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Complex Regional Pain Syndrome-Like Changes Following Surgery and Immobilization

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Abstract

The study of Complex Regional Pain Syndrome (CRPS) in humans is complicated by inhomogeneities in available study cohorts. We hoped to characterize early CRPS-like features in patients undergoing hand surgery. Forty-three patients were recruited from a hand surgery clinic that had elective surgeries followed by cast immobilization. On the day of cast removal, patients were assessed for vasomotor, sudomotor, and trophic changes, edema and pain sensitization using quantitative sensory testing. Pain intensity was assessed at the time of cast removal and after one additional month as was the nature of the pain using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS). Skin biopsies were harvested for the analysis of expression of inflammatory mediators. We identified vascular and trophic changes in the surgical hands of most patients. Increased sensitivity to punctate, pressure and cold stimuli were observed commonly as well. Moreover, levels of IL-6, TNF-alpha and the mast cell marker tryptase were elevated in the skin of hands ipsilateral to surgery. Moderate to severe pain persisted in the surgical hands for up to one month after cast removal. Exploratory analyses suggested interrelationships between the physical, QST and gene expression changes and pain related outcomes.

Keywords

Complex Regional Pain Syndrome; Pain; Cytokine; Nerve Growth Factor; Quantitative Sensory Testing

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Disclosures

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Introduction

Complex regional pain syndrome (CRPS) is a painful, disabling and often chronic condition principally affecting the extremities. While acute CRPS sometimes improves spontaneously or with aggressive physical therapy, CRPS present for a period of one year or greater seldom spontaneously resolves³³, and worsens in many patients from years 1 to 8 after onset⁴². Trauma to the distal extremities is a frequent cause of CRPS⁴³. For example, the estimated incidence of CRPS after extremity surgery depends to a degree on the specific procedure, but by all accounts the problem is common. The rate of CRPS is 8.3% after carpal tunnel surgery⁹ and greater than 30% after distal radius fracture in some series². Immobilization in the setting of trauma is a widely recognized factor predisposing patients to the development of CRPS with 47% of all CRPS sufferers in one study having a history of medically imposed limb immobilization¹. Moreover, the nature of the syndrome is dynamic. The affected limb often progresses through an acute phase in which the limb is sensitive, swollen and displays an elevated temperature to a chronic phase in which the inflamed appearance has resolved, but the pain and disability remain⁶.

The heterogeneous nature of CRPS both in terms of etiology and duration in available study populations has made the study of the syndrome and its treatments challenging. This has led to the assembly of clinical research networks, the identification of new animal models, and the development of new approaches to the use of human subjects. One innovative approach to assembling more suitable study populations has been to model CRPS in humans without inducing the formal clinical syndrome. The application of a thumb spica cast to the upper extremity of healthy volunteers for four weeks caused warmth and sensitization to both cold stimuli and skin fold pressure in the casted limb reminiscent of acute CRPS³⁹, as well as changes in capsaicin-induced neurogenic inflammation⁴⁰. In neither published report using the cast immobilization technique did a subject develop clinical CRPS. While clearly a useful model, this volunteer procedure requires a healthy individual to wear a cast for four weeks, and, unlike most cases of CRPS, does not involve trauma to the affected limb.

We sought to identify CRPS-like changes in the limbs of patients undergoing extremity surgery followed by immobilization. We hypothesized that patients undergoing hand surgery, a population at high risk for developing CRPS, would in fact display vascular, trophic and nociceptive changes at the time of cast removal similar to those with acute CRPS, and that some patients would exhibit persistent changes. Furthermore, we hypothesized that postsurgical patients would express elevated cutaneous levels of IL-1 β , IL-6, TNF α , NGF and tryptase, based on previous studies looking at elevated inflammatory mediator expression in CRPS patient skin blister fluid and skin biopsies^{17, 20, 28}, and skin from a rat fracture/cast immobilization model of CRPS^{22, 30}. The advantages of using such a population to study specific features of acute CRPS include, 1) the lack of requirement for an inconvenient or potentially harmful intervention to generate the model, 2) the homogeneity of the circumstances leading to the pathophysiological features under study, 3) the potential opportunity to study the progression or resolution of changes in the surgical limb, and 4) the potential ability to study interventions applied either during the early post-surgical period or immediately following cast removal.

