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Effectiveness of Decision Support to Treat Complex Regional Pain Syndrome

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Abstract: Background: Complex regional pain syndrome (CRPS) type 1 is a rare but disabling pain condition, usually involving distal extremities such as the wrist, hand, ankle, and foot due to either direct or indirect traumas. CRPS type 1 is characterized by a complex set of symptoms where no correlation can be identified between the severity of the initial injury and the ensuing painful syndrome. Over the years, numerous treatment strategies have been proposed for CRPS management, but therapies remain controversial. At present, no successful therapeutic intervention exists for this condition. The aim of the present study was to propose and assess the effectiveness of a rehabilitative treatment algorithm for CRPS, which is actually in use at our institution. Methods: We retrospectively reviewed all the patients that underwent physical rehabilitative treatment algorithm for hand CRPS between 2011 and 2017 at our Institution. Results: All the parameters taken into consideration, namely the Purdue Pegboard Test (PPT), Disability of the Arm, Shoulder and Hand (DASH), Visual Analog Scale (VAS), as well hand edema, were significantly improved at the end of the rehabilitation protocol. Conclusions: The results obtained in the present study demonstrated that our rehabilitation protocol was able to achieve substantial improvement in pain and quality of life scores. Thus, an early and skillful rehabilitation intervention is of paramount importance for CPRS type 1 management to achieve a stable and optimal functional recovery while preventing the onset of deformities.

Keywords: complex regional pain syndrome; CRPS type 1; algodystrophy; hand rehabilitation; hand therapy; conservative treatment; reflex sympathetic dystrophy

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1. Introduction

Complex regional pain syndrome (CRPS) type 1, or algodystrophy, is a painful and disabling condition that usually manifests in response to trauma or surgery [1,2]. CRPS type 1 is a frequent disorder usually involving distal extremities such as the wrist, hand, ankle, and foot. It is characterized by a complex set of symptoms where no correlation can be identified between the symptoms reported by patients and the putative cause [3]. Severe pain is the most common feature of CRPS, together with a various array of accompanying symptoms ranging from cutaneous dyschromia to altered cutaneous temperature, severe edema, hyperesthesia/allodynia, regional osteoporosis, reduced range of motion (ROM), and trophic changes [3–6].

According to the International Association for the Study of Pain criteria, the characteristic features required to establish CRPS type 1 diagnosis are: (i) the presence of an initiating noxious event or a cause of immobilization; (ii) continuing pain, allodynia, or hyperalgesia with pain disproportionate to any inciting event; (iii) evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain; and (iv) the exclusion of medical conditions that would otherwise account for the degree of pain and dysfunction [7]. Motor disturbances and trophic changes, such as altered nail and hair growth, may be observed in some cases. Beyond CRPS type 1, which occurs without preceding nerve injury, CRPS type 2 has the same clinical features as type 1, except for the presence of clinical signs and history consistent with a nerve injury [8].

Given its different clinical manifestations, CRPS has been divided by many authors into three distinct phases, which are not necessarily progressive, in relation to the time elapsed from the manifestation of signs and symptoms to diagnosis.

Stage I (0–3 months), or the inflammatory, acute phase, is characterized by severe, deep pain coming from deep tissues such as muscles and bones, which is exacerbated by direct contact and a declined position [3,9]. Hyperesthesia or allodynia are usually reported by patients, and the skin is red, warm, and oedematous. Hand ROM is also restricted as a consequence of pain during its mobilization. Stage II (3–6 months), or the dystrophic phase, is characterized by pain reduction, edema organization, and increased articular stiffness. The skin turns cold, cyanotic, and exudative with trophic change to the nails [3,9]. Stage III (6–9 months), or the atrophic phase, is usually prevented by prompt diagnosis and treatment. It is characterized by fluctuating pain, and the skin appears smooth, having lost its skin folds, with a pearly appearance and decreased temperature. Subcutaneous as well as muscular tissues are atrophic, and severe articular contractures are usually present with an important reduction in the normal ROM and palmar fibrosis [3,9].

