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CASE REPORT

Mesotherapy for Complex Regional Pain Syndrome: A retrospective case series and literature review

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ABSTRACT

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a complex and disabling condition occurring frequently after a traumatic trigger event like fracture or surgery. Despite the therapeutic options available, the management remains often challenging for the patient and for the practitioner.

MATERIAL AND METHODS

This is a retrospective case series with data collection on 18 patients with CRPS meeting the Budapest criteria and treated with mesotherapy at the Department of Physical Medicine and Rehabilitation at Mohammed VI University Hospital in Oujda between January 2022 and July 2024. The mesotherapy protocol used consisted of a mixture of 1 ml of local anesthetic (2% lidocaine), 1 ml of nonsteroidal anti-inflammatory drug (20 mg piroxicam), and 1 ml of 100 IU calcitonin for 4 patients, with the addition of 1 ml of normal saline to dilute the mixture. The visual analog scale (VAS) and the complex regional pain syndrome (CRPS) severity score were the main scores reported and compared before and after the mesotherapy sessions, with a one-year follow-up.

RESULTS

The VAS and CSS score improved in 14 patients, and did not change in 4 patients, The main improvement was observed during the six months after the last mesotherapy session.

CONCLUSIONS

Mesotherapy may have a role to play in management of CRPS patients, larger controlled prospective studies are needed to draw reliable conclusions.

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KEYWORDS

Complex Regional Pain Syndrome; Mesotherapy; Chronic Pain; Case series

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a complex, persistent, painful and disabling condition with highly variable prognosis, occurring most frequently after acute trauma or surgery [1].

Two types have been described, CRPS type 1 (formerly known as Algodystrophy or Dystrophic Sympathetic Reflex) which is not associated with nerve damage, and CRPS type 2 (formerly known as Causalgia Algoneurodystrophy) in which nerve damage can be identified [2]. However, this distinction is not without criticism, given that provocative mechanisms can cause nerve damage, as in the case of fractures or surgery for example although they are frequently classified CRPS type 1 [3].

EPIDEMIOLOGY AND RISK FACTORS

This syndrome remains rare with an estimated incidence of between 5.5 and 26.2 per 100,000 population (H) in the USA [4]. Lower incidences have been reported in Iceland at around 1.3 per 100,000 H or are declining as in Groenveld's retrospective study which focused solely on CRPS following radius fractures [5, 6]. A Korean cohort, spanning 7 years from 2009-2016, reported an incidence of 15.83 per 100,000 H, with a downward trend in each age group [7].

Several factors have been associated with the development of CRPS. The results of a large Danish study that analysed data from 647 cases of CRPS showed the following findings [8]: Women are 4 times more affected than men. The upper limb is more affected than the lower limb (2.5 to 1). CRPS was more frequent in surgical patients than in patients receiving orthopaedic treatment (3 to 1). Indeed, trauma accounts for 75% of all cases of CRPS, with fractures leading the way and accounting for almost half of these triggering events (45%), followed by sprains (18%) and elective surgery (12%) [9]. Case reports of spontaneous CRPS have been reported but remain rare [10]. Another potential risk factor is prolonged immobilization. Terkelsen and his colleagues showed in an experimental study that 4-week immobilization of the forearm caused SDRC-like symptoms (skin temperature change, mechanical and thermal sensitivity) in healthy subjects [11].

These experimental results are also supported by prospective studies, showing a higher complication rate in patients treated with cast immobilization versus those treated surgically [8,12].

Paediatric population can be also affected with CRPS, especially in girls; the type 1 is the most frequently reported in this population [13-15]. In contrast to adults, the lower limb appears to be more affected than the upper limb [16,17].

PATHOPHYSIOLOGY

The pathophysiology of CRPS has yet to be fully elucidated, but current data seem to converge on the incrimination of several mechanisms arising from a complex interplay between the immune system, neural systems (central and peripheral), and genetic predisposition [8,18,19]

The Inflammatory and Autoimmune Response:

The role of inflammation has been widely implicated with a main hypothesis of a "facilitated neurogenic inflammation" probably due to impaired inactivation of neuropeptides such as Calcitonin Gene Related Peptide (CGRP) and Substance P (SP) or increased receptor availability [20]. This hypothesis would explain the limb oedema and high levels of cytokine expression observed in CRPS patients [21]. The role of other inflammatory cytokines has also been identified, notably TNF and interleukins 6 and 8 [22].

The role of autoimmunity mediated by antibodies has recently been put forward. Indeed, several studies have shown that 70% of CRPS patients have levels of autoantibodies (Immunoglobulin G) targeting the surface of autonomic neurons in the bloodstream [23-25]. IgM has also been reported to play a role in sensitization to nociception [26,27]. T cells also appear to play a role, with CD14+ monocytes also elevated in CRPS patients, and the number of cells correlated with the severity of allodynia [28].

Vasomotor Dysfunction

Vasomotor disturbances are common in CRPS, and the current evidence base supports that central disturbances in efferent sympathetic pathways are dominant in the acute phase of CRPS, while disturbances in neurovascular transmission and the development of blood vessel hyperreactivity to circulating catecholamines appear to predominate in the chronic stage [29-31]. This dysfunction of the sympathetic nervous system may also play a role in pain phenomena through sensitization of nociceptors to catecholamines [32].