Methods

Participants

The study protocol was first approved by the local Institutional Review Board. Forty-three participants were recruited from the weekly Hand and Upper Extremity clinic at the VA Hospital in Palo Alto CA. Five women and thirty-eight men were enrolled after giving written informed consent. The principal inclusion criteria were: 1) ages 18 – 75, and 2)

status post hand/wrist surgery and cast immobilization of 12 days and available for testing within 36 hours of cast removal. The principal exclusion criteria were: 1) ongoing infection in either hand, 2) anticoagulation with agents other than aspirin, 3) neurological deficits potentially interfering with pain testing, neuropathic pain or a history of complex regional pain syndrome, and 4) history of inflammatory skin diseases (psoriasis, dermatitis, etc.).

Study Setting

Participants were met in the Hand and Upper Extremity clinic after their cast removal clinic appointment and were escorted to a private clinic space for enrollment and testing. The room was uniformly lit and temperature controlled to 21°C. A single research coordinator (AP) interacted with the study participants, performed all testing procedures and collected all subjective data. Participants were seated at a table across from the research coordinator for all testing. For participants who elected to have a skin biopsy, procedure was performed immediately after the conclusion of sensory testing in the same room. Follow up phone calls were arranged for 28 days following cast removal.

Surgical and medical information

After providing written informed consent, the date, type, and location of surgery were collected in addition to any complications since the surgery. Hand dominance was recorded. The patients were queried as to pre and postoperative pain medication use and duration of use, and these results were checked against the electronic medical record. The medical record was also reviewed for ongoing use of angiotensin converting enzyme inhibitors (ACE inhibitors). Histories of psychological disease were recorded.

Pain intensity and characteristics

The nociceptive versus neuropathic nature of the patient's pain was assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) ⁴. For assessment upon phone follow-up, we used the short form of the LANSS (S-LANSS) which has similar sensitivity and discriminatory properties to the parent scale, and a specificity of approximately 80%⁵.

Pain intensity was assessed on the day of cast removal and one month later in both the surgical and contralateral hands.

Average pain - At the time of cast removal and one month later average pain from the preceding 7 days was assessed using a verbally administered 0–10 numerical rating scale (NRS). This scale is both sensitive and has relatively robust statistical properties ⁴⁴.

Dynamic pain - At the time of cast removal and one month later pain experienced immediately after opening/closing the hand to make a fist 4 times excluding movement of any digits involved in surgery was assessed using the 0–10 NRS scale.

Physical observations

Both distal forearms and hands were visually assessed for erythema, difference in hair growth, difference in nail texture and sweating. All observational and pain testing measurements were conducted first on the contra lateral hand followed by the surgical hand.

Temperature - The temperature at 3 locations (center of the dorsum, pulp of digit 3, and the center of the palm) was recorded with an infrared thermometer (Exergen DT-1000 Infrared Dermal Thermometer, Exergen Corp, Watertown MA USA).

Edema - Hands were assessed for edema using a flexible measuring tape and the figure-of-eight measurement technique to quantify circumference. This method has sensitivity and inter-tester reliability similar to that of standard volumetry²¹.

Mechanical allodynia - To assess allodynia, a cotton ball was lightly brushed three times along the dorsum of the contra lateral hand as described by Bennett⁴. Participants were asked if this was a normal sensation. The cotton ball was then lightly brushed three times along the dorsum of the operative hand at least 4cm distant from the surgical incisions and asked whether this was a normal sensation or unpleasant or unusual in any way, e.g. by evoking tingling or nausea. Unpleasant sensation experienced in the surgical hand was recorded as allodynia.

Quantitative sensory testing

The QST modalities tested reflected some of those most robustly changed in reports involving large CRPS patient cohorts and in a previously reported human model of CRPS involving cast immobilization^{14, 39}.

Punctate mechanical pain - Punctate mechanical pain thresholds were measured on the dorsum of the hand at least 4 cm distant from the operative location. These measurements were accomplished using an electronic von Frey anesthesiometer (Electronic von Frey Anesthesiometer model 2390, IITC INC. Life Science, Woodland Hills, CA USA) fitted with a supplied rigid tip. During testing, the palm of the hand rested on a solid surface. The von Frey anesthesiometer was pressed perpendicularly against the skin of the dorsum, and pressure was applied at a constant rate until pain was reported. The thresholds were determined by averaging three individual measurements on each hand assessed in matched locations.