In recent years, some European countries have developed their own guidelines for the management of CRPS patients [10–13]. To date, there is no gold standard for CRPS management, a multidisciplinary and integrated approach would be optimal. Both the Dutch (2006) [14] and English (2012) [15] guidelines, as well as the Cochrane systematic review of 2016 [6], highlight how a multidisciplinary approach is of pivot to evaluate and treat, as best as possible, every single aspect of CRPS and how setting up an early rehabilitation intervention is fundamental to have the most favorable prognosis. Unfortunately, as explained by Grieve and colleagues [16], great difficulty persists in recognizing both the signs and symptoms (Budapest criteria) as well as in making a correct and early diagnosis by all health professionals. Within this frame, rehabilitative therapies remain the mainstay of CRPS management.

It is well recognized that an early rehabilitation program performed by specialized hand therapists plays a paramount role in the timely and accurate management of these patients within a multidisciplinary team approach. Despite countless rehabilitation protocols reported in current literature, at present, no universal treatment for all forms of CRPS emerged; rather, rehabilitation protocol should be tailored to each patient's symptoms and clinical phase to obtain the most from every approach. Again, treatments should be complementary and sequential to move patients away from each CRPS phase [17–19].

To date, suggested pain management approaches comprise mirror therapy for brain functional reprogramming, physical therapy with transcutaneous electrical nerve stimulation (TENS), pain desensitization techniques, and the pulsating electromagnetic field technique [15,20–31]. Edema management involves compressing, bandaging, and therapeutic massages [32–37]. Furthermore, functional re-education is commonly achieved with active hand mobilization, together with paraffin thermal therapy and custom-made braces with thermo-modeling materials for both static and dynamic use [35–37].

Given the complexity of CRPS clinical presentation and treatment, we developed a decision tree for deciding upon the most effective treatment strategy.

Therefore, the primary goal of the present study is to propose and evaluate the effectiveness of the rehabilitation protocol for CRPS we employed for tailoring treatments to each patient. In particular, patients' dexterity, hand disability, edema, and pain severity were evaluated.

2. Materials and Methods

We retrospectively reviewed all the patients that underwent physical rehabilitation for CRPS between 2011 and 2017 at the Hand and Reconstructive Microsurgery Unit AOU-University of Pisa. Written informed consent was obtained from all participants, and research was carried out according to ethical guidelines and the Helsinki declaration. In order to be included in the study patients had to: (i) be diagnosed with CRPS in accordance with the Budapest criteria [38,39]; (ii) be aged between 18 and 75 years old, without neurologic or rheumatologic disorders; and (iii) have completed the proposed rehabilitative protocol. Moreover, patients who reported additional hand trauma during the follow-up were excluded from the study.

2.1. Data Collection

Between 2011 and 2017, 216 patients were treated for CRPS type 1 at our institution; nevertheless only 180 met the inclusion criteria of the study, and hence were included in the present work.

Of these 180 patients, 152 (84.44%) were male, while 28 (15.55%) were female. Patients had a mean age of 56.96 years (SD ± 7.56). Twelve (6.66%) patients had diabetes. A hundred forty-seven patients (81.7%) were affected in the right hand, 33 patients (18.3%) were affected in the left hand, and the concordance rate between the affected hand and the dominant one was 76.66% (Table 1).

Table 1. Patients' demographics and clinical characteristics.

	Patients' Demographics			Hand Trauma			Time between Trauma and CRPS Diagnosis (Months)	Length of Immobilization (Days)	Length of Rehabilitation (Months)
	n. of Patients	Age (Mean ± SD)	Male/Female (n)	Right	Left	Dominant Hand Concordance			
Path A	96	57.60 (SD ± 7.08)	81/15	78	18	73.9%	2.58 (SD ± 0.53)	29.57 (SD ± 8.34)	6.93 (SD ± 1.23)
Path A + B	13	56.84 (SD ± 7.90)	11/2	10	3	76.9%	1.92 (SD ± 0.64)	27.31 (SD ± 10.4)	6.31 (SD ± 1.25)
Path A + B + D	10	58.4 (SD ± 6.93)	8/2	8	2	80.0%	3 (SD ± 0.0)	34.2 (SD ± 0.79)	8.2 (SD ± 0.79)
Path A + C	24	55.12 (SD ± 7.64)	20/4	19	5	75.0%	2.79 (SD ± 0.41)	31.75 (SD ± 5.52)	7.83 (SD ± 0.87)
Path A + C + D	37	56.11 (SD ± 9.16)	32/5	32	5	88.5%	3 (SD ± 0.0)	33.11 (SD ± 1.66)	7.59 (SD ± 0.64)

Patients' demographics, comorbidity (e.g., diabetes), type of trauma, immobilization length, time elapsed between the putative trauma and CRPS diagnosis, length of the rehabilitation phase, and treatment strategy were collected through electronic medical records. We also characterized rehabilitation treatment and detailed follow-up care.

