-consistency.

A possible presence of overlapping could be the pairs (34, no pain), (34, mild pain) and (34, moderate pain) while the two pairs (43, mild pain) and (48, moderate pain) represent ordered pairs and the two pairs (43, severe pain) and (48, moderate pain) exemplify disordered pairs. The cut-off positions of the visual analogue line, which define a discrete VAS that is unbiased to the VRS data, are constructed by pairing off the two sets of frequency distribution to each other and by identifying the cut-off positions in VAS that corresponds to the change in category of the VRS. This procedure creates pairs that are in complete order. Thus the condensed discrete scale based on the continuous VAS records will, under this circumstance, show a total order consistency and no systematic disagreement (be unbiased) relative the VRS.

The number of disordered pairs, out of all possible different pairs, was calculated and defines the measure of disorder, D. The level of order-consistency is defined by the coefficient of monotonic agreement, MA, which can be calculated by MA=1-2D and ranges from -1 to 1.

A high level of order consistency between scales with the same number of categories requires a high percentage agreement, PA, where the proportion of identical pairs defines the PA and a lack of systematic disagreement (bias) of the pairs of data, RP and RC equals unity.

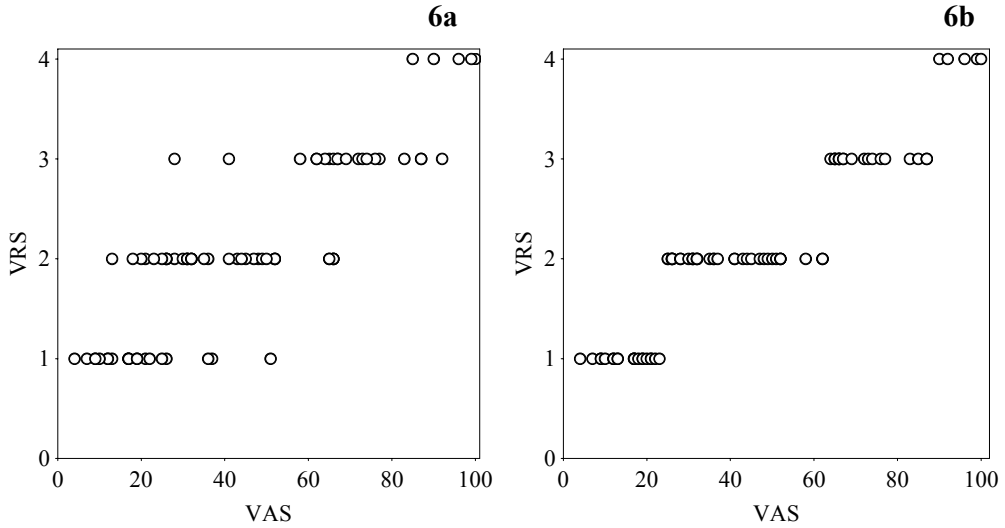

Fig. 6a-b. Paired data of rated pain intensity on a continuous VAS, 0-100, and on a discrete five category VRS. Fig. 6a show the raw data on the two scales demonstrating overlap between the different categories. Fig. 6b The paired data in total order demonstrating the cut off positions on the VAS.

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Other used statistical measurements and tests

The Spearman rank order correlation coefficient (rs) was used for evaluation of possible relationship between variables *(Study V)*. The Wilcoxon signed rank test was used to evaluate change in continuous quantitative variables *(Study V)*.

The Wilcoxon-Mann-Whitney U test was used for test of the differences in assessments between groups *(Study I, III)*. The Sign test with correction for continuity was used for test of the hypothesis of no change in paired assessments (*Study II, III, V*).

A two-sided *p*-value less than 0.05 was regarded as significant. To adjust for multiple tests, the individual p-values were corrected according to Holm's stepwise adjustment for multiple tests when appropriate *(Study III)* in order to obtain an overall p-value less than 5% in the study (Holm, 1979).

The software package of Statistica, 6.0 (*Study I-IV*) and 7.0 *(Study V)*, were used for descriptive statistics and SYSRAN 1.0 for Matlab 6 was used to calculate D, MA, RP, RC, RV and the corresponding 95% confidence intervals for the measures.

Table 3. An overview of assessed variables, data level, descriptive statistics, aim/research question and statistical methods.