Joint pressure pain – Joint pressure pain thresholds were tested in the MCP joints of digits 2–4 of the contralateral and surgical/immobilized hand. This was performed with a pressure algometer (Commander, JTECH Medical, Salt Lake City, Utah, USA). During testing, the palm of the hand rested on a solid surface. The rod with a curved fingertip attachment was pressed perpendicularly against the skin above the MCP joints, and pressure applied at a constant rate of 2N/s until pain was reported. Three measurements per joint were made and all measurements averaged for each hand.

Interdigital skin fold pressure pain – The pressure algometer described above fitted with a 1cm² rubber-tipped rod was used to assess pressure pain on a dermal fold between digits. The skin between digits 2 and 3 was used as the larger first interdigital skin fold was often within a few centimeters of the surgical area. Participants' palms rested against a solid surface with fingers slightly abducted. The pressure algometer was pressed perpendicularly against the skin between the digits at a constant rate (2N/s) until pain was reported. Three measurements per hand were made and measurements averaged for each hand.

Cold Hyperalgesia – Cold pain thresholds (CPT) was assessed using a thermal sensory analyzer and a 32×32mm probe (Medoc TSA 2001 thermal sensory analyzer probe, Medoc Instruments Ramat, Yishai Israel). During testing the palm of the hand being tested rested on a solid surface while the research coordinator held the probe against the dorsum. The participants' contralateral hand operated a mouse to stop cooling when cold pain was first sensed. For determination of CPT, five successive stimulations starting from a baseline temperature of 32°C decreasing by 1 degree per second were averaged for each hand.

Skin Biopsy

Participants were presented with the option of participating in the skin biopsy portion of the study. If the subject elected to undergo biopsies, the procedures were performed directly after completion of other testing. One 3mm punch biopsy was collected from the dorsum of each hand with the surgical hand biopsy at least 4cm from any incision using a commercially available kit (Acuderm Inc. Ft Lauderdale, FL). The biopsy sites were cleaned with alcohol and a small amount of 1% lidocaine was injected via a 30ga needle. A 3mm disposable punch biopsy instrument was used. Inward pressure was placed on the instrument while it was rotated. When subcutaneous fat was reached, the instrument was removed. The circular biopsy was elevated and the base freed using an iris scissor. Pressure was applied to assure hemostasis. Topical antibiotic was applied and a small bandage placed. No sutures were necessary.

Tissue Processing and Quantification of Gene Expression

Immediately after harvest, the skin biopsies were stored in *RNAlater* stabilization reagent solution (Qiagen, Valencia, CA) for 1 to 4 months at -80°C . Total RNA from the samples was then extracted using RNeasy Micro Kit (Qiagen, Valencia, CA) and quantified using a NanoDrop ND-1000 UV-Vis spectrophotometer (NanoDrop Technologies, Wilmington, DE). At that point cDNA (20 μL final volume) was synthesized from 500 ng RNA using a QuantiTect Reverse Transcription Kit (Qiagen, Valencia, CA). Real-time polymerase chain reactions (PCRs) were performed with fluorescent probes using either QuantiFast duplex PCR detection kits (Qiagen, Valencia, CA) or QuantiTect SYBR Green-based real-time PCR Kit (Qiagen, Valencia, CA) in ABI PRISM 7900HT Sequence Detection System (Life Technologies, Grand Island, NY) according to the manufacturer's instructions. TNF- α , TPSAB-1 (tryptase), NGF, IL-1 β , and IL-6 transcripts were individually subjected to duplex analyses with GAPDH using two different fluorescent dyes, while IL-1 β and GAPDH were detected by separate reactions with singleplex expression analyses for each dye. To validate the primer sets used, we performed dissociation curves to document single product formation. The data were analyzed by the comparative CT (cycle threshold) method, as described in the manufacturer's manual. All assays were performed in triplicate for each sample.

Data Handling and Statistical Analysis

The patient database was kept on password protected equipment in a locked room, and data files on portable devices were encrypted. The data security plan was approved by the Institutional Review Board. Statistical analysis of data and the preparation of data plots were performed using Prism 5 software (Graphpad Software, LaJolla, CA). Comparisons of mean values for parametric data were conducted using t-testing. Correlational analysis was conducted using the Pearson approach for parametric data and the Spearman approach for non-parametric data, e.g. LANSS scores. Data are presented as means $\pm$ standard deviation or as box and whisker plots. The minimum level of significance was $p < 0.05$.

