PAIN® 151 (2010) 870–876

PAIN®

www.elsevier.com/locate/pain

Development of a severity score for CRPS

R. Norman Harden [a,*], Stephen Bruehl [b], Roberto S.G.M. Perez [c,d], Frank Birklein [e], Johan Marinus [d,f], Christian Maihofner [g], Timothy Lubenow [h], Asokumar Buvanendran [h], Sean Mackey [i], Joseph Graciosa [a], Mila Mogilevski [a], Christopher Ramsden [a], Tanja Schlereth [e], Melissa Chont [b], Jean-Jacques Vatine [j]

[a] *Rehabilitation Institute of Chicago, Chicago, IL, USA*
[b] *Vanderbilt University School of Medicine, Nashville, TN, USA*
[c] *VU University Medical Center, Amsterdam, The Netherlands*
[d] *Trauma Related Neuronal Dysfunction Consortium (TREND), The Netherlands*
[e] *University Medical Center Mainz, Mainz, Germany*
[f] *Leiden University Medical Center, Leiden, The Netherlands*
[g] *University of Erlangen-Nuremberg, Erlangen, Germany*
[h] *Rush University Medical Center, Chicago, IL, USA*
[i] *Stanford University Medical Center, Stanford, CA, USA*
[j] *Reuth Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

ARTICLE INFO

Article history:
Received 26 July 2010
Received in revised form 17 September 2010
Accepted 24 September 2010

Keywords:
Complex Regional Pain Syndrome
Reflex Sympathetic Dystrophy
CRPS
RSD
Psychometric
SF-36
Function
Prediction
CRPS Severity Score

ABSTRACT

The clinical diagnosis of Complex Regional Pain Syndrome (CRPS) is a dichotomous (yes/no) categorization necessary for clinical decision-making. However, such dichotomous diagnostic categories do not convey an individual's subtle and temporal gradations in severity of the condition, and have poor statistical power when used as an outcome measure in research. This study evaluated the validity and potential utility of a continuous type score to index severity of CRPS. Psychometric and medical evaluations were conducted in 114 CRPS patients and 41 non-CRPS neuropathic pain patients. Based on the presence/absence of 17 clinically-assessed signs and symptoms of CRPS, an overall CRPS Severity Score (CSS) was derived. The CSS discriminated well between CRPS and non-CRPS patients ($p < .001$), and displayed strong associations with dichotomous CRPS diagnoses using both IASP diagnostic criteria (Eta = 0.69) and proposed revised criteria (Eta = 0.77–0.88). Higher CSS was associated with significantly higher clinical pain intensity, distress, and functional impairments, as well as greater bilateral temperature asymmetry and thermal perception abnormalities (p's < .05). In an archival prospective dataset, increases in anxiety and depression from pre-surgical baseline to 4 weeks post-knee arthroplasty were found to predict significantly higher CSS at 6- and 12-month follow-up (p's < .05). Results indicate the CSS corresponds with and complements currently accepted dichotomous diagnostic criteria for CRPS, and support its validity as an index of CRPS severity. Its utility as an outcome measure in research studies is also suggested, with potential statistical advantages over dichotomous diagnostic criteria.

1. Introduction

The diagnosis of Complex Regional Pain Syndrome (CRPS; aka reflex sympathetic dystrophy, causalgia) has historically been a controversial issue, with internationally accepted diagnostic criteria only available since 1994 (published by the International Association for the Study of Pain's [IASP] committee on taxonomy) [32]. Validation research over the past 10 years has led to a proposed revision of these diagnostic criteria (the "Budapest Criteria" [19,23]). Both these current and proposed CRPS diagnostic criteria result in dichotomous (yes/no) diagnostic decisions. While necessary for clinical decision-making, dichotomous diagnoses provide no information about individual differences in severity or lability of CRPS signs and symptoms and provide poor statistical power as an outcome measure. This latter issue may impact particularly on prospective studies necessary to identify factors contributing to CRPS development, given the relatively infrequent occurrence of CRPS following injury. Availability of a well-validated continuous CRPS score that corresponds with dichotomous CRPS diagnoses might facilitate CRPS research and provide a simple means of communicating the severity of CRPS both inter-patient and intra-patient over time.

* Corresponding author. Address: Center for Pain Studies, Rehabilitation Institute of Chicago, 446 E. Ontario St., Suite 1011, Chicago, IL 60611, USA. Tel.: +1 312 238 5654; fax: +1 312 238 7624.
E-mail address: nharden@ric.org (R.N. Harden).

0304-3959/$36.00
doi:10.1016/j.pain.2010.09.031

Various proposals for CRPS scores have been described in the literature for more than 20 years [4,12,14,15,18,28,29,42,44,45]. These were often proposed as a method of CRPS diagnosis, with "cut scores" on these continuous measures suggested as a criterion for making clinical diagnostic decisions (e.g., [18,15,44]). A weakness common to most such scoring systems was that they were rationally-derived, and not followed up with systematic empirical validation to document their appropriateness or utility.