Functional, subjective, and objective outcome measurements were collected during the first evaluation, and then every week until the end of the rehabilitation program.

Patients' dexterity was determined with the Purdue Pegboard Test (PPT). Hand disability was measured with the Disability of the Arm, Shoulder and Hand (DASH) Score, while the pain was acquired through the Visual Analog Scale (VAS). Moreover, hand edema was recorded with a hand volumeter because it represents one of the major targets in the treatment of CPRS.

2.2. Assessment of Patients' Dexterity

Dexterity was tested with the Purdue Pegboard Test (PPT). In detail, the participants are asked to place pegs into the holes of a rectangular board, gifted with 2 vertical sets (rows) of 25 small holes running vertically and 4 concave cups at the top [40]. Its outcome measure is the number of pegs placed correctly on the row within 30 s with the hand. For this study, only the unimanual subtest (affected hand) was completed.

2.3. Assessment of Hand Disability

The DASH questionnaire consists of a 30-item scale containing 21 physical function items, 5 symptom items, and 4 social role items. Each item has five response options concerning the patient's symptom severity and function of the upper extremity in activity during the previous week. The DASH scores range from 0 to 100, where 100 reflects the most severe disability [41].

2.4. Assessment of Pain Severity

Patients' resting pain was assessed using the Visual Analog Scale (VAS), where 0 corresponds to "no pain", while 10 corresponds to "intractable pain". The VAS is one of the most commonly used measurements and it represents a valid and reliable for assessing pain, depression, and anxiety [42].

2.5. Measurement of Edema

The amount of affected hand swelling was recorded with a hand volumeter. In detail, the upper extremity was immersed in a volumeter (Baseline, Boise, ID, USA) until the third interdigital space contacted a cylindric dowel located at the base of the volumeter. The patient was instructed not to move the extremity until the end of the water displacement test. The volume of displaced water was measured in cc (Figure 1).

Figure 1. Illustration of hand edema measurement through a hand volumeter. The third interdigital space is placed straddling the dowel of the volumeter. The displaced water is measured by a graduated cylinder.

2.6. Statistical Analysis

Statistical analysis was performed employing the values collected prior to the 1st rehabilitative session and during the last one. To ensure that the data were normally distributed, hence parametric in nature, the Bartlett's test for equal variances was performed prior to a one-Way ANOVA. When data were not parametric in nature, the nonparametric Mann–Whitney U test was employed. Statistical significance was given for $p < 0.05$. For hand edema recorded with a hand volumeter, statistical significance ($p < 0.05$) was determined by paired t-tests. Results were given as means ± standard deviation (SD).

3. Results

During the first two months, patients underwent rehabilitative treatment three times a week; eventually, sessions were reduced to twice a week. Once ROM was almost completely restored and the pain disappeared, hand rehabilitative treatment occurred once a week until complete resolution (Figure 2).

