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Treatment Modalities Of Complex Regional Pain Syndrome After Hand Surgery A Systematic Review and Meta-Analysis Study

Ali Ahmed Mahmoud Hassan, [1] M.B.B.CH, Fawzy Ahmed Hamza, [1] MD, Tarek El bastawesy Zayid, [1] MD.

** Corresponding Author:*
Ali Ahmed Mahmoud Hassan
alibakkar2017@gmail.com

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[1]Plastic Surgery And Burn Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

ABSTRACT

Background: complex regional pain syndrome is a complex medical condition. Physical/occupational treatments, psychiatric counseling, neuropathic pain medicines, anti-inflammatories, and surgical intervention are utilized to treat complex regional pain syndrome (CRPS).
Aim of the study: The aim of this work is to do meta-analysis study of complex regional pain syndrome treatment modalities after hand surgery in most recent literatures.
Patients and Methods: After full-text screening 12papers were included in this systemic review and meta-analysis.This research was conducted and reported following PRISMA (for systematic review and meta-analysis recommended reporting items). From 2016 to 2021.
Results: 10 studies showed Responders with a high event in bisphosphonate than in Ketamine study with highly significant heterogeneity among included studies p-value 0.0005. 12 studies were included 6 studies showed adverse events with highly significant heterogeneity p-value <0.0001.
Conclusion: Although there has yet to be good therapy for CRPS, years of study have taught us a lot about the disorder and our knowledge of it is still growing. Furthermore, in comparison to CRPS type I, the evidentiary foundation for CRPS type II is limited. As a result, further research is required to determine which patient subgroups might benefit the most from presently available treatments. Because of the syndrome's complexity, focusing on a single mechanism is unlikely to be beneficial. Therapy combination, like with other chronic disorders, maybe the future of CRPS management, and research into this will be required.

Keywords: *Complex Regional; Hand Surgery; Pain Syndrome.*

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a condition marked by persistent pain that seems to be disproportionate in duration or severity to the course of any recognized trauma or another injury. The pain is regional rather than dermatomal, and aberrant sensory, motor, sudomotor, vasomotor, and/or trophic abnormalities frequently predominate towards the distal end. The condition progresses in a variety of ways throughout time. [1]

CRPS is classified into many groups depending on whether or not a primary nerve injury is found. When no apparent significant nerve injury is present, type I is historically compatible with reflex sympathetic dystrophy, and type II is historically consistent with causalgia when nerve damage is present. The authors of the 2013 clinical recommendations additionally added a CRPS not otherwise described category, which includes cases when the diagnostic criteria are not fully satisfied but the symptoms are not explained by any other diagnosis or entity. [2]

The pathogenesis of CRPS is now widely acknowledged as a complex procedure with both peripheral and central features. [3]

In most cases, symptoms and signs appear about one month from the initial trauma; the others may be delayed for months. The severity of pain and edema vary from one to another. The features of CRPS remain in chronic patients, causing mild morbidity while the majority cure within a year. [4]

Because early CRPS is generally straightforward to cure, the prognosis is excellent, and complete

recovery may be predicted within an acceptable time frame, early diagnosis and treatment of CRPS seem to be advantageous. Chronic CRPS, on the other hand, is a debilitating disorder with a bad prognosis and few therapy choices. Early detection of CRPS, as well as fast treatment, is critical to prevent irreversible loss of function. Patients who do not improve with physical and occupational therapy are usually given medication, psychological counseling, and interventional treatments. [5]

The goal of the research was to perform a meta-analysis of complex regional pain syndrome therapeutic options after hand surgery.

PATIENTS AND METHODS

This study was carried out and reported following PRISMA (for systematic review and meta-analysis recommended reporting items).

Strategy for research: PubMed, PLOS, and Cochrane central register of controlled trials, as well as Scopus and Clarivate, were used to perform the search. Treatment methods for complex regional pain syndrome were the search phrase. The past five years were the time limit. Each publication or report found via the search had its reference list evaluated, as well as any previously published meta-analysis.

Criteria and modes of study selection: We included publications in any language on the area of interest, and two of our seniors worked separately from each other, resolving disagreements by consensus.

Evaluation of study quality: The Cochrane risk of bias tool utilized to assess the risk of bias in the included investigations: Biases in selection, attrition, detection, and performance

Data collection and analysis: Published data, journal name, country and patient demographics, prevention and treatment options

Analytical statistics: Rev Man was used to examining the data.

The research evaluated contemporary treatment options for complex regional pain syndrome after hand surgery.

RESULTS

The database search resulted in a total of 41 articles. 10 articles were excluded as they were duplicated. 13 were excluded because they referred to the contribution of non-anesthesia providers (e.g., acupuncturists) or employed techniques that are not commonly used (e.g., manual lymphatic drainage, low-level laser therapy, trans cranial stimulation). Another 6 trial was excluded because they did not analyze data, After full-text screening 12papers were included in this systemic review and meta-analysis (Figure 1).

Fig 1: flow chart of the study.