Mismatched neuroplasticity: Central Sensitization (Central Nervous System):

The phenomenon of Central Sensitization (CS) is defined as an amplification of neuronal signalling within the CNS that causes hypersensitivity to pain [33]. Several forms of this phenomenon have been described in several chronic pain pathological conditions, including CRPS [34]. The sensitization process appears to distort or suppress non-noticeable sensations. Thus, sensitized spinal nociceptive neurons become more reactive to peripheral signals and may even be activated in the absence of such signals [35]. As such, SC can lead to chronic pain, hyperalgesia and allodynia, as well as the spread of pain to adjacent uninjured areas [35]. Furthermore, recent data from functional Magnetic Resonance Imaging (MRI) studies speculate that CRPS symptoms result from altered antinociceptive response via the periaqueductal gray, and altered thalamo-cortical and putamen functional connectivity, and changes in basal ganglia and motor loops, although these findings require validation in larger cohorts [36,37].

Genetic Factors

Genetic predisposition to the development of CRPS has been suggested, and several genes have been studied [38]. Human leukocyte antigen (HLA) genes have been shown to be linked to many neurological disorders [39]. A comprehensive study of 150 patients with CRPS and fixed dystonia revealed a significant association between HLA-B62 and HLA-DQ8 genes and CRPS with fixed dystonia [40]. In addition, several experimental studies in rats have identified signalling pathways in CRPS, including the CXCL/CXCR5 pathway and the JAKSYAT pathway. These discoveries may pave the way for new therapies in the future [41,42].

Other pathophysiological mechanisms have also been reported, notably psychological and environmental factors [43,44]. In summary, CRPS appears to be the result of several pathophysiological mechanisms, with variable inter-individual and even intra-individual heterogeneity over time [8].

DIAGNOSIS

The diagnosis of CRPS is based on the Budapest criteria established in 2007 by the International Association for the Study of Pain (IASP) [45]. These criteria are widely used and include sensory abnormalities, temperature asymmetry, colour changes, oedema, sweating and motor dysfunction. In 2021, the Valencia Consensus was published by the IASP Special Interest Group with updates to clarify the assessment of fluctuating symptoms and the extension of CRPS symptoms beyond a single limb, and to better define the terms “asymmetry” and “changes” [46]. According to this consensus, CRPS type 2 should not be considered as neuropathic pain and is characterized by the extension of symptoms beyond the territory of the injured nerve [46]. Among the new features of this consensus is the introduction of a third subtype, “CRPS on Partial Remission Features”, which defines previously documented patients who fully meet the CRPS criteria (type 1 or 2), but who subsequently “present” with insufficient criteria to fully meet the diagnostic criteria. Also, the term CRPS Not Otherwise Specified-(CPRSNOS) is to be reserved only for patients who have never been documented as meeting IASP criteria. In other words, these patients now have some, but not all the features required for the diagnosis of CRPS, and no other diagnosis better explains their clinical picture. The Valencia group also estimated that there was not yet sufficient evidence to create subgroups based on clinical presentations, such as Hot/Cold CRPS or Early/Persistent CRPS.

The diagnosis of CRPS remains a clinical diagnosis of elimination, and no paraclinical examination is specific to it. However, several paraclinical tests have been evaluated in patients suffering from CRPS. Among these, the diagnostic contribution of Bone Scintigraphy (BS) has been studied, with meta-analyses concluding the non-benefit of BS to clinical diagnostic criteria [47,48]. Of all the imaging modalities available, Radionuclide Scintigraphy (NRS) and Triphasic Bone Scintigraphy (TBS) appear to be the most sensitive and specific in detecting abnormalities usually seen in this pathology [49].

MRI has also been evaluated as a diagnostic tool in CRPS. The results show a lower sensitivity than that of scintigraphy [50]. As a result, several authors recommend the use of MRI to rule out differential diagnoses in patients with CRPS [50,51]. Standard radiography (SR) is a more common and readily available diagnostic tool, as the appearance of diffuse and heterogeneous demineralization is reported in the literature but lacks specificity and sensitivity [52].

MANAGEMENT

The management of CRPS is complex and demanding, both for the patient and his family, and for the practitioner as well. Most authors agree on the objectives of management: patient education, pain reduction, and restoration of function to the affected limb [53,54]. Therapeutic means are divided into 3 groups: pharmacological means, interventional means, and rehabilitation.

Pharmacological Means

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Several molecules have been evaluated in the therapeutic management of CRPS. Published data have shown little efficacy of NSAIDs in the treatment of CRPS [55]. However, the Royal College of Physicians (RCP) recommends prescribing simple analgesics, including NSAIDs whenever possible, to reduce the pain associated with trauma and facilitate the mobilization process [56].

Corticosteroids

Several Randomized Clinical Trials (RCTs) have shown the positive effect of corticosteroids in improving symptoms in CRPS patients, especially pain [57, 58]. Kalita showed in his recent RCT that prednisolone prescribed at 20 mg was not inferior to results with 40 mg, with dose safety even in diabetic patients [59]. Furthermore, a narrative systematic review confirmed these positive results, nevertheless the studies included in this review comprised only three RCT, which highlights the need for a full systematic review with more qualified studies to better draw conclusions [60].