The best-validated continuous CRPS index available, the Impairment level SumScore (ISS), was designed specifically to assess CRPS-related impairment [33,35]. The ISS has several components, including a visual analog scale and McGill Pain Questionnaire pain ratings, goniometric measures of active range of motion, temperature asymmetry as reflected in infrared (IR) thermometry, and edema assessed via volumetry. Assessed values for each component are transformed into 1–10 scores, which are then combined into a total ISS score. Although the ISS has proven to be a useful outcome measure in some studies (e.g., [41]), it was not intended to be a summary measure of CRPS severity. As a result, it does not reflect several clinical features included in the current IASP diagnostic criteria for CRPS (e.g., hyperalgesia, allodynia, sweating and skin color changes), and reflects even less the more extensive features included in the proposed "Budapest Criteria" [19,21,23]. The need for quantitative testing and to transform these quantitatively-derived values into a scaling system before summing the components may make available scoring systems cumbersome for routine use [12,14,18,33].

The current project sought to empirically test the validity of a continuous-type CRPS Severity Score (CSS) that better reflects features of CRPS included in current and proposed diagnostic criteria, and that can be calculated by any clinician based solely on a series of simple "bedside" tests. It was hoped that a severity score reflecting CRPS diagnostic features normally identified during standard clinical history and physical examinations might prove useful as an overall index of CRPS severity for both communicating clinical status and for research purposes.

2. Methods

2.1. Design

A prospectively-obtained, international, multi-site sample was evaluated in a cross-sectional design to assess the potential utility of a continuous-type CRPS score as an index of CRPS severity.

2.2. Subjects

Subjects included a series of 114 CRPS patients who presented for evaluation and treatment at the data collection sites. All CRPS patients met published IASP diagnostic criteria for the disorder [32]. Both CRPS-I (80.7% of the sample) and CRPS-II (19.3%) patients were included in the study, with this diagnostic distinction reflecting the clinical absence versus presence (respectively) of "major" (not defined) peripheral nerve injury. Both groups otherwise met identical IASP criteria for CRPS. Presence of nerve injury was confirmed by EMG/NCV testing in 86% of the CRPS-II patients in this study. Fracture was the single most common initiating event in the CRPS group (36.3%), with surgery and crush injuries contributing in an additional 33.7%. Distribution of CRPS patients across the study sites was: Reuth Medical Center (Israel; 32.5%), University of Erlangen-Nuremberg (Germany; 12.3%), VU University Medical Center (Netherlands; 12.3%), Rehabilitation Institute of Chicago (US; 11.4%), Leiden University Medical Center (Netherlands; 11.4%), University Medical Center Mainz (Germany; 8.8%), and Rush University Medical Center (US; 6.1%).

A group of 41 non-CRPS neuropathic pain patients (i.e., neuropathic pain in the limbs without significant autonomic features) presenting for evaluation and treatment at the study sites were also included in the study for two purposes. First, the non-CRPS comparison group permitted examination of the continuous-type CRPS Severity Score in terms of its correspondence with dichotomous CRPS/non-CRPS diagnoses using the IASP criteria and proposed modified "Budapest Criteria" [19]. Second, given the absence of low CRPS Severity Scores in the CRPS patient group (see below; the lowest CRPS Severity Score was 7 on a 0–17 scale in the CRPS group), availability of the non-CRPS group insured that a less restricted range of CRPS Severity Scores was available for evaluating the utility of these scores as an index of CRPS severity in correlational analyses. That is, to demonstrate that higher CRPS scores are associated with greater pain, distress, and functional impairments, it was also necessary to show that low CRPS Severity Scores were associated with lower levels on these measures. The non-CRPS patient group underwent evaluation procedures identical to the CRPS group. Diagnoses in the non-CRPS group included peripheral neuropathy in a single extremity isolated to a specific nerve distribution (45%), radiculopathy (30%), diabetic peripheral neuropathy (15%), and carpal or tarsal tunnel syndrome (10%). Non-CRPS neuropathic pain disorders were diagnosed by the presence of spontaneous pain with clear neuropathic etiology supported by relevant testing where appropriate (e.g., EMG and clinical examination consistent with pain and symptoms restricted to a specific peripheral nerve distribution following known injury to that nerve, extremity pain coexisting with known diabetes mellitus, pain in a radicular pattern with disk herniation confirmed by MRI, etc.). Distribution of non-CRPS patients across the study sites was: University Medical Center Mainz (Germany; 24.4%), Leiden University Medical Center (Netherlands; 19.5%), VU University Medical Center (Netherlands; 19.5%), Reuth Medical Center (Israel; 14.6%), Rush University Medical Center (US; 12.2%), and Stanford University Medical Center (US; 9.8%). Summary data regarding the two groups of study patients are presented in Table 1. Additional data regarding the samples are provided in related work [21].