Results

Demographics and treatment characteristics of the study cohort

Our study cohort consisted of 43 patients attending a hand surgery clinic at a single medical center. Most patients were middle aged, and strong bias existed towards male participants characteristic of a Veteran's Affairs medical center (Table 1). Approximately one third of the patient cohort had a psychiatric diagnosis of depression or anxiety at the time of surgery. The most common procedures performed on the patients included carpometacarpal arthroplasty for degenerative disease followed by stabilization of fractures involving the

hand, bone fusion procedures and soft tissue operations such as tendon transfers. The period of immobilization averaged between 4 and 5 weeks.

Vascular, sudomotor and trophic changes in the surgical limbs

On the day of cast removal the surgical and contralateral limbs were inspected. Table 2 and Figure 1 provide data demonstrating that differences between the limbs for each of these characteristics were found in many but not all patients. Erythema and trophic changes of the nails were relatively common though abnormal sweating was seldom evident based on physical examination. Both edema, defined as a measured circumference at least 0.5cm greater than that of the contralateral hand, and elevated skin temperature, defined as a temperature $>1^{\circ}\text{C}$ above the contralateral hand, were common as well. Most patients had multiple observable changes in the surgical limbs.

Spontaneous and dynamically evoked pain

Patients were asked to rate the average pain in their surgical extremities over the preceding week using a 0–10 NRS scale. These assessments were made at the time of cast removal and one month following cast removal. For the week preceding cast removal the mean average pain intensity was 3.9 and one month later was 3.0 ($p=0.08$, paired t-test). Even one month from the time of cast removal, 42% (18/43) of patients reported moderate to severe pain in the surgical hand (Figure 2A). Likewise mean dynamic pain at the time of cast removal was 3.5 and one month later was 1.8 ($p<0.001$, paired t-test). For this measure 23% (10/43) continued to experience moderate to severe pain (Figure 2B).

The quality of the pain in the operative hands at the time of cast removal and one month later

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) helped differentiate the post-operative pain as primarily neuropathic versus nociceptive. This scale has been used to detect neuropathic contributions to pain after surgery and other forms of trauma^{26, 34}. Use of this instrument indicated that 10/43 patients (23%) experienced pain having a neuropathic versus nociceptive character on the day of cast removal, while one month later 15/43 (35%) met LANSS criteria for pain of neuropathic character. Pain intensity for those experiencing pain of nociceptive versus neuropathic character was similar at the time of cast removal (3.6 vs. 4.6, $p>0.05$), but significantly higher for those experiencing neuropathic symptoms one month after cast removal (2.1 vs. 4.6, $P<0.001$). Of the 15 patients experiencing pain of neuropathic character one month after cast removal, only 6 had positive LANSS scores at the time of cast removal. Thus in the month following cast removal 9 patients experienced the emergence of pain having neuropathic characteristics, a trend similar to that previously reported for postsurgical patients³⁴.

Quantitative sensory testing

Figure 3 presents data demonstrating robust decreases in punctate pain thresholds in hands ipsilateral to surgery versus the paired contralateral hands. The average decrease in punctate pain threshold was 36%. Significant reductions in pressure pain thresholds were also found when the stimulus was applied either to the interdigital skin folds (24%) or metacarpophalangeal joints (20%). Finally, an increase in the cold pain threshold was observed (6.1°C in surgical hands vs. 4.3°C in the contralateral hands). Thus multiple testing modalities demonstrated a relative pain sensitization of the hand on the operative side.

Biochemical markers in skin tissue

Skin biopsies were harvested from both the surgical and contralateral hands at the time of cast removal from 19 patients willing to undergo the biopsy procedure. Processing this tissue for analysis at the mRNA level was conducted for the cytokines IL-1 β , IL-6, TNF α , the neurotrophin NGF and the mast cell marker enzyme tryptase. Analysis revealed a statistical increase in IL-6, TNF α and tryptase expression in the surgical hand skin versus the contralateral hand (Figure 4).

Exploratory analyses

Our studies were designed primarily to describe physiological and sensory changes occurring in the hands of patients after surgery and immobilization. Our dataset did support, however, exploratory analyses of possible links between patient characteristics, biochemical alterations and sensory changes and our selected pain outcomes.