12 studies were included showing complex regional pain syndrome treatment modalities following hand surgery.

Author	type of study
Alimian M et al. 6	RCT
Eriksen LE et al. 7	Retrospective
Strauss S et al. 8	RCT
Kirkpatrick AF et al. 9	Retrospective
Eraghi AS et al. 10	RCT
Park S et al. 11	Retrospective
Kotiuk V et al.12	RCT
Park J et al. 13	Retrospective
Goebel A et al.14	RCT
Varenna M et al.15	Retrospective
Sadatsune EJ et al.16	RCT
Alkosha HM et al.17	Retrospective

Table 1: Study characteristics.

Among included 12 studies 6 were retrospective and 6 were RCT as shown in table 1.

There were several methods of treatment in included studies vitamin C, Spinal cord stimulation, graded motor imagery (GMI), Ketamine, Aspirin, steroids, mirror therapy, sympathetic ganglion block,

Immunoglobulin, bisphosphonate, Gabapentin, and Thoracic Sympathectomy as shown in (Table 2).

Author	Treatment method
Alimian M et al. 6	vitamin C
Eriksen LE et al. 7	Spinal cord stimulation
Strauss S et al. 8	graded motor imagery (GMI)
Kirkpatrick AF et al. 9	Ketamine
Eraghi AS et al. 10	Aspirin
Park S et al. 11	Steroids
Kotiuk V et al.12	mirror therapy
Park J et al. 13	sympathetic ganglion block
Goebel A et al.14	Immunoglobulin
Varenna M et al.15	Bisphosphonate
Sadatsune EJ et al.16	Gabapentin
Alkosha HM et al.17	Thoracic Sympathectomy

Table 2: Method of treatment.

A total of 633 cases were included with male\female 214\387, mean age 50.015 years as shown in (Table 3).

As regards side affected was right in (48) and left in (36) and the mean disease duration was 30.3 months as shown in (Table 4).

Disease subtype was warm(237), cold (52), NA(21) as regard localization was Upper limb in (158) cases and Lower limb in (119) cases, as regard Predisposing event was either due to distal radius fractures, wrist fracture, other surgeries, carpal tunnel surgical intervention, cervical spine, Ischemic cerebral infarction, Hemorrhagic cerebral infarction, Traumatic brain injury, as shown in (Table 5).

10 studies showed Responders with the high event in bisphosphonate then in Ketamine study with highly significant heterogeneity among included studies p-value 0.0005. (Table 6).

12 studies were included 6 studies showed adverse events with highly significant heterogeneity p-value <0.0001. **(Table 7).**

Author	number	age	m\f
Alimian M et al. 6	35	45	22\13
Eriksen LE et al. 7	51	51.3	19\32
Strauss S et al. 8	20	54.2	3\17
Kirkpatrick AF et al. 9	114	39.7	25\89
Eraghi AS et al. 10	15	60.27	8\7
Park S et al. 11	34	63.4	14\20
Kotiuk V et al.12	30		
Park J et al. 13	15	48	11\4
Goebel A et al.14	52	43.7	19\33
Varenna M et al.15	194	57.1	72 /122
Sadatsune EJ et al.16	20	51.5	0\18
Alkosha HM et al.17	53	47	21\32

Table 3: Patient's characteristics.

Author	Side	Disease duration (month)
Alimian M et al. 6		
Eriksen LE et al. 7		38.4
Strauss S et al. 8	right(15),left(5)	61
Kirkpatrick AF et al. 9		70.8
Eraghi AS et al. 10	right(12),left(3)	1.2
Park S et al. 11	right(14),left(20)	1.6
Kotiuk V et al.12		
Park J et al. 13	right(7),left(8)	63.5
Goebel A et al.14		27.6
Varenna M et al.15		4
Sadatsune EJ et al.16		
Alkosha HM et al.17		5

Table 4: Side and disease duration.

Author	Disease subtype,	Localization	Predisposing event
Alimian M et al. 6			distal radius fractures
Eriksen LE et al. 7	warm(38) ,cold (13),		
Strauss S et al. 8		Upper limb(20)	wrist fracture(4),other surgery(8),carpal tunnel surgical intervention(5),cervical spine (2)
Kirkpatrick AF et al. 9			
Eraghi AS et al. 10			extra-articular distal radius fractures
Park S et al. 11			Ischemic cerebral infarction (12), Hemorrhagic cerebral infarction(14), Traumatic brain injury(8)

Kotiuk V et al.12			distal radius fractures (30)
Park J et al. 13	warm(13) ,cold (2),	upper limb(15)	
Goebel A et al.14	warm(44) ,cold (6),NA(2)		
Varenna M et al.15	warm(142) ,cold (31),NA(21)	Upper limb(75),Lower limb(119)	Fracture(83),Trauma(43),Surgery(28),Others(11),Unknown(29)
Sadatsune EJ et al.16		upper limb(18)	Carpal tunnel syndrome surgery(18)
Alkosha HM et al.17			In this research, crushing injuries were the most prevalent mechanism of injury (30 cases, or 56.6 percent), followed by clean-cut injuries (18 cases, or 34 percent), traction injuries (3 cases, or 5.7 percent), and lastly, other injuries (3 cases, or 5.7 percent). gunshot wounds (2 cases, 3.8 percent)

Table 5: Characteristics of the syndrome.