2.3. Procedures

Subjects provided written informed consent, and then completed the Rand-36 Health Survey to characterize their pain, emotional state, and functional level [43]. Next, for all patients in both groups, a study physician conducted an evaluation of CRPS signs and symptoms using the CRPS checklist detailed below (results for both patient groups are summarized in Table 2). This involved obtaining a patient history to assess symptoms, as well as conducting a standardized physical examination to assess signs. Both a standard protocol and a video example of examination procedures were provided to all sites to enhance consistency. To better characterize range of motion limitations identified during the physical examination, active range of motion was objectively assessed using a standard goniometer provided to all study sites. Flexion and extension in the affected elbow/knee (upper/lower extremity pain) and affected wrist/ankle (upper/lower extremity pain) were evaluated by this quantitative range of motion examination. To better characterize the degree of temperature asymmetry noted on the physical examination, temperatures in the center of the affected hand (palmar surface) or foot (plantar surface) and the contralateral hand/foot were determined while in a room temperature environment (minimum 30 min of acclimatization) using standard infrared (IR) thermometers provided to all study sites (Exergen Corp., Watertown, MA). This simple temperature assessment methodology was used in an attempt to provide quantitative confirmation of clinically-discerned temperature asymmetry.

Thermal Quantitative Sensory Testing (tQST; Medoc TSA-II, Medoc Inc, Tel Aviv, Israel) was also carried out for patients at

Table 1
Sample characteristics by diagnostic subgroup.

Variable	Diagnosis	
	CRPS (n = 114)	Non-CRPS (n = 41)
Gender (female%)*	63.0	41.5
Age (years)**	40.5 ± 15.74	52.6 ± 15.15
Pain duration (median (IQR) in months)*	19.1 (52.74)	40.9 (95.78)
Affected extremity (% lower extremity)**	48.7	74.3
Affected side (% right)	55.8	58.3
Affected side cold perception threshold (°C)*	28.3 ± 3.28	25.5 ± 4.98
Affected side warmth perception threshold (°C)**	37.2 ± 3.48	41.1 ± 3.71
Affected side heat pain threshold (°C)**	42.8 ± 4.19	46.0 ± 2.41
Mean asymmetry by IR thermometry (°C)*	−0.62 ± 1.82	0.13 ± 0.98
Affected side AROM – elbow/knee flexion (°)*	111.9 ± 37.37	127.3 ± 28.57
Affected side AROM – elbow/knee extension (°)	10.8 ± 45.41	8.4 ± 36.54
Affected side arom – wrist/ankle flexion (°)	37.2 ± 33.91	39.0 ± 32.39
Affected side AROM – wrist/ankle extension (°)	35.2 ± 30.39	41.6 ± 34.58
Rand 36 – physical functioning	41.4 ± 25.03	41.8 ± 25.29
Rand 36 – role limitations – physical health	15.0 ± 30.20	23.8 ± 37.53
Rand 36 – role limitations – emotional problems	43.7 ± 45.75	46.2 ± 44.34
Rand 36 – energy/fatigue	37.3 ± 22.41	39.5 ± 22.70
Rand 36 – emotional well-being	56.2 ± 21.35	60.3 ± 24.76
Rand 36 – social functioning	48.0 ± 26.73	52.8 ± 28.66
Rand 36 – Pain	28.1 ± 20.10	33.2 ± 21.24
Rand 36 – general health	50.80 ± 20.83	49.5 ± 23.64
CRPS Severity Score**	13.3 ± 2.35	7.0 ± 3.34

Note: Summary statistics are presented as percentages or mean ± SD. A negative value for mean asymmetry by IR thermometry indicates the affected side was cooler. Lower Rand 36 scores indicate greater pain, distress, or dysfunction. IQR, interquartile range; AROM, active range of motion.

* $p < .05$.

** $p < .01$.

the study sites in Israel and Germany, as well as the Rehabilitation Institute of Chicago and Stanford sites (data were only obtained for a subset of subjects at these latter two sites due to equipment availability and time constraints). tQST data were available for a total of 58 CRPS patients and 13 Non-CRPS patients. A standardized protocol was used across all study sites obtaining these data. The tQST protocol employed a computer-controlled 30 × 30 mm Peltier thermistor probe that was used to evaluate cold and warmth perception thresholds and heat pain threshold (mean of 3 trials each) using the 'method of limits' program standard on the device. For upper extremity CRPS, the probe was placed sequentially on three adjacent sites on the volar forearm of the affected extremity. For lower extremity CRPS, the probe was similarly placed on three adjacent sites on the dorsal mid-calf. Prior to each trial, the probe was maintained at an adaptation temperature of 32 °C.

All study procedures were approved by the relevant ethical review boards at participating institutions.

Table 2
Diagnostic signs and symptoms included in the CRPS Severity Score by subgroup.

Variable	Diagnosis	
	CRPS	Non-CRPS
Self-reported symptoms (% yes)		
Allodynia, Hyperpathia**	88.6	65.9
Temperature asymmetry**	87.7	36.6
Skin color asymmetry**	90.4	29.3
Sweating asymmetry**	63.2	14.6
Asymmetric edema**	88.6	41.5
Trophic changes**	75.4	39.0
Motor changes**	89.5	46.3
Decreased active range of motion**	86.8	34.1
Signs observed on examination (% yes)		
Hyperpathia to pinprick**	78.9	43.9
Allodynia**	71.1	29.3
Temperature asymmetry by palpation**	64.9	14.6
Skin color asymmetry**	84.2	34.1
Sweating asymmetry**	38.6	12.2
Asymmetric edema**	64.9	26.8
Trophic changes**	69.3	31.7
Motor changes**	78.1	39.0
Decreased active range of motion**	86.0	36.6

* $p < .05$.