Calcitonin

RCTs evaluating the role of calcitonin are dated. Positive results have been reported by Sahin and colleagues using calcitonin at a dose of 200 IU per day, but a closer look reveals no significant difference between the 2 groups enrolled in this trial (calcitonin/paracetamol), and both groups benefited from physical therapies [61]. Moreover, current data do not support the use of calcitonin in advanced stages of CRPS [62]. In addition, the use of long-term calcitonin should be cautious, given the risk of potential association with various cancers in postmenopausal women on calcitonin-containing replacement therapy [63].

Bisphosphonates (BP)

Since Brunner's systematic review in 2008 showing a potential effect of BP in reducing pain in osteoporotic CRPS patients [64]. Several RCTs have been published with positive results on pain improvement with neridronate in particular [65, 66]. These results are supported by a recent meta-analysis and systematic review recommending the use of BP as a first-line treatment [67].

Opioids

Few studies on the opioids effect in CRPS were reported with controversial results, among which two RCTs showing positive effects with intravenous and topical administration of ketamine even though the follow-up period was short in both trials [68, 69]. Currently, two RCTs are in the recruitment phase for the evaluation of several molecules, including the University of Southern California's NCT06419985 trial, which will assess the effects of extended-release ketamine in CRPS, and the New York trial (NCT06306157), which will evaluate the therapeutic effects of a low-dose of Naltrexone.

Antiepileptics and Antidepressants

Gabapentin's positive results in neuropathic pain prompted its evaluation in CRPS. A previous RCT showed moderate effects on pain reduction with gabapentin [70]. Another RCT compared the analgesic effects of gabapentin versus amitriptyline in CRPS and neuropathic pain in children [71]. Both molecules showed significant

results in pain reduction, with no difference between the two groups [71]. However, the number of patients included for each group was very small and the duration of monitoring was very short (6 weeks).

Local Anaesthetics

Zhu's systematic review and meta-analysis evaluating intravenous administration of lidocaine in neuropathic pain showed positive effects in the short term without lasting effects, and with more adverse effects, but which remained negligible [72]. Cases series reported positive results with the use of lidocaine infusion in CRPS patients [73]. Furthermore, a systematic review of intravenous therapy in CPRS supported the use of IV lidocaine in addition to immunoglobulin, BP, and Ketamine in selected CRPS patients [74].

Botulinum Toxin

The use of botulinum toxin type A (BT-A) as an analgesic remains controversial, and off label. Safarpour's RCT evaluating the effect of cutaneous and subcutaneous administration of BT-A on pain showed no significant results [75]. The use of BT-A in lumbar sympathetic ganglion blocks in CRPS patients was also tested in an RCT, the results showed increased temperature and pain reduction of the affected limb [76]. A systematic review of three RCT including the two cited above showed positive primary findings with the use of BT-A. Nevertheless, larger controlled studies are needed to determine the safety and the efficacy of BT-A in CRPS management. In summary, a recent meta-analysis and systematic review of 23 RCTs concluded that ketamine and bisphosphonates were superior in terms of long-term efficacy and side effects [78].

Interventional Procedures

Sympathetic nerve blocks

Sympathetic nerve blocks are the first line of interventional treatment, the most used being the stellate ganglion block at cervical level and the lumbar ganglion nerve block. A recent systematic review and meta-analysis showed positive effects on pain reduction, with some side effects [79]. Nevertheless, the RCTs included in this review are very heterogeneous with small sample sizes.

Neuromodulation

In the Neuropathic Pain Special Interest Group (NeuPSIG) recommendations on interventional treatment in neuropathic pain in 2013, the use of Spinal Cord Stimulation (SCS) in CRPS type 1 was of low recommendation with a proposal by the authors to reserve this therapy for patients unresponsive to other interventional therapies [80]. Furthermore, a recent systematic review and meta-analysis demonstrated the efficacy and superiority of SCS compared with conventional therapeutic means [81]. Looking at complication rates and side effects, percutaneous SCS appears to be safer than conventional SCS [82]. Another SCS route, is Dorsal Root Ganglion Stimulation (DRGS), which was approved by the Food and Drug Administration (FDA) in 2016 for the treatment of refractory pain in CRPS [83]. SGRD is equally or even more effective than SCS, especially in certain areas such as the foot [84]. This is probably due to the superior precision of DRGS, given that the probes used are guided in the intervertebral foramen and placed right next to the dorsal root ganglion.

Intrathecal Administration

Epidural administration of several molecules such as opioids and local anaesthetics has been reported with variable response rates [85]. Cutaneous and epidural superinfections and catheter migration are the main complications reported [86]. These interventional therapies are clearly not the first-line treatment for CRPS. However, in cases that are refractory to drug or physical therapy, interventional approaches take their place, with sympathetic nerve blocks as the first line of treatment.

Rehabilitation

Rehabilitation is an integral part of the management of CRPS, and is prescribed for both analgesic and functional purposes, as most of these patients present with joint stiffness [56, 87-88]. Although with low quality results, several systematic reviews and meta-analyses have shown positive results of rehabilitation, notably with Mirror Therapy (MT), and Graded Motor Imagery (GMI) programs (in comparison with routine rehabilitation interventions) on pain and disability at 6 months follow-up [89,90]. In their overview of systematic reviews (9 reviews) dealing with different types of interventions and objectives, Shafiee and colleagues concluded on the positive results of adopting movement representation techniques such as MT and IMG programs for the treatment of pain and disability in patients with CRPS [91].