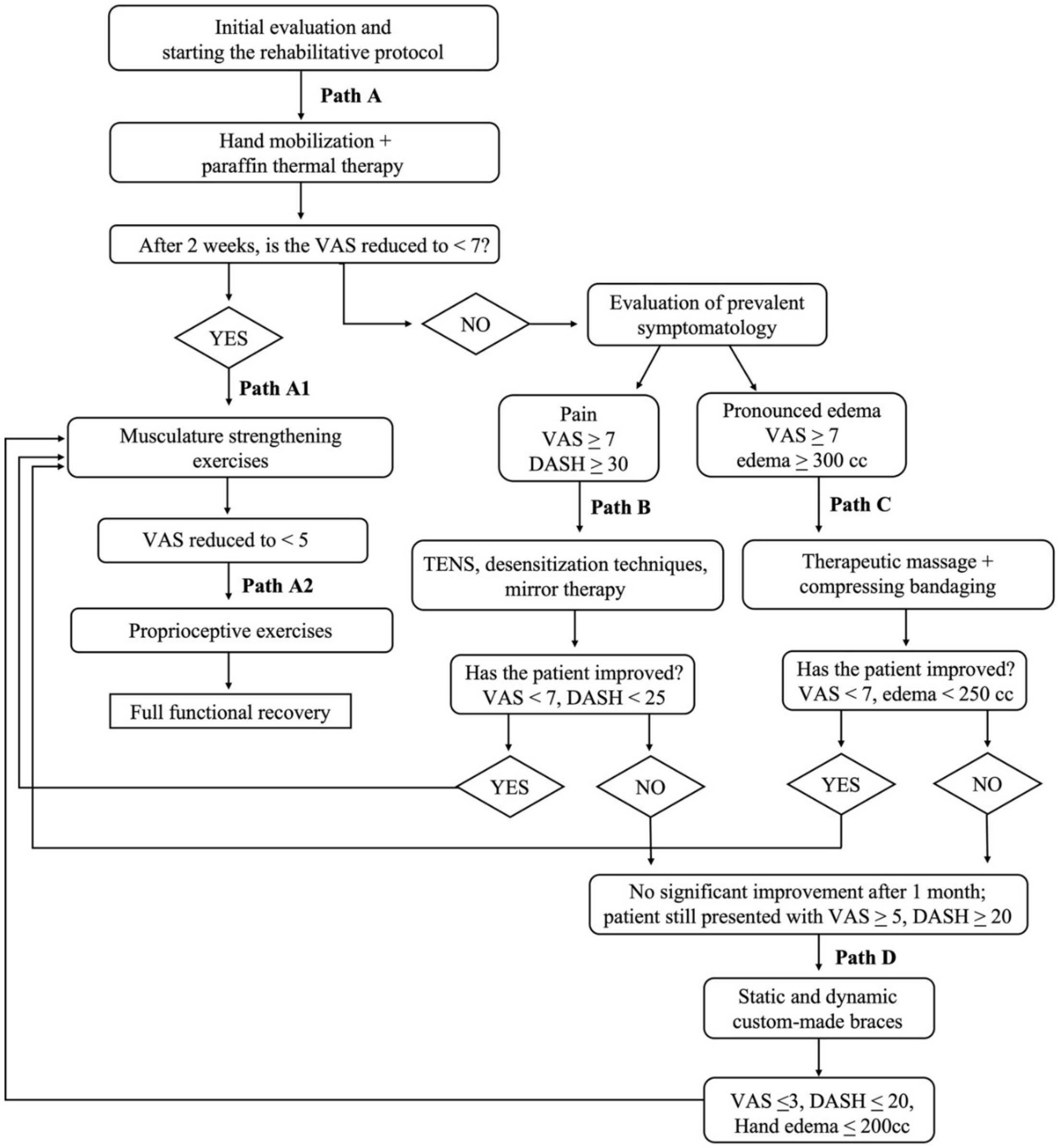

Figure 2. Flowchart to illustrate the decision tree rehabilitation protocol. Both the stages (paths) of the rehabilitation process and the criteria for the progression throughout the stages are reported.

After an initial evaluation, the rehabilitative protocol started for all the patients with active hand mobilization, together with paraffin thermal therapy (Path A) (Figures 2 and 3). Once VAS was reduced to <7, rehabilitation progressed to A1, where musculature strengthening exercises were performed. When VAS was further lowered to <5, proprioceptive exercises were also performed (A2) in order to obtain a full functional recovery (Figure 4).

Figure 3. Illustration of a session of paraffin thermal therapy performed within Path A rehabilitative protocol.

Figure 4. Illustration of sessions of musculature strengthening and proprioceptive exercises performed within Path A1 and Path A2 rehabilitative protocol.

However, if patients did not seem to improve at the end of the second rehabilitative week with Path A, they were redirected to either Path B or Path C depending on their prevalent symptomatology (Figure 2). In detail, if the patients presented pain as the predominant symptom, VAS $\geq$ 7, and DASH $\geq$ 30, they underwent Path B consisting of TENS, desensitization techniques, and mirror therapy (Figure 5); while patients who still presented pronounced edema, VAS $\geq$ 7, and hand volumeter measure $\geq$ 300cc underwent Path C consisting of therapeutic massage and compressing bandaging to be kept for four hours each day. Once patients improved (VAS < 7, plus DASH < 25 for Path B; hand volumeter measure < 250 for Path C), they were re-directed to Path A1, as previously described.