** $p < .01$.

2.4. Measures

2.4.1. CRPS database checklist

In order to insure standardized assessment of signs and symptoms across study sites, a CRPS database checklist similar to that used in our past multi-site research work was employed [7,8,20]. This checklist presented a complete list of the signs and symptoms traditionally used to diagnose CRPS, as well as other signs/symptoms (e.g., trophic changes, motor abnormalities) reported to be associated with the disorder in previous literature but not incorporated in the IASP diagnostic criteria [27,32,36,38,39,42,40]. These latter signs and symptoms are included in the proposed Budapest diagnostic criteria [21]. Categorical measures (e.g., presence or absence) were used to assess all signs and symptoms because of the potential for decreased inter-rater reliability using interval rating scales [26,34]. Written standardized procedures and an instructional video to demonstrate the data collection procedures were provided with the checklist to maximize uniform assessment across sites. Investigators at all sites were highly proficient in English, thereby minimizing the potential impact of language issues. Copies of the database checklist and instructions are available from the authors.

2.4.2. Rand-36 Health Survey

The Rand-36 Health Survey consists of the same 36 items included in the SF-36 questionnaire frequently employed in medical outcomes research [43]. The Rand-36, however, employs a simpler unweighted scoring system for these items [Rand Health Sciences Program, 1992]. Validated versions of the questionnaire were available in German [10], Hebrew [30], and Dutch [1] for use with patients at non-English speaking data collection sites. The Rand-36 assesses eight health-related areas including pain, general health, and the impact of pain or disease in six specific domains of life function. Each scale falls in 0–100 range, with *lower* scores indicating greater pain or dysfunction.

2.4.3. CRPS Severity Score

To provide a continuous type quantitative index of the signs and symptoms of CRPS, the CRPS Severity Score (CSS) was created. For each patient, the history and physical examination as recorded on the CRPS Database Checklist was coded so that 1 = presence and 0 = absence for each of 17 diagnostic CRPS features (see Table 2). Scores for each of these CRPS features were then summed (unweighted) to create the overall CRPS Severity Score. Signs and symptoms were included as separate elements in this score given work showing that they do not necessarily correspond, due in some part to the subjectivity of historical symptoms and to the lability of CRPS signs which may result in relevant clinical features being missed on any 'spot' physical examination [20]. Self-reported CRPS symptoms included in the CSS were hyperpathia/allodynia (e.g., increased or prolonged pain to a mildly noxious stimuli, mechanical or thermal allodynia [pain to normally innocuous stimuli]), bilateral temperature asymmetry, skin color changes, edema,

sweating asymmetry, trophic/dystrophic changes (hair, nails, or skin), motor changes (e.g. weakness, tremor, dystonia), and decreased active range of motion. CRPS signs (present on examination at the time of data collection) that were included in the CSS were hyperpathia/hyperalgesia to pinprick, allodynia (to light touch [brush], cold, warm, vibration, or deep manual joint pressure), temperature asymmetry, skin color changes, edema, sweating asymmetry, trophic/dystrophic changes, motor changes, and decreased active range of motion. The resulting CSS ranged potentially from 0 to 17, with higher scores indicating greater CRPS severity. As an example, a patient self-reporting hypersensitivity to touch, edema, skin color changes, and weakness who displays only hyperalgesia and edema 'objectively' on examination would have a CRPS Severity Score of 6. In the combined patient groups the scores ranged from 2 to 17 (overall mean ± SD = 11.7 ± 3.84; range 7–17 if CRPS subjects only). Internal consistency reliability of the 17 items comprising the CRPS Severity Score was high (alpha = 0.88), indicating that combining all items into a single summary score was justified.

2.5. Statistical analysis

Analyses were conducted using PASW Statistics 18 for Windows (SPSS Inc., Chicago, IL). A number of approaches were used to validate and evaluate the potential utility of the CSS derived in this study. First, its association with known CRPS and non-CRPS diagnostic groups was examined. These analyses examined CRPS as diagnosed according to the current IASP diagnostic criteria [32] and according to the proposed Budapest clinical and research criteria for CRPS [19,21]. Differences in the CSS between CRPS and non-CRPS diagnostic groups were examined using *t*-tests as an index of discriminative validity. Strength of associations between continuous CSS and dichotomous diagnostic categories was also examined using the nonlinear correlation coefficient, Eta. A second analytic approach was to evaluate the associations (using Pearson correlation coefficients) between CSS and psychometric measures reflecting pain, emotional status, and function, as well as objective measures of temperature asymmetry, active range of motion, and sensory function (tQST). These analyses were designed to help demonstrate the concurrent validity of the CSS. It was hypothesized that higher CSS values, if a valid index of CRPS severity, would be associated with greater pain, distress, and dysfunction, more impaired range of motion, and more abnormal sensory function. Finally, the CSS as described above was derived in an archival prospective total knee arthroplasty dataset detailed fully in our previous work (see [21,22]), and its utility as a CRPS outcome measure was evaluated. Specifically, given our previous work showing in a prospective design that pre-surgical anxiety was a significant predictor of early post-surgical dichotomous CRPS diagnoses [22], we re-evaluated the ability of pre-surgical anxiety and depression and early post-surgical changes in these psychological factors to predict longer-term CRPS sign and symptom burden as reflected in continuous CSS values at 6 months ($n = 76$) and 12 months ($n = 65$) post-surgery. These analyses were designed in part to demonstrate the potential advantages of continuous over dichotomous measures of CRPS in the research context due to enhanced statistical power. These latter analyses used linear regression procedures.