MESOTHERAPY

History and definition:

Mesotherapy is a medical procedure involving the administration of pharmaceuticals by injections into the superficial layers of the skin, with the aim of delivering a maximum dose with minimum side effects [92]. The French physician Michel Pistor first described this method in 1952 [93]. Since then, the development of this new "medical therapy" has been gradual, with the creation of the French Society of Mesotherapy (SFM) in 1965, followed by the International Society of Mesotherapy in 1983. In 2001, mesotherapy was included in medical acts for the treatment of pain by the French National Medical Insurance Fund [94]. Currently, several French universities have created University Diplomas in Mesotherapy. This rise in popularity, seen above all in Europe and South America, was met with resistance in North America, where the emphasis is on evidence-based medicine rather than experimental medicine. However, significant advances in basic scientific research into mesotherapy have been made in the last decade, particularly in aesthetic medicine [95].

Indications

Mesotherapy has been used for several pathological conditions, notably rheumatological pathologies, sports medicine, and aesthetic medicine. In musculoskeletal pain, a Turkish RCT evaluated the efficacy of mesotherapy administration of a mixture of tenoxicam + thiocolchicoside + lidocaine with intravenous administration of dexketoprofen in the management of various musculoskeletal lesions in emergency departments [96]. In this trial, the Visual Analogue Score (VAS) was recorded before administration and after 10, 30, 60 and 120 minutes. The results showed a significant superiority of mesotherapy over intravenous administration. However, the limited number and very short follow-up of patients are clear limitations of this trial. Another Turkish RCT published with virtually the same methodology and research limitations also converged on the same conclusions [97]. From another angle, mesotherapy was evaluated in the management of Pes-Anserine bursitis in the context of knee arthrosis. The results of this trial, which included 117 patients concluded that intradermal administration of

NSAIDs was effective and well tolerated compared with oral administration of NSAIDs [98]. The follow-up period in this study was up to three months. A call for action was issued in 2021 by the Italian Society of Mesotherapy (ISM) encouraging practitioners to help health authorities consider mesotherapy in the prevention, the treatment, and the rehabilitation pathways for patients [99]. The same society had published a consensus report in 2011, stressing the need for more large-scale clinical trials to determine the benefits and limitations of mesotherapy in certain pathologies [100]. The practice of mesotherapy is not without its risks, and this must be clearly explained to patients before embarking on the procedure. Thus, several studies have reported side effects of varying degrees of severity. The ENATOME 1 study reported in the National Institute of Health and Medical Research (INSERM) assessing of the efficacy of therapeutic mesotherapy, which involved 2,839 observations, reported the following side effects [101]: - Neurovegetative reactions: sweating, paleness, transient malaise: 1.2%. - Flush 2.7% - Local reactions: Pain 9.2%, Haematoma 5.3%, Pruritus 1.8%, Erythema 0.7%. Apart from this study, most published side effects are case descriptions or small case series [102]. A recent systematic review and meta-analysis evaluating the safety and efficacy of mesotherapy in musculoskeletal disorders showed that mesotherapy was a safe procedure with temporary side effects such as fatigue, sweating, headache, dizziness, bruising, bleeding, and allergic reactions at injection sites [103]. Finally, ISM has published an update on evidence-based recommendations for mesotherapy. In this update, the use of mesotherapy in localized musculoskeletal pain was graded 1A with 100% expert agreement, while its use in individual rehabilitation and sports injuries was graded 1B with 95.6% expert agreement [104].

Methods

Data were collected from the files of patients suffering from CRPS and treated with mesotherapy at the Physical Medicine and Rehabilitation department of Mohammed VI University Hospital of Oujda between January 2022 and July 2024. The diagnosis of CRPS was based on the IASP criteria with minimal exploration based on X-rays and biological tests (Blood counts, C Reactive Protein, and vitamin D).

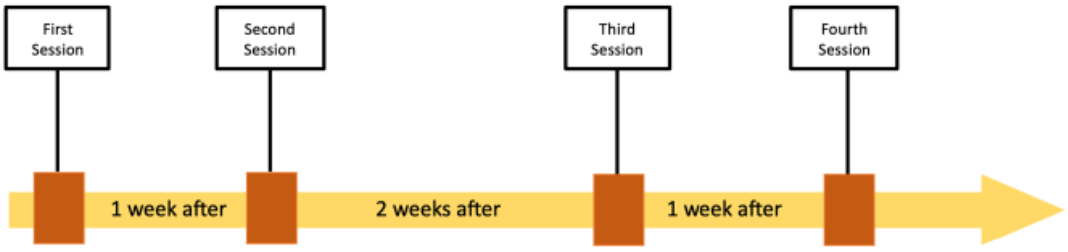

Figure 1: The schedule of the four injection sessions, completed by the 18 patients.

Demographic and clinical information including age, sex, anatomic region, trigger events, vitamin C intake, VAS and CRPS severity score (CSS) and other information were recorded. Two mixtures were used, depending on the availability of Calcitonin for some patients. The first mixture was made of 1 ml of Piroxicam 20 mg + 1 ml of lidocaine 2% + 1 ml of saline 0,09 % (for 14 patients). The second one was the same as the first one, in addition to 1ml of Calcitonin 100 IU (4 patients received this mixture). The choice of the mixture was based only on Calcitonin availability. The injections were performed using a 0.4 mm 28-gauge needles. All the 18 patients

completed 4 sessions of mesotherapy with one week-interval between two consecutive sessions, expect between the second and the third session (Figure 1).