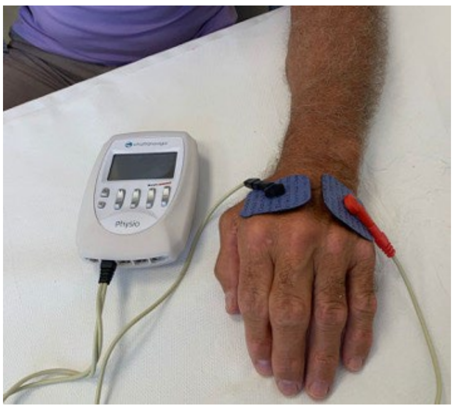

Figure 5. Illustration of a session of transcutaneous electrical nerve stimulation (TENS) performed within Path B rehabilitative protocol.

If no significant improvement could be achieved after one month of rehabilitation and the patients still presented with VAS ≥ 5 and DASH ≥ 20, they underwent Path D, where static custom-made braces with thermo-modeling materials were made for hand protection while at rest, and dynamic ones were also made to increase the articular ROM. In order to progress from Path D to Path A1, patients had to present with VAS ≤ 3, DASH ≤ 20, and hand volumeter measure ≤ 200 cc (Figure 2).

CRPS always followed hand immobilization as a consequence of direct trauma with either conservative (n = 137, 76.11%) or (n = 43, 23.88%) surgical management (117 radio-ulnar joint fractures, 10 phalangeal fractures, 15 carpal tunnel syndromes, 24 metacarpal fractures, 12 distortive traumas, 1 deep flexor tendon injury, and 5 Dupuytren). The mean hand immobilization time was 30.68 days (SD ± 7.22).

The time elapsed between the trauma and the diagnosis of CRPS was 2.67 months on average (SD ± 1.17), while the required rehabilitative therapy had a mean duration of 7.21 months (SD ± 1.41) (Table 1).

Natecal D3® was administered to 157 patients (87.22%) together with e.v. administration of bisphosphonate, while 90 patients (50%) required biophysical stimulation with a portable device for 6-8 consecutive hours each day for 1 month.

Ninety-six patients (53.33%) underwent Path A only and had a mean duration of 6.94 months (SD ± 1.24). Thirteen patients (7.22%) underwent Path A + B with a mean duration of 6.31 months (SD ± 1.25), while 10 patients (5.55%) underwent Path A + B + D with a mean duration of 8.2 months (SD ± 0.79). Twenty-four patients (13.33%) underwent Path A + C, while 37 patients (20.55%) underwent Path A + C + D with a mean duration of 7.83 (SD ± 0.87) and 7.59 months (SD ± 0.64), respectively (Table 1).

At post-treatment (T1) evaluation, significant improvements were revealed regarding all the parameters taken into consideration (PPT, DASH, VAS, and hand volumeter). All data are resumed in Table 2.

Table 2. Pre (T0) and post-treatment (T1) scores for PPT, DASH, VAS, and hand volumeter.

	PPT			**DASH**			**VAS**			**Hand Volumeter**		
	T0	**T1**	***p***	**T0**	**T1**	***p***	**T0**	**T1**	***p***	**T0**	**T1**	***p***
Path A	7.9 (SD ± 1.1)	18.62 (SD ± 1.7)	<0.0001	45.02 (SD ± 2.37)	25.18 (SD ± 1.97)	<0.0001	8.02 (SD ± 0.43)	2.85 (SD ± 0.61)	<0.0001	335.62 (SD ± 13.75)	264.22 (SD ± 22.94)	<0.0001
Path A + B	7.69 (SD ± 0.63)	16.77 (SD ± 0.93)	<0.0001	44.15 (SD ± 1.91)	26.85 (SD ± 2.97)	<0.0001	8.61 (SD ± 0.51)	3.23 (SD ± 0.93)	<0.0001	336.15 (SD ± 8.7)	265.38 (SD ± 9.67)	<0.0001
Path A + B + D	7.6 (SD ± 0.52)	18.5 (SD ± 1.27)	<0.0002	45.5 (SD ± 0.97)	24.5 (SD ± 1.27)	<0.0002	8.1 (SD ± 0.32)	2.4 (SD ± 0.52)	<0.0002	345 (SD ± 9.72)	288 (SD ± 9.19)	<0.0001
Path A + C	7.67 (SD ± 0.7)	17.83 (SD ± 2.14)	<0.0001	45.25 (SD ± 1.67)	32.91 (SD ± 2.22)	<0.0001	8 (SD N/A)	2.83 (SD ± 0.38)	<0.0001	355.83 (SD ± 10.18)	308.33 (SD ± 9.17)	<0.0001
Path A + C + D	7.19 (SD ± 0.66)	17.4 (SD ± 1.69)	<0.0001	46.16 (SD ± 1.21)	32.32 (SD ± 2.42)	<0.0001	8.22 (SD ± 0.42)	2.86 (SD ± 0.35)	<0.0001	351.08 (SD ± 7.74)	308.65 (SD ± 10.58)	<0.0001