3. Results

3.1. Associations between CRPS Severity Scores and dichotomous CRPS diagnoses

Table 1 compares CSS values between CRPS and non-CRPS diagnostic groups. The mean CSS in patients diagnosed with CRPS according to IASP criteria was nearly double that in patients with non-CRPS neuropathic pain diagnoses, a difference that was statistically significant [$t(153) = 13.10$, $p < .001$]. The continuous type CSS demonstrated large associations with dichotomous CRPS diagnostic categorizations. Using an IASP diagnosis of CRPS as the dependent measure, the magnitude of association with continuous CSS values was Eta = 0.69 (similar to other correlation coefficients, Eta ranges potentially from 0 to 1.00 to indicate increasing magnitude of association). Using the Budapest research diagnostic criteria as the dependent measure, the association with continuous CSS values was larger (Eta = 0.77). Finally, associations with the Budapest clinical criteria showed the strongest association (Eta = 0.88), indicating 77% shared variance between the dichotomous and continuous-type CRPS measures.

3.2. Concurrent associations between CRPS Severity Scores and outcome indices

Table 3 summarizes the pattern of zero-order correlations between CSS values and outcome indices obtained at the time of the history and physical examination from which data for deriving CSS values were obtained. As predicted, higher CSS values were associated on the Rand-36 measure with significantly higher pain intensity, worse physical and social functioning, greater role limitations due to physical and emotional problems, lower energy level, and lower emotional well-being (i.e., greater distress). These findings corroborated the hypothesis that the CSS is a valid index of CRPS severity, in terms of deleterious effects on psychosocial function across several key domains. CRPS Severity Scores were not associated significantly with the Rand-36 measure of general health, indicating that the CSS is not simply a surrogate measure of overall physical health.

Higher CSS values were associated with significantly greater quantitative temperature asymmetry (affected extremity colder) based on the IR thermometry measure. Results of thermal QST evaluation indicated that higher CSS values were also associated with significantly higher cold perception threshold ($p < .05$) and lower warmth perception threshold ($p < .01$), as well as significantly greater heat hyperalgesia ($p < .01$). Finally, higher CSS values were associated with significantly lower elbow/knee flexion

Table 3
Zero-order correlations between CRPS Severity Scores and concurrent outcome indices.

Outcome index	CRPS Severity Score correlation
Rand 36 – physical functioning	−0.19*
Rand 36 – role limitations – physical health	−0.25**
Rand 36 – role limitations – emotional problems	−0.22*
Rand 36 – energy/fatigue	−0.20*
Rand 36 – emotional well-being	−0.19*
Rand 36 – social functioning	−0.27**
Rand 36 – Pain	−0.38**
Rand 36 – general health	0.03
Affected side cold perception threshold (°C)	0.26*
Affected side warmth perception threshold (°C)	−0.31**
Affected side heat pain threshold (°C)	−0.23†
Temperature asymmetry by IR thermometry (°C)	−0.22*
Affected side AROM – elbow/knee flexion (°)	−0.23**
Affected side AROM – elbow/knee extension (°)	0.02
Affected side AROM – wrist/ankle flexion (°)	−0.11
Affected side AROM – wrist/ankle extension (°)	−0.20*

Note: Negative correlations for Rand 36 scores indicate that higher CRPS scores were associated with greater pain, distress, and dysfunction. The negative correlation for temperature asymmetry indicates that higher CRPS scores were associated with greater asymmetry in which the affected side was colder.

† $p < .10$.

* $p < .05$.

** $p < .01$.

($p < .01$) and wrist/ankle extension ($p < .05$) on goniometric testing, consistent with functional deficits noted on the Rand-36.