Study	Variables/ instruments	Data level	Descriptive statistics	Aim/ Research question	Statistical methods
I	Age	Quant cont	Mean (SD)		
	EST	Ordinal	Median (Range)	Test-retest,	PA, RP, RV,
	EPT			Diff between groups	Wilcoxon-Mann-Whitney U test
II	Age	Quant cont	Mean (SD)		
	EST	Ordinal	Median (Range)	Change,	Sign test, RP, RV
	EPT		Proportions	Diff between groups	95% CI proportions between groups
III	Age	Quant cont	Mean (SD)		
	Gestational age		Median (Range)		
	Number of pregnancies		"		
	Duration, pain		"		
	Pain and associated variables	Ordinal	Median (Range) Frequency	Change, Difference between groups	Sign test, RP, RV Mann-Whitney U test
	VAS		"		
	NHP		"		
IV	Age	Quant cont	Mean (SD)		
	Duration, pain		Median (Range)		
	Pain intensity	Ordinal	"	Interchangeability,	MA, Concordance
	VAS		Proportions	Concordance,	
	VRS		"	Test-retest	PA, RP, RC, RV
V	Age	Quant cont	Mean (SD)		
	Heart rate	"	"		
	Blood pressure	"	"		
	Duration, pain	"	Frequency	Association	Spearman rank order
	Duration, stress	"	"	between urinary	correlation coefficient
	Urine CRF-LI concentration	"	Median	CRF-LI concen-tration and rated	
	Associated variables	Ordinal		stress-related symptoms	
	NHP			Change after	Wilcoxon signed
	CPRS-A			treatment	rank test
					PA, RP, RV

CPRS-A= Comprehensive Psychopathological Rating Scale – Affective; CRF-LI=Corticotropin releasing factor like immunoreactivity; EST=electrical sensory threshold; EPT=electrical pain threshold; NHP=Nottingham Health Profile; PA=percentage agreement; Quant cont=quantitative continuous; RP=relative position; RC=relative concentration; RV=relative rank variation; SD=standard deviation; VAS=Visual Analogue Scale; VRS= Verbal Rating Scale.

Study I

The percentage agreements, PA, within one PainMatcher, PM value (PA ± 1 PM value) were described for test-retest of between-days and within-days variability in assessments of electrical sensory threshold, EST, and electrical pain threshold, EPT. The differences in assessed EST and EPT between the groups of healthy female subjects and female patients in pain were analyzed by the Wilcoxon-Mann-Whitney U test.

Study II

The response to transcutaneous electrical nerve stimulation, TENS, was evaluated by describing the proportions of subjects within the groups of women and men

respectively, who assessed increased, unchanged and decreased electrical sensory threshold, EST, and electrical pain threshold, EPT, post-TENS versus pre-TENS. The Sign test with correction for continuity was used for test of the hypothesis of no change in the paired assessments. The response pattern was further evaluated by calculating the systematic change, RP, as well as the individual variation, RV. The 95% confidence interval, CI, for proportions and for the difference between women's and men's increased thresholds was also calculated.

Study III

The response to two modes of acupunctural stimulation on pregnant women's pelvic pain was evaluated by calculating the proportions of women that rated a lower level, the same level or a higher level of pain intensity at rest and during functional movements. Also, the same proportions were calculated regarding the rated variables from the Nottingham Health Profile (NHP) questionnaire. The sign test was used to test hypothesis of no change in rated pain and associated variables (pain, emotional reactions and loss of energy according to NHP). The Holm's stepwise adjustment for multiple tests was used.

Study IV

To test the inter-scale concordance in pain intensity assessments between Visual Analogue Scale, VAS, and a discrete five category Verbal Rating Scale, VRS, the measure of disorder, D, was calculated. Also, the level of order consistency was described by the measure of monotonic agreement, MA. To test the intra-individual stability of both scales, test-retest reliability was calculated including percentage agreement, PA, and evaluation of systematic disagreement calculating the measures of RP and RC.

Study V

For test of a possible relationship between the corticotrophin releasing factor-like immunoreactivity, CRF-LI, concentrations of urine samples and the ratings of the variables of depression and anxiety, the Spearman rank order correlation coefficient (rs) was used. The Wilcoxon signed rank test was used for the evaluation of change in CRF-LI concentrations in response to treatment. The level of change in common for the group as well as for the individual was evaluated with the measures of RP and RV.