In detail, when assessing patients' manual dexterity, a two-fold increase in PPT performance at time T1 compared with T0 occurred in all rehabilitative paths was seen (Figure 6).

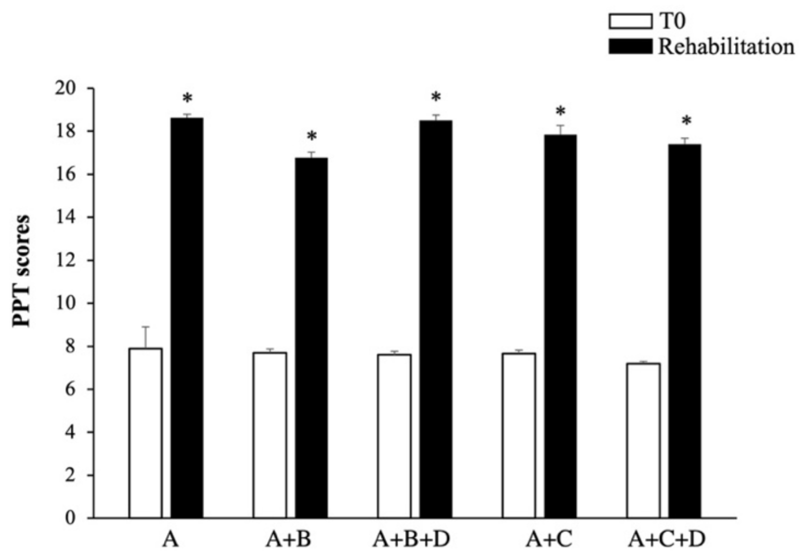

Figure 6. The graph reports the number of pegs placed in 30 s. * $p \leq 0.05$ compared with T0.

With reference to hand disability, DASH scores were significantly lower (nearly halved) at the end of all rehabilitation paths (Figure 7).

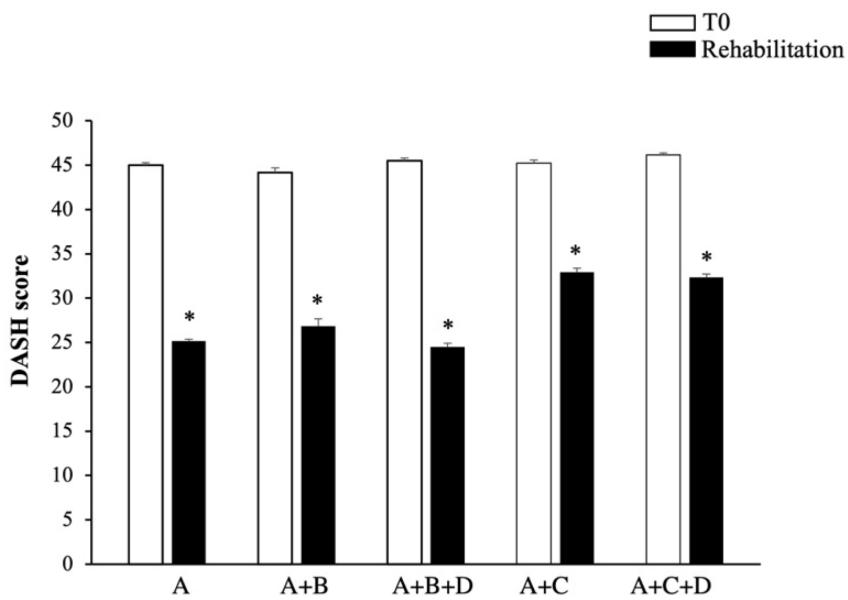

Figure 7. Score distribution of Disability of the Arm, Shoulder, and Hand (DASH) before (T0) and after (T1) the different rehabilitation paths. Higher values indicate greater disability. * $p < 0.05$ compared with T0.