Clinical assessment was based on VAS and CSS score before and after the sessions up to one year follow up.

RESULTS

Among the 18 patients, 12 were women and 6 were men, the median age was 58,72 ranging from 24 years to 78 years old + 13,55. Patient's characteristics are given in table 1. All the patients completed the 4 sessions of mesotherapy, and the patients have received before the mesotherapy sessions multiple medication including NSAIDs, Codeine, Gabapentin, tramadol in addition to rehabilitation. The patients were evaluated after every session for adverse effects and then for the first month and then every three months up to one year after the last mesotherapy session. All the patients have received before the mesotherapy sessions multiple medication including NSAIDS, Codeine, Gabapentin, tramadol in addition to rehabilitation.

Table 1: Patients demographic and clinical characteristics.

Patient No	Sex	Age	Anatomic Region Concerned	Triger Event	Orthopedic Treatment	Immobilization	SDR C Type	VAS	CSS
1	F	60	Wrist	Wrist Fracture	Surgery	2 Weeks	1	5	60
2	M	72	Ankle	Ankle Fracture	Cast + Immobilization	3 Months	1	6	73
3	M	68	Wrist	Wrist Fracture	Surgery	2 Weeks	1	4	50
4	M	59	Shoulder + Hand	Cerebral Stroke	-	-	1	8	81
5	F	66	Shoulder + Hand	Cerebral Stroke	-	-	1	7	123
6	M	45	Shoulder + Hand	Cerebral Stroke	-	-	1	7	117
7	F	24	Ankle	Ankle Fracture	Surgery	6 Weeks	1	7	111
8	F	49	Shoulder + Hand	Cerebral Stroke	-	-	1	7	132
9	F	63	Shoulder + Hand	Cerebral Stroke	-	-	1	8	143
10	F	69	Shoulder + Hand	Cerebral Stroke	-	-	1	8	123
11	F	78	Shoulder + Hand	Cerebral Stroke	-	-	1	8	97
12	F	70	Shoulder + Hand	Cerebral Stroke	-	-	1	7	93
13	F	67	Ankle	Ankle Sprain	Cast + Immobilization	40 Days	1	8	55
14	F	56	Wrist + Hand	Wrist Fracture	Surgery	2 Weeks	1	8	37
15	F	73	Hand	Finger Fracture	Cast + Immobilization	2 Months	1	6	87
16	F	38	Ankle	Ankle Fracture	Surgery	6 Weeks	2	9	61
17	M	53	Shoulder + Hand	Cerebral Stroke	-	-	1	9	76
18	F	47	Ankle	Ankle Sprain	Splint + Immobilization	40 Days	2	8	97