RESULTS

Study I

The intra-individual reliability of the repeated threshold assessments was expressed as the Percentage Agreements, PA, within ±1 PainMatcher value. For the assessed electrical sensory threshold, EST, the PA was in the group of healthy subjects, n=35, and patients in pain, n=36, 94% and 92% and for the electrical pain threshold, EPT, the PA were 49% and 78%, respectively. The variability in the EST assessments could possibly be explained by a slight bias (disagreement), while the individual variations were negligible between the two occasions. The assessed EPT were unbiased in both groups, while individual disagreements were evident among the healthy subjects but negligible among the pain patients. The EST was found to be increased in pain patients compared with healthy subjects ($p<0.03$), and the EPT decreased in pain patients compared with healthy subjects ($p<0.001$).

The results in this study indicate stable and reliable assessments of EST and EPT. The used threshold assessment procedure may be a valuable tool in the clinical evaluation of sensory and pain assessments in pain patients.

Study II

The electrical thresholds were assessed pre-TENS, during TENS, and post-TENS in healthy women and men. In pre-TENS assessments compared with post-TENS assessments, equal levels of systematic changes towards increased electrical sensory thresholds, EST, were seen in women and men (RP, 0.35; 95% CI 0.07 to 0.63, and RP 0.36; 95% CI 0.17 to 0.53, respectively). Comparing assessment of the same points of time, systematic changes towards increased electrical pain thresholds, EPT, were seen in women (RP, 0.43; 95% CI 0.27 to 0.60), but were unchanged in men (RP, −0.01; 95% CI −0.13 to 0.10). Significant additional individual variations were found in the women's responses of assessed EST and EPT only.

It is concluded that both women and men responded with a significant increase of the EST to high frequency TENS, but only women responded with increase of the EPT. The individual changes of the responses were obvious in women.

Study III

After acupunctural stimulation of pregnant women's, n=47, pelvic pain, significant systematic group changes towards lower levels of pain intensity at rest and in daily activities, as well as in rated emotional reaction and loss of energy, were seen. The results also showed evidence of individual variation in most variables. In this study, no differences between the effects induced by the superficial and deep acupunctural stimulation modes were observed.

In summary, individually designed acupunctural stimulation may be a valuable treatment to ameliorate suffering in the condition of pelvic pain in late pregnancy.

Study IV

Concerning the consistency between assessments an overlapping of the recorded levels on the Visual Analogue Scale, VAS, relative the Verbal Rating Scale, VRS, categories was seen in all pain groups (chronic/idiopathic, n=30; nociceptive, n=30; and neuropathic, n=19). The cut-off positions between the VAS pain level and the corresponding VRS categories differed in the groups and were found lower in patients

with nociceptive pain relative patients suffering from chronic/idiopathic and neuropathic pain. When comparing the VAS records, transformed into an equidistant five-category scale with the VRS records, systematic disagreements between the scales was shown in all groups. Furthermore, in the test-retest, a low proportion of the patients in the three groups agreed to the same pain level on the VAS, Percentage Agreements, PA, 11% to 26%, while the opposite hold for the VRS, PA 87% to 100%.

The pain intensity assessments on VAS and VRS are not interchangeable due to an overlap of pain records between the two scales, systematic disagreements when comparing the two scales, and a low percentage intra-scale agreement for the VAS assessments. Furthermore, the lower VAS cut-off positions relative the VRS categories indicate different meaning of the rated pain intensity depending on pain etiology. It is also indicated that the scales have non-linear properties and that the two scales probably have different interpretations.

Study V

The concentration of the 24-hour urinary corticotropin releasing factor-like immunoreactivity, CRF-LI, was found to be associated with indicators of rated depression and the depression sub-variables mood and inability to take initiative. After massage, the urinary CRF-LI concentrations were found to be decreased as well as the indicators of anxiety, ache and pain, and associated variables like emotional reactions. In the group that received guided relaxation, the ratings of the variable emotional reactions were systematically decreased after the treatments.

The 24-hour urinary CRF-LI concentration may be used as a biochemical marker of stress-related symptoms like depression in patients with fibromyalgia, and possibly also other conditions characterized by chronic pain. Therapies such as massage and guided relaxation could be taken into consideration as a complement in treatment strategies aimed to decrease physiological as well as psychological distress.