We first examined correlations between QST parameters and pain outcomes. Table 1 supplemental provides data demonstrating correlations between QST measurements and pain outcomes such as dynamic pain, NRS average pain intensity and LANSS score at the time of cast removal and one month later. Potential correlations were observed between lower punctate pain thresholds in the hands of patients ipsilateral to surgery and both higher dynamic pain ratings as well as higher LANSS scores at the time of cast removal. Likewise, experiencing cold pain at a higher temperature was associated with the same two pain-related outcomes.

Demographic factors may influence susceptibility to CRPS. Because of the nature of the sample, only 5 female patients, we were not able to examine the effect of sex on the outcome parameters. Correlations between age and QST measurements were, however, very suggestive. Inverse (age protective) correlations were observed between age and punctate pain ($r^2=-0.30$, $p<0.05$) as well as joint pressure ($r^2=-0.31$, $p<0.05$) and cold ($r^2=0.37$, $p<0.05$) contralateral-ipsilateral differences at the time of cast removal. Age was poorly correlated with the pain outcomes, though advancing age had a marginal correlation ($r^2=-0.28$, $p=0.07$) with lower LANSS scores at the time of cast removal.

We also examined the relationship between skin levels of the measured inflammatory mediators and pain outcomes. For these analyses we attempted to correlate the ratio of mediator expression in the skin of surgical vs. contralateral hands with pain outcomes at the time of cast removal and one month later. These revealed correlations between the skin NGF expression ratio and both dynamic ($r^2=0.55$, $p<0.05$) and NRS ($r^2=0.55$, $p<0.05$) pain at one month after cast removal along with the skin IL-1 β ratio and LANSS at one month after cast removal ($r^2=0.52$, $p<0.01$).

Discussion

Complex Regional Pain Syndrome is a problematic condition. The condition has its peak incidence in middle age, particularly in women^{11, 31}, though children can be affected as well³⁷. Disability is very common in the setting of CRPS, and can be progressive^{36, 42}. The condition itself is enigmatic in its etiology and frequently changes in its clinical characteristics over time⁸. Though significant progress has been made using newer rodent CRPS models^{15, 27} and by applying carefully designed experimental paradigms to human volunteers in pain laboratories³⁹, translating these findings into clinical populations has been difficult due to the limited availability of subjects and the heterogeneity of the assembled cohorts in terms of etiological factors, duration of the symptoms and histories of treatment. In the present set of studies we characterized the limbs of patients who underwent hand and wrist surgery followed by several weeks of immobilization, a set of factors known

to predispose patients to develop CRPS. Many of the post-surgical patients exhibited CRPS-like changes immediately after cast removal in terms of surgical extremity warmth, edema, pain sensitization and the production of inflammatory mediators in the skin (Figures 1, 2, Table 2). These postsurgical patients may be useful in CRPS research as well as in understanding the broader issue of the transition from acute to chronic postoperative pain.

Pain-related changes occurring after distal upper extremity surgery and cast immobilization were assessed using several approaches. At the time of cast removal most patients had at least mild movement induced pain in the hand, and experienced at least mild pain over the preceding week (Figure 2). This pain decreased over the first month for many patients, but it is remarkable that 42% of patients (18/43) persisted in showing moderate to severe levels of pain (4/10 or greater) 4 weeks after cast removal, or about 8–9 weeks on average from the time of surgery. Though the LANSS questionnaire has important limits in terms of sensitivity and specificity, scores indicated that many patients experienced pain having neuropathic characteristics more than one month after cast removal. Nociceptive-type pain was less severe on average. Evidence of neuropathia was associated with more severe pain in a recent population-based study of persistent postoperative pain¹⁸. Importantly, 9 patients appeared to convert from a primarily nociceptive to a primarily neuropathic-type pain by one month after cast removal. This observation is similar to the increasing neuropathic symptoms observed in patients in the months following thoracotomy³⁴. The Budapest CRPS diagnostic criteria include the evaluation of patients for signs related to sensory, vasomotor, sudomotor/edema and motor/trophic changes¹⁶. All of our patients showed sensory changes in at least one of the QST tests, and almost all patients had one or more additional signs consistent with the Budapest CRPS criteria (Table 2). Importantly, our study was not designed to determine the incidence of CRPS itself after surgery, particularly at the one month post-cast removal time point. However, the location of pain in non-surgically involved tissues, the neuropathic character of the symptoms, and the observation of trophic and vascular changes in the limbs of many of the patients suggest pain occurring after cast removal in surgical limbs may arise from causes other than those involved in the primary healing process.