In addition, a reduction of roughly 60% in perceived pain assessed by VAS was observed at the end of all rehabilitation paths (Figure 8).

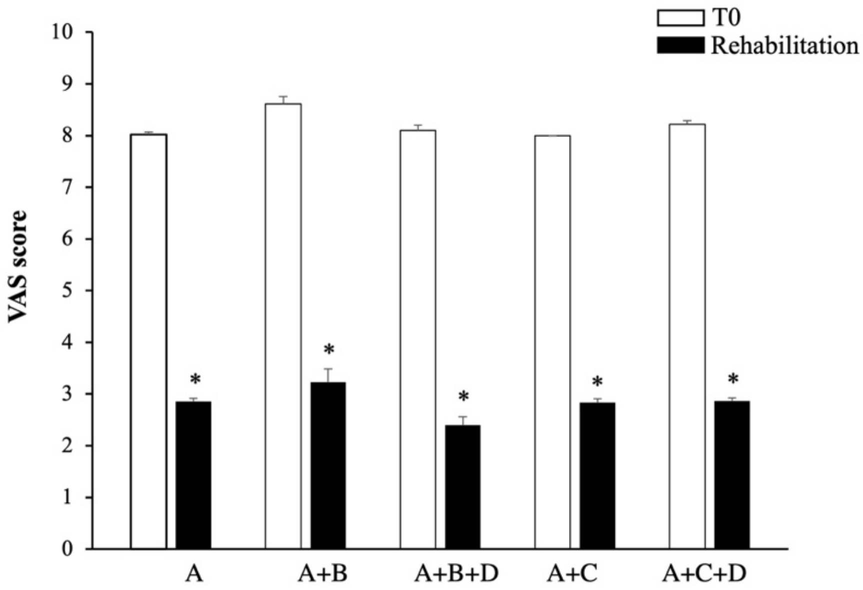

Figure 8. Pain intensity as visual analog scale (VAS) score before (T0) and after (T1) the different rehabilitation paths. * $p < 0.05$ compared with T0.

Finally, at the end of the rehabilitation program, the reduction in hand edema volume was remarkable in all groups (Figure 9).

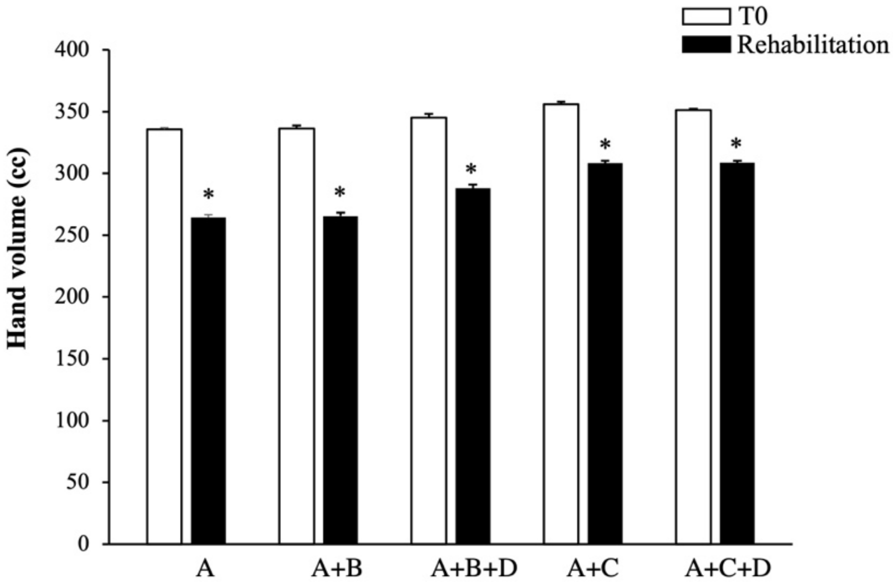

Figure 9. Amount of volumetric edema measured by a hand volumeter before (T0) and after (T1) the different rehabilitation paths. * $p \leq 0.05$ compared with T0.