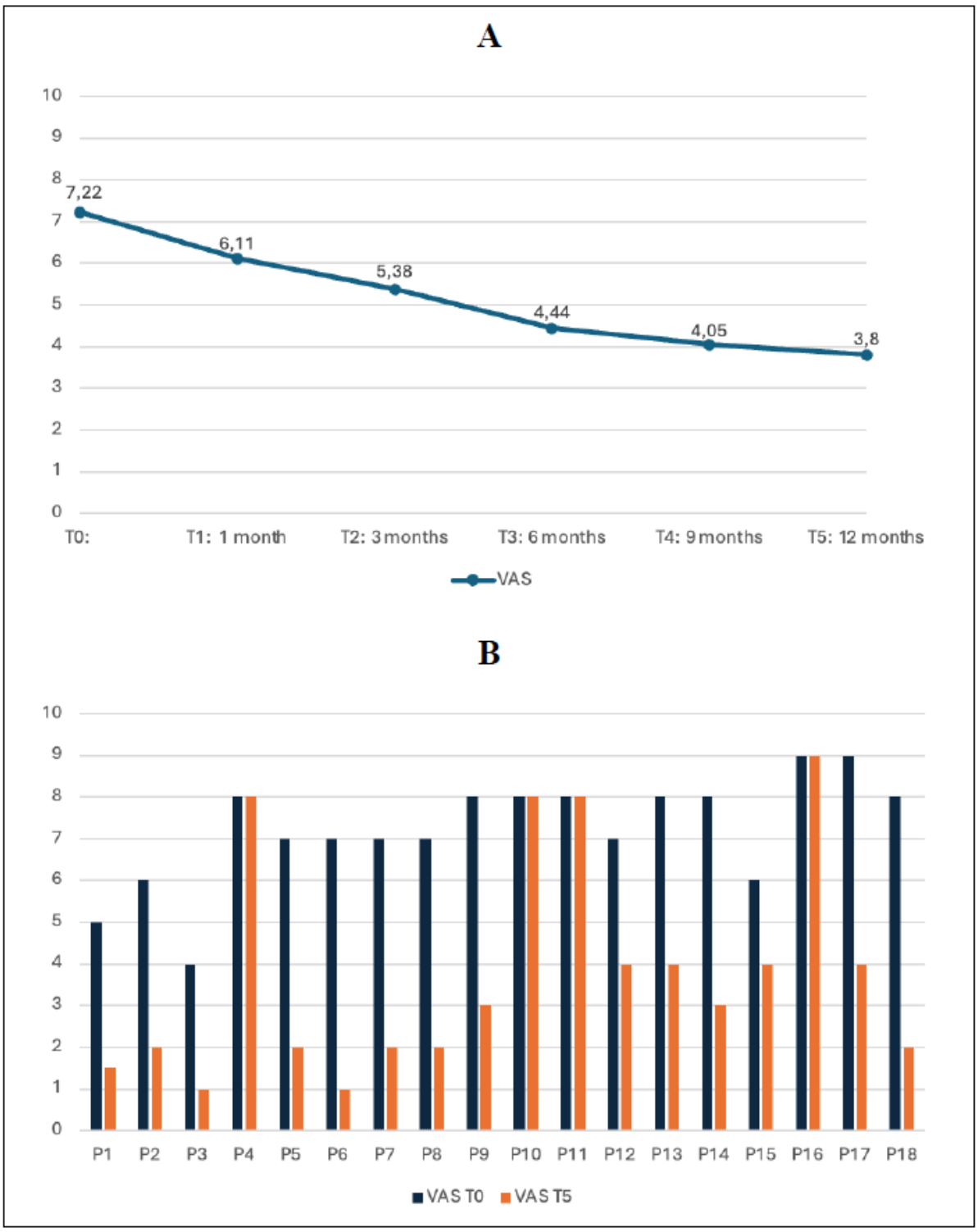

Figure 2: VAS evolution before and one year after the last session of mesotherapy. A: The median score evolution after the mesotherapy sessions. B: Visual analogic individual scores of every patient before and after the sessions. VAS: Visual Analogic Scale. TO: VAS evaluation before the mesotherapy sessions. T5: VAS evaluation at one year after the last session.

The VAS score improved in 14 patients, and did not improve in 4 patients, the median VAS score improved by 3.42 points between the last session and after 1 year (Figure 2). The CSS score also improved in all patients except for one patient; the median score went from 12.77 to 7.11 one year after (Figure 3). The main improvement of VAS and CSS score was during the first six months of mesotherapy, during which they improved by 2.78 and

5.05 respectively. After six months, the improvement in VAS and CSS scores was limited by 0.64 points and 0.61 points, respectively. No adverse effect from mesotherapy was noted or reported by any of the 18 patients and all of them continued their rehabilitation programs during and after the mesotherapy sessions.