3.3. CRPS Severity Scores as a prospective CRPS outcome measure

In a prospective study, we found that pre-surgical anxiety but not depression significantly predicted dichotomous CRPS diagnoses at 4 weeks post-surgery in total knee arthroplasty patients [22]. Due in part to the low statistical power related to use of a dichotomous diagnostic measure and subject attrition over time in this previous study, there were no significant findings for psychological predictors at more extended follow-up [22]. This dataset was re-analyzed using continuous CSS values as described in the current study as an alternative CRPS outcome measure. Although baseline (pre-surgical) anxiety (State Trait Anxiety Inventory [37]) and depression (Beck Depression Inventory [3]) did not predict CRPS sign and symptom burden as reflected in CSS values at 6- or 12-month follow-up, early post-surgical changes in these measures (from pre-surgical baseline to 4 weeks post-surgery) were found to significantly predict CSS values at extended follow-up. Specifically, greater early post-surgical increases in depressive symptoms predicted higher CSS values at both 6-month follow-up [beta = 0.24; $t(73) = 2.10$, $p < .05$] and 12-month follow-up [beta = 0.26; $t(62) = 2.06$, $p < .05$]. Similarly, greater early post-surgical increases in anxiety predicted higher CSS values at 6-month follow-up [beta = 0.25; $t(73) = 2.16$, $p < .05$], although it failed to predict CSS status at 12-month follow-up ($p > .10$). It was notable that CSS values at 6-month follow-up were also positively associated with concurrent clinical pain intensity as reflected in McGill Pain Questionnaire-Short Form total scores ($r = 0.40$, $p < .001$) [31]. Similar associations at the 12-month follow-up were in the same direction but failed to achieve statistical significance ($r = 0.22$, $p < .11$). For direct comparison of continuous type versus dichotomous CRPS measures, logistic regression analyses modeled after those above were conducted using dichotomous IASP CRPS diagnoses as the outcome measure. These analyses did not reveal significant predictive effects for baseline or early post-surgical changes in anxiety or depression at long-term follow-up (p's > .10).

4. Discussion

Dichotomous (yes/no) CRPS diagnoses are necessary for clinical decision-making, but do not adequately capture differences in the severity or lability of the CRPS, the clinical presentation of which can be quite variable between patients or over time within a given patient [7,13]. Dichotomous diagnostic schemes also have inherently poor statistical power when used as outcome measures in research studies, a weakness particularly important in prospective studies of CRPS following injury, given the relative infrequency of the syndrome. A variety of continuous-type CRPS scores have been proposed, although few have been subjected to adequate empirical validation [4,12,14,15,18,28,29,42,44,45]. One continuous CRPS-related measure has been well-validated (ISS; [33,35]). However, because the ISS was intended to index CRPS-related impairment, it does not capture the full spectrum of CRPS-related signs and symptoms incorporated in accepted or proposed CRPS diagnostic criteria [23,32]. The current study sought to pilot the development and validation of a simple continuous CRPS Severity Score that does not require specialized testing, training or equipment, and which corresponds well with the current and proposed dichotomous diagnostic criteria. This continuous-type CRPS Severity Score (CSS) may be useful to communicate CRPS severity efficiently between clinicians and monitor intra-patient status over time, and have substantial statistical advantages over dichotomous CRPS diagnoses as an outcome measure in CRPS research studies.

The 17 signs and symptoms comprising this CSS (directly derived from the proposed "Budapest Criteria" [19,21,23]) were found to have high internal consistency reliability, supporting their use as components of a single summary score. The validity of the CSS was demonstrated in several ways. As designed, it discriminated well between CRPS and non-CRPS diagnostic groups. Moreover, it demonstrated a strong association with diagnoses determined based on current IASP diagnostic criteria for CRPS [32], and an even stronger association with the revised Budapest diagnostic criteria that have been proposed, especially the "clinical" criteria [19,21,23]. The CSS demonstrated a pattern of significant positive associations with pain intensity, emotional distress, and impaired function as would be expected if it were a sensitive index of CRPS severity. In addition, higher scores were associated with reduced active range of motion and greater bilateral temperature asymmetry as was predicted. The results above support the discriminative and concurrent validity of the CSS.

An existing prospective archival dataset was also used to test the sensitivity of the CSS as an outcome measure reflecting CRPS. We had previously shown that pre-surgical anxiety (but not depression) was a significant predictor of dichotomous CRPS diagnoses at 4 weeks following total knee arthroplasty, but not at longer-term follow-up [22]. Results of our re-analysis of this archival dataset revealed that greater increases in anxiety and depression from pre-surgical baseline to 4 weeks post-surgery were a significant predictor of CSS values at 6-month (anxiety and depression) and 12-month follow-up (depression). In contrast, neither affective measures significantly predicted dichotomous IASP CRPS diagnoses at either follow-up. This latter finding highlights the statistical advantages of a continuous-type CRPS index over traditional dichotomous diagnostic outcomes. Given the known positive associations between psychological distress, catecholamine release, and sympathetic nervous system (SNS) activity, and the role of these latter two factors in CRPS pathophysiology, the current findings are consistent with the hypothesized impact of psychophysiological interactions in CRPS (see [5] for a review; [24]). Despite these predictive effects, the current study results were not consistent with previous reports suggesting that CRPS patients are more emotionally distressed than non-CRPS chronic pain patients [9,11,17,16,25]. The current results provide further support for arguments that findings of greater distress in CRPS patients, when noted, may be biased by sample selection effects in clinics receiving large numbers of referrals with severe CRPS [6].