4. Discussion

Complex regional pain syndrome (CRPS) is a debilitating condition that usually develops subsequent to trauma or surgery and where the painful experience appears disproportionate, in time and intensity, to the level of injury [1–3,43–45]. Despite numerous studies reported in current literature, the underlying pathophysiology of CRPS is poorly understood. Thus, CRPS still remains a contemporary medical challenge with a natural history characterized by chronicity and relapses which result in a significant disability over time [46].

Although numerous treatment modalities have been claimed to be useful in the management of CRPS, at present, there is no clear consensus regarding the most effective treatment for this condition. These include pharmacologic therapies, physiotherapy, behavioral modification and psychotherapy, neuromodulation, surgical procedures, and miscellaneous complementary and alternative therapies [6,8,15,20–37]. Most of these therapies are directed at managing the signs and symptoms of the disease and no single drug has proven to be efficacious for all patients with CRPS. In addition, ongoing reassessment of the adequacy of pain relief and careful attention to drug side effect profiles are needed to make meaningful decisions about drug initiation or continuation [8]. Only a few studies have evaluated mechanism-based treatment options [47–50]. On the other hand, the available evidence is difficult to compare due to heterogeneous inclusion criteria, inappropriate or absence of adequate controls, lack of adequate power due to small sample sizes, and lack of blinding or randomization [51]. At the same time, long-term follow-up studies are scarce.

Remarkably, from the present study, it clearly emerges that rehabilitation treatment is a key aspect of the therapeutic program that should be started as soon as possible. In fact, the timeliness of an adequate diagnostic and therapeutic approach avoids the unfavorable evolution of CRPS which is configured with functional limitation, pain, and stiffness. Therefore, initiating early diagnosis and early post-traumatic/surgical rehabilitation, where possible, is important for minimizing permanent loss of function. In addition, avoiding prolonged hand immobilization may be crucial for the return of normal limbs. Moreover, these CRPS patients will miss the possible benefits of early treatment, which may jeopardize the complete resolution of the syndrome. In fact, as evidenced in Table 1, the longer the time elapsed between the trauma and CRPS diagnosis and the longer the hand immobilization time, the longer the time to achieve patients' clinical and functional recovery.

5. Conclusions

In recent years, the number of CRPS patients has significantly increased. Given the existing limitations and uncertainty within the current literature, CRPS still remains a diagnostic and therapeutic dilemma for clinicians, and addressing this problem is currently challenging. At the same time, scientific works regarding the rehabilitation process are scarce.

While phase I CRPS may resolve with a complete recovery of the affected limb, CRPS in phase II or III, despite specific therapeutic treatments, often persists and develops lasting pain and hand disability. In our experience, patients treated in phase II may also achieve a complete and adequate recovery. The success of the rehabilitation treatment does not rely on the severity of the trauma, but it rather depends on the timeliness of early diagnosis, which allows an adequate multidisciplinary therapeutic treatment; this, in turn, is pivotal to ensuring patients' optimal outcomes.

Unfortunately, the constellation of signs and symptoms and their evolution does not facilitate the use of a standardized therapeutic approach. It also appears extremely difficult to group patients with the very same clinical picture. Therefore, the rehabilitation protocol must be patient-tailored and focused on the specific disease stage, as well as promptly adapting to the patient's need, tolerability, and varying clinical manifestations. Treatments must be complementary and sequential in order to obtain the greatest benefit, as much as possible, while accompanying the patient throughout the entire course of the disease.

Therefore, there is a clear need for further research into CRPS pathophysiology to improve the diagnostic and preparatory process. An early diagnosis along with a timely and adequate treatment is crucial to avoid the evolution of the syndromic picture and to completely resolve the pathology while minimizing the loss of limb function. Within this frame, specialized hand physiotherapists are at the forefront of promptly and adequately managing the evolution of the CRPS.

Future studies should be conducted to assess the efficacy of physiotherapy interventions for treating the pain and disability associated with CRPS in a prospective, controlled fashion.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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