DISCUSSION

Pain is a personal subjective experience influenced by a number of different components. Pain can, therefore not be regarded as a single entity but rather a complex multivariate problem and it has to be defined by its different components in assessment, treatment and evaluation. Given the variability and complexity of the subjective pain, it is important to evaluate the group as well as the individual responses in order to understand the patient's pain and to optimize the treatment decision-making.

Assessment of pain

As a uniquely personal experience without certainty, being to equal the physiological process of nociception, the reliance on patients' self-report of pain - its intensity, unpleasantness, or interaction with thoughts and life - is essential. Assessment methods, even though they are defined as objective and sophisticated, are most likely influenced by patients' motivation and psychological state but are, as such, a valuable complement to the verbal report (Kanda et al., 2002; Petrovic and Ingvar, 2002; Donaldson et al., 2003; Chang et al., 2003).

Furthermore, the patient's rated level versus the ratings of a physician, another member of the medical team, or a parent, is reported as not concordant, which makes the use of ratings outside the patient's own dubious (Mantyselka, 2001; Berntson and Svensson; 2001). Since there is no gold standard in pain assessment, the patient's preference for different assessment instruments may also improve the possibility to communicate the perceived pain.

Rating scales

In daily clinical activity, uni-dimensional rating scales are often used for pain assessment. In our study we used the Visual Analogue Scale, VAS, and the Verbal Rating Scale, VRS, for comparison of interchangeability. It was shown that the individual assessment of pain intensity within 30 minutes on the two scales, resulted in different responses and it is concluded that the assessments on the two scales, therefore, are not interchangeable. It was also demonstrated that the VAS and VRS have non-linear properties and, thus, probably have different meaning, i.e. could be interpreted differently (*Study IV*). Although pain rating assessment instrument are not regarded interchangeable, information from various pain assessment methods could, however, be preferred for the purpose of understanding the patient's pain better, and to contribute to optimized treatments.

Threshold assessments

Pain threshold concepts attempt to identify the perceived point on an individual continuum of an increasing stimulus intensity that distinguishes painful from non-painful experience. The assessed threshold level may be influenced by disturbances and thereby changed with regard to the pain condition itself.

In our results, there was an agreement between the repeatedly assessed electrical sensory threshold, EST, and electrical pain thresholds, EPT, suggesting that the thresholds could be reliably assessed. Furthermore, in pain patients compared with healthy subjects it was found that the EST was found to be increased and the EPT decreased, possibly indicating consequences of the pain condition (*Study I*).

Our results also show that among healthy subjects, women have lower EPT as compared with men suggesting that gender aspects should be taken into account in threshold assessment *(Study II)*. The threshold assessment procedure followed in this study may be a valuable tool in the clinical evaluation of sensory and pain assessments in pain patients given gender separated analysis.

Variables associated to pain

The importance of using various forms of pain rating methods but also assessment of related symptoms has been high-lighted during the last decade. A new international standard for function and disability (ICF) have been presented (Weigl et al., 2006) for the assessment of the consequences of disease and/or dysfunction including pain. In our study of pregnant women with pelvic pain, the women reported complaints such as emotional reactions, loss of energy and pain, using the multi-item instrument Nottingham Hill profile, NHP, illustrating the complexity of pain. Using the same instrument, a similar pattern was seen in women with fibromyalgia, who reported complaints concerning emotional reactions and pain. Interestingly, in the latter group the urinary concentration of corticotrophin releasing factor-like immunoreactivity, CRF-LI, was found to be associated with indicators of rated depression, mood, and inability to take initiative, according to the Comprehensive Psychiatric Rating Scale – Affective, CPRS-A, questionnaire suggesting that CRF-LI concentration may be used as a biochemical marker of stress-related symptoms in patients with fibromyalgia and possibly other chronic pain conditions (*Study V*).

Statistical considerations

In clinical work, the phenomenon of pain is both considered and treated differently. Irrespective of the origin of the pain, the attempt of capture the perceived pain, i.e. to assess and evaluate the perceived pain, is of great importance.