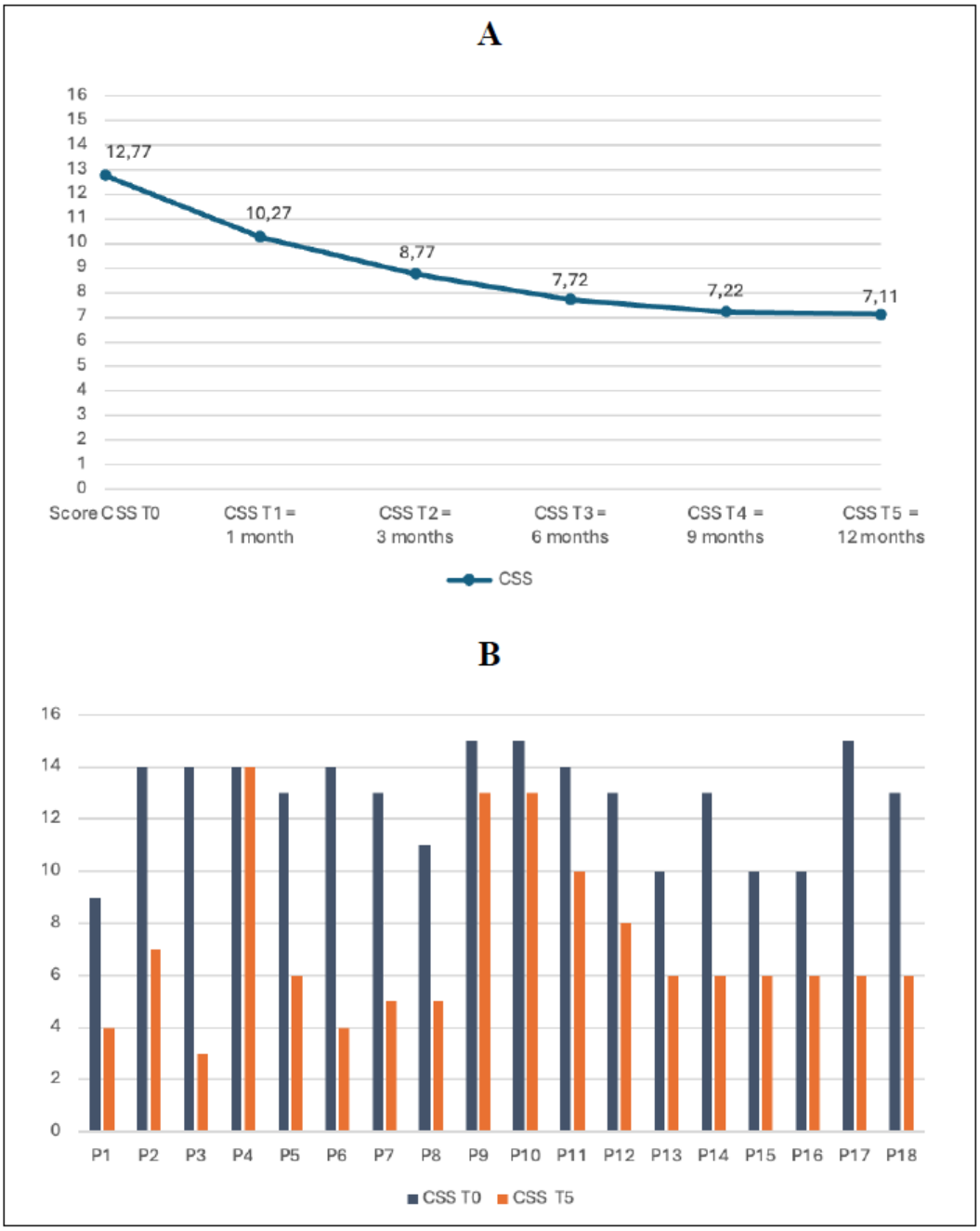

Figure 3: CSS evolution before and one year after the last session of mesotherapy. A: The median score evolution after the mesotherapy sessions. B: Individual CRPS severity scores before and after the sessions. CSS: Complex Regional Syndrome Severity Score. CSS TO: CSS evaluation before the mesotherapy sessions. CSS T4: CSS evaluation at one year after the last session.

DISCUSSION

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) consider CRPS as a rare condition [105,106]. It mainly affects elderly women but can also be seen in young subjects and children [107]. Its incidence increases with age, peaking between the ages of 50 and 80 [108,109]. In our cases, the average

age was 58, and women were much more affected, accounting for 2/3 of patients. Furthermore, the upper limb appears to be more affected than the lower limb in CRPS [109]. Simultaneous involvement of both upper and lower limbs has also been reported [110,111]. The upper limb (wrist, hand, shoulder) was affected in 72% of our case-series, mainly post-stroke and fractures of the lower end of the radius. Patients with lower limb involvement had all presented with a traumatic event of the limb concerned (ankle fractures or sprains). Most patients in this study with a traumatic trigger had prolonged immobilization following the traumatic event. However, these patients did not have a specific medical history. Among the other patients with CRPS complicating a stroke, 3 had a history of hypertension and one was being followed for type 2 diabetes. Several studies have shown that prolonged immobilization is associated with a higher risk of CRPS [107,112]. Moreover, diabetic women with scaphoid fractures were more likely to develop CRPS according to Gong's observational, multicenter study [113].

In addition, Roh and colleagues also investigated factors associated with CRPS in patients surgically treated for distal radius fractures. They concluded that patients with high-energy trauma, severe fractures and female gender were at greater risk of developing CRPS [114]. In the same vein, Lorente's meta-analysis evaluating the incidence and risk factors of CRPS in fractures of the lower extremity of the radius reported an incidence of 13.63% and identified - among other factors - female gender, BMI, psychiatric disorders, complex fracture type, and significant tissue damage as risk factors for the development of CRPS in these fractures [115]. On the other hand, in post-stroke CRPS, several studies have shown a significant association between limb immobility and the occurrence of CRPS [116-118]. A recent meta-analysis evaluating the frequency and risk factors for post-stroke CRPS showed a positive association between upper limb paralysis, spasticity, and shoulder subluxation and the occurrence of CRPS [119]. The value of early rehabilitation and mobilization of the paralyzed limb is therefore essential in the prevention of CRPS. Another protective factor has also been studied, namely vitamin C intake in patients with wrist fractures. The American Academy of Orthopaedic Surgeons (AAOS) recommends the preventive intake of vitamin C (500mg/day for 1 month) to prevent CRPS after distal radius fractures. A validity test of this recommendation was carried out in 2015 showing its practical value [120]. In 2015, a meta-analysis of randomized controlled trials showed a conflicting and non-significant effect of vitamin C intake in the prevention of CRPS [121]. However, several more recent metaanalyses and systematic reviews have shown a positive effect of vitamin C intake in the prevention of CRPS [122-124].

The distinction between type 1 and 2 is controversial, given the clinical indifference and even management recommendations of some authors [125,126]. As mentioned earlier, CRPS type 2 should not be considered as neuropathic pain [46]. In our study, type 1 CRPS was the most common, while patients who presented with neuropathic pain outside the territory of the injured nerves were classified as type 2. In 2010, Harden's team developed the CRPS Severity Score (CSS), which was subsequently validated as a measure of CRPS severity in an international prospective study in 2017, suggesting its usefulness also for clinical follow-up and outcomes research [127,128]. The authors were able to show in the validity study that the calculated value of the smallest real difference showed that a change in CSS of ≥4.9 scale points would indicate real differences in CRPS symptomatology (with a 95% confidence level) [128]. CSS scores in our study before and after sessions showed an improvement of 5.66 at 1 year.

To our knowledge, there are no published studies evaluating the efficacy of mesotherapy in CRPS, and most studies published concern the dermatological and cosmetic use of mesotherapy (androgenic alopecia, acne, cellulite...). Although, a few studies evaluating the efficacy of mesotherapy in other areas of chronic pain, such as chronic musculoskeletal pain have been published, including Brauneis's randomized controlled trial evaluating the efficacy of mesotherapy in spinal pain. Despite the remarkable limitations of this trial, positive results were observed [129]. Another randomized trial comparing the administration of NSAIDs and corticoids by mesotherapy versus the systemic route in acute low-back pain reported positive and similar results in both groups, with better tolerance in the mesotherapy group [130].