The QST testing performed on areas of the hand 4cm removed from the surgical site demonstrated pain sensitization in the limbs ipsilateral to surgery in comparison to the contralateral limbs (Figure 3). The testing modalities were selected based on the results of testing performed on humans with CRPS in previous studies^{13, 14, 35}. While no single testing modality shows profound changes in every CRPS patient, mechanical allodynia, cold hyperalgesia and pressure hyperalgesia are found in approximately 30–70% of CRPS patients, and most patients show a combination of modes of sensitization¹⁴. Our measurements demonstrating lateralized decreases in punctate mechanical pain thresholds were clear, and demonstrated a 36% decrease on average. Likewise our pressure pain measurements in joints and inter-digit skin folds showed thresholds reduced 24% and 20% respectively in the ipsilateral versus contralateral hands with most patients showing sensitization in the surgical hand for both these traits. Interestingly, pressure pain threshold was the QST parameter most frequently found to be changed in patients with CRPS1 in a review of the results of 298 patients with this diagnosis¹⁴.

We extended our observations to the biochemical level. Several studies have found that inflammatory mediators, including IL-6 and TNF α are elevated in the venous blood, skin blister, and skin of CRPS-affected limbs^{17, 20, 28, 32}. These cytokines have been linked to pain or pain sensitization in numerous human and animal studies. We found IL-6 and TNF α expression was significantly increased in the skin of the surgical compared to contralateral limbs, though the range of the increases for these mediators was broad (Figure 4). It was concluded that keratinocytes are the major, but not necessarily only, source of these

mediators in a rat tibia fracture/cast immobilization CRPS model²². Prior studies using this rat model of CRPS also demonstrated elevated levels of IL-1 β and NGF in the skin after 4 weeks cast immobilization^{24, 30}. While we did observe trends towards increases of these mediators, they were not significantly changed. Lastly, prior skin studies in CRPS patients and in the rat fracture/cast CRPS model indicate that mast cell derived tryptase is elevated in the injured extremity^{17, 23}. Mast cells may act through the liberation of any of a number of mediators in addition to tryptase itself to support pain sensitization including histamine, PGE2, leukotrienes and TNF α ^{25, 41}. The skin biopsies collected after removal of the casts from the surgical patients showed an increase in tryptase expression. Collectively, these results suggest that the biochemical changes in the skin of patients after hand/wrist surgery and immobilization are similar to those observed in CRPS patients.

While this study was designed primarily to examine the physiological, sensory and biochemical changes in the limbs of patients undergoing surgery and extended immobilization, we did perform exploratory analyses attempting to identify interrelationships between the traits and factors we assessed. Limitations in study power restrict our ability to rely on the negative results, and the multiple comparisons intrinsic to performing correlative analysis on large data matrices suggest caution in interpreting positive findings. However, our findings do suggest that QST measures such as punctuate and cold pain thresholds may be related to pain, particularly the neuropathic contributions to that pain experienced in the immediate post-immobilization period. Potentially highly significant for mechanistic studies, the changes in the levels of IL-1 β and NGF in skin measured at the time of cast removal appeared to be related to pain experiences up to one month later. Correlations involving NGF may be especially important as they were identified between skin levels of this mediator and dynamic pain as well as average NRS pain over the preceding week. This neurotrophin has been linked strongly to multiple forms of pain including CRPS using a fracture/cast pain model involving 4 weeks of immobilization, an immobilization period similar to the average immobilization imposed on our patients (33 days)³⁰. Moreover, anti-NGF agents have proven beneficial in controlling pain in clinical populations though concerns over the consequences of long term use have arisen^{7, 19, 29, 38}. More broadly, it has been suggested that immunotherapies of various types might be helpful in controlling CRPS^{40, 42}. If future studies are consistent with the current results it may be reasonable to determine if perioperative or short-term postoperative suppression of cytokine or NGF signaling, or perhaps inhibition of mast cell activity could reduce sub-acute postoperative pain, the occurrence of CRPS or enhance the functional outcomes of limb surgeries.