In statistical analysis of pain data, it is discussed whether pain scales are equidistant or not, considering different assumptions for distribution of the collected data, and with implications for choice of method of analysis. This choice of method for pain analysis may, however, influence the quality and validity of the results, having possible implications on evidence based decisions and choice of recommendations of pain treatment. Though challenging and difficult to assess and evaluate, the statistical evaluation of variables like pain are of great importance to take into consideration. Otherwise, important information may be missed and the basic data for decision-making could be misleading.

In our studies, we have applied a statistical approach (Svensson, 1993) that is suitable for data from scale assessments, and the approach requires no other assumptions of the data than the ordered structure, which means that the results are valid and reliable for all types of ordered data.

The method used is applicable to different sorts of data based on the raw data as they are, no matter if they have linear or dichotomy properties. By this rank-based approach it is possible to evaluate a systematic disagreement in repeated assessments separately from an additional individual disagreement. When the aim is statistical evaluation of inter- or intra-rater reliability, the measures of systematic disagreement reveals bias, and the measure of individual disagreement reveal poor scales or lack of validity.

When the aim is statistical evaluation of change, i.e. treatment effect, the measures of systematic disagreement indicate a common group change (treatment effect) and the measure of individual disagreement is a sign of individual variations in change.

Thanks to this possibility of a comprehensive evaluation of repeated assessments it is possible to extract clinically valuable information that is not possible to obtain by other statistical methods.

For instance, the relative position indicates evidence a treatment's effects in common for the group and individual variation indicates that the treatment should preferably be individually designed. Interestingly, the methods also allocate the calculation of concordance between assessments made on scales with different numbers of possible values. It was shown in *Study V* that the applied type of analysis is suitable even for small samples.

The VAS is often used for pain assessments and was proposed by Aitken (1969) for within-subject evaluations but is now also used for comparison between groups (Huskisson, 1974; McCormack et al., 1988; De Loach et al, 1998). Even though the VAS is often used, there has been criticism of its scoring intervals and of the reliability, validity, and the interpretation of results from VAS assessments (Aitken, 1969; McCormack et al., 1988; Jaeschke et al., 1990; Cox et al., 1992).

Our results demonstrated a low percentage agreement of intra-individual pain assessment on VAS, thereby questioning the reliability regarding pain assessments using VAS. Also, the findings on disagreement between different pain scales are supported by recent studies. The concordance between VAS and a numerical scale used for pain assessment was evaluated (Svensson, 2000a; Berntson et al., 2001). A large individual variability in the position of marks on the VAS for each ordered category of the numerical discrete scale was found to result in an overlap of the responses. Hence, it is concluded that any position on the VAS was unrelated to the numerically labelled intensity of pain, even though both scales lacked operational definitions of the levels of pain intensity. Although continuous VAS assessments generate an impression of sensitive and reliable measurements expressed in millimetres this may not be true (Svensson, 2000a; Svensson, 2000b; *Study IV*).

According to Turk and Melzack (2001), the appropriate psychometric properties in any new assessment methods are needed to be taken into account. Normative information of rated pain intensity among patients' with the same diagnosis is suggested important to answer the question whether the rated pain level is abnormal or not. Taking the assessment variability of different dimensions into account, this could seem very difficult. However, possibly the assessment of pain thresholds could serve as a sort of reference for the degree of the disturbance in the pain system influencing the rated pain.

Sensory stimulation for pain treatment

In physiotherapeutic practice, different modalities of sensory stimulation for pain alleviation are used. The scientific basis for the use of these methods is still scanty and further experimental and clinical studies are needed. The use of TENS is established as supportive treatment in patients' home environment. It has also been shown to be effective in the amelioration of chronic knee osteoarthritis (Law 04; Lundberg et al., 2006). Our results show that when using TENS there was a change in EPT towards higher levels, especially in women, suggesting that there are differences between genders in response to TENS. Gender related responses to pharmacological treatment have been reported by Gear and collaborators (1999). Gender aspects on responses to sensory stimulation may be speculative since the number of subjects in our study was limited, although our results are rather robust (*Study II*). The evidence for the usefulness of acupuncture has been questioned, but has recently been reported to be evidently efficient in reducing low back pain (Lundberg et al., 2006) and for the treatment of knee osteoarthritis (Witt et al., 2005). In pregnant women with pelvic pain, acupuncture resulted in rated lower pain intensity during rest but also during

daily activities (*Study III*). Our results are supported by Elden and collaborators (2005). Both TENS and acupuncture are regarded safe and cost-effective and, therefore, warrant consideration in pain treatment (Chabal et al., 1998; White, 2004; Wonderling et al., 2004; Thomas et al., 2005).