Mesotherapy has also been evaluated in chronic low back pain, with Koszela's retrospective study showing positive results from mesotherapy with 1% lignocaine and type 1 collagen at three months' follow-up [131]. Nevertheless, the absence of a control group given the retrospective nature of this study is a very limiting factor. Roconi and his colleagues also evaluated the efficacy of diclofenac versus lysine acetylsalicylate for the treatment of nonspecific chronic low back pain. The results showed an improvement in patients' feelings and functional scores [132]. The retrospective nature and the short three-month follow-up constitute a limiting factor of this study. An Egyptian randomized trial comparing the efficacy of oral versus intradermal NSAIDs in chronic low-back pain patients was published in 2019 [133]. In this trial 25 patients were randomized to each treatment group: The mesotherapy group received 4 weekly sessions of Ketoprofen 100 mg (2 ml) + lidocaine 1% (1 ml) and normal Saline 0,9% (2 ml) and the oral group received Ketoprofen 100 mg / day for 1 month. A significant improvement in VAS within and between the two treatment groups was noted. However, looking at the results, the mean VAS score of the oral group was higher than that of the mesotherapy group. Despite this observation, repeated measurement of the mean VAS score for each group showed a statistically significant reduction. An improvement in functional scores was also reported.

Knee osteoarthritis is another condition where mesotherapy has been tested. Chen's study evaluated the efficacy and safety of mesotherapy in patients followed for knee osteoarthritis [134]. In this study, the authors enrolled 2 groups of patients, one group treated with conventional NSAIDs for 1 month and the second group treated with two mesotherapy mixtures as follows:

-Mix 1: Piroxicam 40 mg (2 ml) + Lidocaine 1% (2 ml) + Calcitonin 100 Ui.
-Mix 2: Procaine 2% (2 ml) + Organic silica (2 ml) + Calcitonin 100 Ui.

The first mixture was administered to patients in the acute phase, while the second mixture was administered in the chronic phase. The results showed similar and significant responses in terms of pain and functional scores with a six-month follow-up. Another Italian observational study assessed the efficacy of mesotherapy for neck pain in fibromyalgia [135].

In this study, the treatment group received mesotherapy sessions based on diclofenac 50mg (2 ml) + thiococolchicoside 4 mg (2 ml) and mepivacaine (10 mg/ml) diluted in 4 ml saline and the control group received saline-based mesotherapy (9 ml). The 7 mesotherapy sessions were performed by the same physiatrist, and the 2

groups received the same rehabilitation protocol (20 sessions). Results obtained at 2 months showed a statically significant improvement in pain in both groups.

Paolucci and his team conducted a systematic review examining new indications for mesotherapy in rehabilitation [136]. Seven studies were included in this review, including randomized and non-randomized trials as well as retrospective studies. Of these 7 studies, 2 treated osteoarthritis of the knee, and 5 treated spinal pathologies (cervicalgia, lumbago, rachialgia). The results showed that mesotherapy improved patients' pain and functional scores. The authors suggest that mesotherapy could be a good therapeutic option in musculoskeletal pain with fewer side effects. Nevertheless, they also highlight the need for a uniform treatment protocol in future randomized trials.

A more recent systematic review with meta-analysis published in 2021 assessed the safety and efficacy of mesotherapy in musculoskeletal pathologies. Seven randomized trials were included in this review [137]. It concludes that mesotherapy is safe, and effective as a treatment for musculoskeletal disorders. Moreover, the results showed that the analgesic effect and functional improvement were significantly more effective with mesotherapy than with systemic therapies in cervicalgia and non-specific low back pain. As for side effects, mesotherapy did not show superior results to systemic therapies [137]. Other side effects reported in the cosmetic use of mesotherapy include skin infections, the development of granuloma annulare, facial oedema, and hypersensitivity reactions [138-140].

Currently, a double-blind randomized controlled trial (MESO-SDRC) evaluating the efficacy of ketamine administered by mesotherapy in SDRC type 1 has been completed (NCT04650074).

In this study, patients are divided into 3 arms:
- Active Comparator group: receiving 4 weekly sessions of mesotherapy based on Lidocaine 20 mg and 2 experimental groups:
- Experimental Group 1: receiving 4 weekly sessions of mesotherapy based on Lidocaine 20 mg + Ketamine 20 mg.
- Experimental group 2: receiving 4 weekly sessions of mesotherapy based on Lidocaine 20 mg + Ketamine 40 mg.

Primary outcomes are VAS before the sessions and after 2 months (Day 56).

Other secondary outcomes will be measured in this study, notably

- Changes in VAS before each mesotherapy session and at two months' follow-up.
- The Brief Pain Inventory (BPI) self-assessment score, also calculated during the sessions and at day 56.
- Side effects up to two months' follow-up
- EQ-5D-5L score (EuroQol health states):
- Visual analog scale and ranking of side effects (benefit/risk balance).

In summary, the need for more randomized controlled trials, and more standardized protocols is clear to define the role of mesotherapy in CRPS.

CONCLUSION

This retrospective case series is limited but suggests a potential positive effect of mesotherapy in treating CRPS patients. Nevertheless, reliable conclusions can only be drawn from future randomized and controlled studies.

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Author Contributions

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DECLARATIONS

Ethics Approval and Consent to Participate

Local institutional ethics board approval is not required for case reports or case series and thus was not obtained.

Consent for Publication

Written informed consent for inclusion in this case series was obtained from all patients.

Competing of Interest

The authors state no conflict of interest.

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