Taken as a whole, the findings of this study support the validity of the proposed CSS measure. The potential utility of this measure can be seen in the analogous situation in the field of psychiatry. For clinical diagnostic decision-making purposes, dichotomous major depression diagnoses based on criteria described in the Diagnostic and Statistical Manual of Mental Disorders are used [2]. However, for most research purposes, continuous type psychometric indices of depressive symptom severity (such as the Beck Depression Inventory [3]) are used due to their ability to capture a range of individual differences in symptom severity and their statistical advantages as outcome measures. The CSS described in this study may be useful for similar reasons. It is not intended to replace other validated measures that assess general aspects of CRPS, such as pain scales or specific measures such as ISS which focuses on CRPS-related impairment [33,35], but may be useful for studies requiring a continuous measure closely related to CRPS diagnostic signs and symptoms.

Several weaknesses of the current study should be noted. Although standardized assessment procedures were used and all investigators were proficient in English, the variety of study sites and issues due to psychometric and clinical evaluations being conducted in multiple languages could have impacted the study results in predictable and unknown ways. Study investigators were

all experienced pain physicians, but independent monitoring was not available to document the reliability of clinical evaluations across study sites. These issues were mitigated somewhat, by design, with written and video instruction. However, it is likely that any unreliability in assessment would have increased error in the dataset and would have reduced rather than exaggerated the validity of the CSS. Thus, the current results may reflect the lower limit of the validity of the CSS. Another issue is that tQST data were only available for a subset of the study patients due to equipment availability issues. Although not the primary focus of this study, it would have been helpful to have more complete information on this measure for the current study as heat hyperalgesia would likely have reached statistical significance with approximately 10 additional patients. Finally, the association between the CSS and dichotomous CRPS diagnoses was higher for the proposed Budapest revised diagnostic criteria (clinical and research versions) than for the currently used IASP criteria. This was likely due in part to the fact that the Budapest criteria include CRPS-related features, such as motor and trophic changes [23], which are included as components of the CSS but are not part of current IASP diagnostic criteria [32]. Nonetheless, the CSS did demonstrate a large association with IASP diagnoses and did discriminate well between CRPS and non-CRPS patients as diagnosed using these IASP criteria. The responsiveness of the CSS to change and as an outcome measure will need to be extensively explored and validated in future studies, however we do not envision that CSS will replace pain scales as primary outcomes in the syndrome. It may after proper validation add a valuable and sensitive measure to capture the variety of related (or seemingly unrelated) signs and symptoms in CRPS that change over time and with intervention.

In summary, the CRPS Severity Score described in this study shows high internal consistency, suggesting that it represents a unitary construct as would be expected if it reflects the syndrome. Scores on this measure are associated with external criteria including pain severity, distress, functional impairment, and objective sensory and other changes in a manner consistent with the scores being a valid reflection of CRPS severity. CSS values also appeared to be sensitive to hypothesized associations between increased post-surgical distress and later elevations in CRPS sign and symptom burden in a post hoc analysis of a prior data set. This clinically accessible CSS complements the extant dichotomous criteria, and better captures the intra- and inter-individual fluctuations in CRPS signs and symptoms. Given that the CSS corresponds well with current and proposed dichotomous diagnostic criteria for the disorder, this measure may be useful as a continuous type outcome measure reflecting the presence and severity of CRPS in future studies. Its sensitivity to treatment-related changes and its potential as a predictor of responsiveness to various treatment strategies remain to be evaluated.

Conflict of interest

None of the authors have a conflict of interest as to this work.

Acknowledgements

This project was supported by a grant from the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA), with matching unrestricted funding from Celgene Pharmaceuticals. The authors gratefully acknowledge the support of Jim Broatch of the RSDSA and the assistance of Heather Cairl and Emily Close MSW, LSW.