In this report we provide data demonstrating that the study of patients undergoing distal limb surgery with subsequent immobilization might provide a useful pain model. These patients exhibit CRPS-like changes at least around the time of cast removal, and many experience moderate to severe pain for at least a month afterward. It seems plausible that this model could be used to study approaches to reducing persistent postoperative pain and other CRPS-like changes if not CRPS itself. On the other hand, the diversity of sensory and biochemical changes after this type of surgery and the correlations that likely exist between some of these factors suggest that larger studies or studies focused on specific factors might enlighten us about fundamental mechanisms supporting or suppressing the development of CRPS or persistent postoperative pain. It should be recognized that our study population was predominantly male, distinct from the overall sex distribution of CRPS sufferers¹⁰, and psychological disease was common. Though a recent report suggests a lack of effect of sex on the propensity to develop CRPS³, caution should be used in generalizing our observations. While this model is unlikely to be suitable to address all questions, it is our hope that this or similar approaches may allow fundamental biological and therapeutic

discoveries to be made by combining experimental investigations with standard clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspective

This study has identified CPRS-like features in the limbs of patients undergoing surgery followed by immobilization. Further studies using this population may be useful in refining our understanding of CRPS mechanisms and treatments for this condition.

Figure 1.

Lateralized differences in skin temperature and hand circumference after surgery. These parameters were measured in the hands of patients ipsilateral and contralateral to surgery on the day of cast removal (n=43). Panel A presents temperature data while panel B displays hand circumference data. The plots display the 75th/25th percentiles (boxes), 95th/5th percentiles (whiskers), median (horizontal line), mean (+ sign), and outliers (spheres).

***p<0.001.

Figure 2.

Pain reported by patients at the time of cast removal and one month later (n=43). In panel A data are presented showing categorical average pain intensity levels for the week preceding cast removal (open bars) and follow-up one month after cast removal (closed bars). Pain scores were categorized as none (0/10), mild (1–3/10), moderate (4–6/10) and severe (7–10/10). Panel B displays the data for reports of dynamic pain at the time of cast removal and after one month.

Figure 3.

Results of quantitative sensory testing (QST) on the hands of patients after surgery and cast immobilization (n=43). Measurements were made on the day of cast removal. Panel A presents data collected using a punctate stimulus, panel B shows cold pain thresholds, panel C provides pain thresholds for pressure applied to the joints, and panel D shows thresholds for the same type of pressure stimulus applied to the interdigital skin folds. The plots display the 75th/25th percentiles (boxes), 95th/5th percentiles (whiskers), median (horizontal line), mean (+ sign), and outliers (spheres). ***p<0.001.

Figure 4.

Lateralized differences in skin mediator levels one month after hand surgery. For these analyses 3mm skin biopsies were collected from skin at least 4cm distant from surgical incisions on the dorsal surfaces of the hands at the time of cast removal and sensory measurements. Samples were processed for mRNA analysis, and target mRNA's were quantified using real-time qPCR. For the purposes of data display the data were normalized to a contralateral side mediator level of 1. The data are displayed as means $\pm$ S. D., * $p < 0.01$.

Demographic, psychiatric and surgical characteristics of the patient cohort (N=43). Demographic and psychiatric information was taken from the patients' electronic medical records. Data pertaining to the surgical procedures, the handedness of the patients and the period of immobilization after the surgical procedures were collected at the time of cast removal.

Table 1

Demographics	Psychiatric Diagnoses	Surgical Procedures
Sex (M/F)	Depression	Type
Age (S.D.)	15	16
	Anxiety Disorder	Arthroplasty
		Fracture
		12
		Fusion
		8
		Soft Tissue
		7
		Dominant Hand
		27
		Days Immobilized (S.D.)
		33 (18)

Table 2

Observations of vascular, sudomotor and trophic findings manifest by patients at the time of cast removal (n=43). Also presented is the distribution of the total number of findings displayed by individual patients.

Type of Finding	# Patients	Total Findings	# Patients
Erythema in surgical hand	16	None	4
Nail growth differences	16	1	10
Hair growth differences	9	2	11
Sweating in surgical hand	4	3	13
Warmth (1 deg. C)	18	4	2
Edema (0.5 cm increase)	33	5	3