The evidence of the use of massage is still discussed and is often reported as non-sufficient (Lundberg et al., 2006). However, there is some support for the use of massage in the treatment of stress (Field et al., 2005). In patients with fibromyalgia, massage resulted in a decrease of stress. Further studies are needed before this modality may be generally recommended (Lundberg et al., 2006).

Future prospects

The personal experience of pain can only be judged by the person in pain. Therefore the evaluation of pain assessment and treatment should take the individual response into account (Dionne et al, 2005; Asenlof et al., 2005). However, present recommendations for treatment are based on studies evaluating the effects preferably on a group level. Using evaluating procedures from recent statistical research developed by E Svensson, individual as well as group effects are possible to calculate. Randomized controlled clinical trials (RCT) have become the gold standard for the evidenced-based medicine. Recommendations based solely on RCT and evaluations of group effects may, therefore, circumvent the possibility of an effect on an individual level.

RCT commonly employ a placebo control group for the control of non-specific effects produced by therapy. The construct of RCT does not allow for evaluation of different types of non-specific effects (Thomas et al., 1991; Hui et al., 2005). Also, it is generally not possible to determine placebo response rates in RCTs, since a natural history group is often lacking.

However, placebo control in studies using sensory stimulation is, per definition impossible, to conduct. Furthermore, in a recent study aimed at elucidating the placebo response rates in RCT it was demonstrated that non-specific treatment effects are more important than the specific ones (Walach et al., 2005). This highlights the importance of evaluating the non-specific treatment effects.

In a future a combination of RCT and naturalistic designs (Thomas and Lundeberg, 1995; Leichsenring, 2004) could be adopted. Naturalistic studies, where the choice of, for instance, mode of stimulation and number of treatments are offered to patients, are less likely to misrepresent the relationship and influence upon the assessed outcome if incorporated into standard (randomized) biomedical designs. By doing this, an optimization of the therapeutic effects would be likely. Furthermore, a naturalistic approach possibly mimics the practical use of an intervention in a clinical context more closely.

Reflections

Recommendations for pain treatment should be based on the patient's specific needs. The methods used should preferably have proven to be efficacious in randomized controlled studies including the individual effects. The use of studies with a naturalistic protocol could give additional information. Therefore, it is important to assess the level of perceived pain taking the individual variation into account. The assessment should according to the result of our study be performed on the same type of scale. To extract as much information as possible from the collected data, appropriate statistical methods are important to use, taking the non-metric property of pain data into consideration and evaluating the systematic as well as the individual responses.

CONCLUSIONS

In conclusion, we have described and discussed both the systematic and the individual responses in different pain assessment methods and, thereby emphasized the need for consideration of individually responses in evaluation of pain and variables associated with pain, but also the need for individually designed treatments regimens. However, evaluation of assessed pain should take both systematic and individual variation into consideration. Threshold assessment may be an additional, valuable tool for clinical evaluation given gender-separated analyses. Our findings suggest that the assessment of pain intensity on the Visual Analogue Scale is not interchangeable with assessment on the Verbal Rating Scale. Biochemical markers, such as urinary CRF-LI concentrations may be used for measurement of stress-related symptoms in pain conditions. Therapies like TENS, acupuncture, massage and guided relaxation may be tried for the amelioration of pain and stress but further studies are required.

According to our results it is concluded that:
Threshold assessment was found stable and reliable in repeated assessments. The sensory thresholds were found increased and the pain thresholds decreased in pain patients as compared to healthy subjects.
Responses to TENS were indicated gender-related, assessed as increased pain thresholds in women but not in men. Women's pain thresholds were found lower than men's.
Suffering of pelvic pain in late pregnancy was reported decreased after treatment with acupuncture.
Pain intensity assessments using VAS and VRS were found not interchangeable due to overlap of pain records between the two scales, systematic disagreement comparing the two scales. It is also indicated that scales can have different interpretations.
Biochemical markers such as urinary CRF-LI concentrations may be used for measurement of stress-related symptoms in pain conditions. Lowered concentrations of CRF-LI and decreased rated symptoms were indicated after massage. Indications of decreased rated symptoms were also seen after guided relaxation.

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