References

[1] Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055–68.
[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychiatric Association; 1994.
[3] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
[4] Blumberg H. A new clinical approach for diagnosing reflex sympathetic dystrophy. In: Bond MR, Charlton JE, Woolf CJ, editors. Proceedings of the VIth world congress on pain. New York: Elsevier; 1991. p. 399–407.
[5] Bruehl S. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology 2010;113:713–25.
[6] Bruehl S, Chung OY, Burns JW. Differential effects of expressive anger regulation on chronic pain intensity in CRPS and non-CRPS limb pain patients. Pain 2003;104:647–54.
[7] Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain 2002;95:119–24.
[8] Bruehl S, Harden RN, Galer BS, Saltz SL, Bertram M, Backonja MD, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. External validation of IASP diagnositic criteria for complex regional pain syndrome and proposed research diagnostic criteria. Pain 1999;81:147–54.
[9] Bruehl S, Husfeldt B, Lubenow T, Nath H, Ivankovich AD. Psychological differences between reflex sympathetic dystrophy and non-RSD chronic pain patients. Pain 1996;67:107–14.
[10] Bullinger M. German translation and psychometric testing of the SF-36 Health Survey: preliminary results from the IQOLA Project. International Quality of Life Assessment. Soc Sci Med 1995;41:1359–66.
[11] Ciccone DS, Bandilla EB, Wu W. Psychological dysfunction in patients with reflex sympathetic dystrophy. Pain 1997;71:323–33.
[12] Davidoff G, Morey K, Amann M, Stamps J. Pain measurement in reflex sympathetic dystrophy syndrome. Pain 1988;32:27–34.
[13] de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. Pain 2007;129:12–20.
[14] Fukui S, Morioka Y, Hayashi T. Objective evaluation of reflex sympathetic dystrophy of the limbs by means of a scoring system and three-phase bone scintigraphy. Pain Clinic 1994;7:117–24.
[15] Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. Clin J Pain 1998;14:48–54.
[16] Geertzen JH, de Bruijn-Kofman AT, de Bruijn HP, van de Wiel HB, Dijkstra PU. Stressful life events and psychological dysfunction in Complex Regional Pain Syndrome type I. Clin J Pain 1998;14:143–7.
[17] Geertzen JHB, de Bruijn H, de Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: early treatment and psychological aspects. Arch Phys Med Rehabil 1994;75:442–6.
[18] Gibbons JJ, Wilson PR. RSD Score: criteria for the diagnosis of reflex sympathetic dystrophy and causalgia. Clin J Pain 1992;8:260–3.
[19] Harden R, Bruehl S. Diagnostic criteria: the statistical derivation of the four criterion factors. In: Wilson PR, Stanton-Hicks M, Harden RN, editors. CRPS: current diagnosis and therapy. Seattle: IASP Press; 2005. p. 45–58.
[20] Harden RN, Bruehl S, Galer B, Saltz SL, Bertram M, Backonja M, Gayles R, Rudin N, Bughra M, Stanton-Hicks M. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain 1999;83:211–9.
[21] Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain 2010;150:268–74.
[22] Harden RN, Bruehl S, Stanos S, Brander V, Chung OY, Saltz S, Adams A, Stulberg SD. Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. Pain 2003;106:393–400.
[23] Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8:326–31.
[24] Harden RN, Rudin NJ, Bruehl S, Kee W, Parikh DK, Kooch J, Duc T, Gracely RH. Increased systemic catecholamines in complex regional pain syndrome and relationship to psychological factors: a pilot study. Anesth Analg 2004;99:1478–85.
[25] Hardy MA, Merritt WH. Psychological evaluation and pain assessment in patients with reflex sympathetic dystrophy. J Hand Therapy 1988:155–64.
[26] Janig W, Blumberg H, Boas RA, Campbell JN. The reflex sympathetic dystrophy syndrome: consensus statement and general recommendations for diagnosis and clinical research. In: Bond MR, Charlton JE, Woolf CJ, editors. Proceedings of the VIth world congress on pain. New York: Elsevier; 1991. p. 373–6.
[27] Janig W, Stanton-Hicks M. Reflex sympathetic dystrophy: a reappraisal. Seattle: IASP Press; 1996.
[28] Kalita J, Vajpayee A, Misra UK. Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. Qjm 2006;99:89–95.
[29] Kozin F, Ryan LM, Carerra GF, Soin JS, Wortmann RL. The reflex sympathetic dystrophy syndrome III: scintigraphic studies, further evidence for the therapeutic efficacy of systemic corticosteroids, and proposed diagnostic criteria. Am J Med 1981;70:23–30.
[30] Lewin-Epstein N, Sagiv-Schifter T, Shabtai EL, Shmueli A. Validation of the 36-item short-form Health Survey (Hebrew version) in the adult population of Israel. Med Care 1998;36:1361–70.

[31] Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30: 191–7.
[32] Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994.
[33] Oerlemans HM, Goris RJ, Oostendorp RA. Impairment level sumscore in reflex sympathetic dystrophy of one upper extremity. Arch Phys Med Rehabil 1998;79:979–90.
[34] Perez RS, Burm PE, Zuurmond WW, Giezeman MJ, van Dasselaar NT, Vranken J, de Lange JJ. Interrater reliability of diagnosing complex regional pain syndrome type I. Acta Anaesthesiol Scand 2002;46:447–50.
[35] Perez RS, Oerlemans HM, Zuurmond WW, De Lange JJ. Impairment level sumscore for lower extremity complex regional pain syndrome type I. Disabil Rehabil 2003;25:984–91.
[36] Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy: a review. Arch Neruol 1987;44:555–61.
[37] Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory. Palo Alto: Consulting Psychologists Press; 1970.
[38] Stanton-Hicks M. Pain and the sympathetic nervous system. Boston: Kluwer; 1990.
[39] Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N, Kotzenburg M, Raj P, Wilder R. Consensus report: complex regional pain syndromes: guidelines for therapy. The Clinical Journal of Pain 1998;14:155–66.
[40] Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995;63:127–33.
[41] Vaneker M, Wilder-Smith OH, Schrombges P, Oerlemans HM. Impairments as measured by ISS do not greatly change between one and eight years after CRPS 1 diagnosis. Eur J Pain 2006;10:639–44.
[42] Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–6.
[43] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
[44] Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, de Lange JJ, van loenen AC. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. Acta Anaesthesiol Scand 1996;40:364–7.
[45] Zyluk A. A new clinical severity scoring system for reflex sympathetic dystrophy of the upper limb. J Hand Surg Br 2003;28:238–41.