Study	Total number	Event	Event rate (%) (Proportion)	(LL–UL) 95% CI of rate (%)
Alimian M et al. 6	35	27	77.143	59.864 – 89.579
Eriksen LE et al. 7	51	45	88.235	76.132 – 95.558
Strauss S et al. 8	114	101	88.596	81.289 – 93.786
Kirkpatrick AF et al. 9	15	15	100.000	78.198 – 100.000
Eraghi AS et al. 10	30	25	83.333	65.279 – 94.358
Park J et al. 13	15	11	73.333	44.900 – 92.213
Goebel A et al.14	52	35	67.308	52.895 – 79.670
Varenna M et al.15	194	139	71.649	64.751 – 77.874
Sadatsune EJ et al.16	20	14	70.000	45.721 – 88.107
Alkosha HM et al.17	53	43	81.132	68.028 – 90.563
Total (fixed effects)	579		78.931	75.412 – 82.157
Total (random effects)	579		80.103	73.270 – 86.148
Test for heterogeneity				
Q	29.6614			
Significance level	0.0005*			
I2 (inconsistency)	69.66%			
95% CI for I2	41.70 – 84.21			

Table 6: Meta-analysis for Responders.

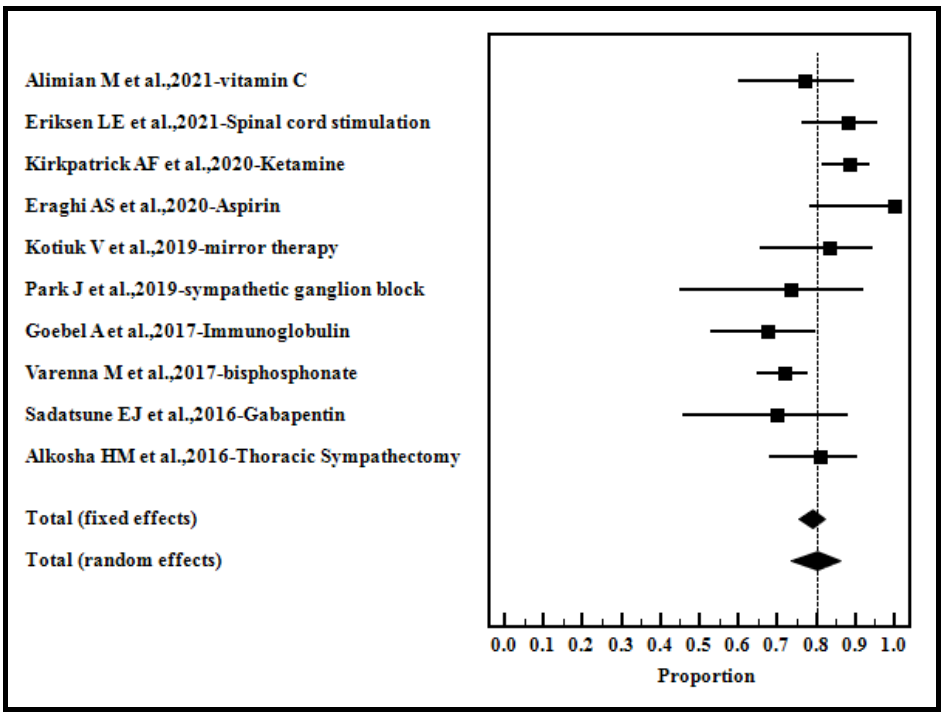

Fig 2: Forest plot for Responders.

Study	Total number	Event	Event rate (%) (Proportion)	(LL – UL) 95% CI of rate (%)
Alimian M et al. 6	35	0	0.000	0.000 – 10.003
Eriksen LE et al. 7	51	0	0.000	0.000 – 6.978
Strauss S et al. 8	20	0	0.000	0.000 – 16.843
Kirkpatrick AF et al. 9	114	64	56.140	46.536 – 65.418
Eraghi AS et al. 10	15	4	26.667	7.787 – 55.100
Park S et al. 11	34	1	2.941	0.0744 – 15.327
Kotiuk V et al.12	30	0	0.000	0.000 – 11.570
Park J et al. 13	15	0	0.000	0.000 – 21.802
Goebel A et al.14	52	1	1.923	0.0487 – 10.255
Varenna M et al.15	194	50	25.773	19.775 – 32.528
Sadatsune EJ et al.16	20	7	35.000	15.391 – 59.219
Alkosha HM et al.17	53	0	0.000	0.000 – 6.723
Total (fixed effects)	633		15.088	12.413 – 18.086
Total (random effects)	633		8.339	1.282 – 20.708
Test for heterogeneity				
Q	213.5867			
Significance level	<0.0001*			
I2 (inconsistency)	94.85%			
95% CI for I2	92.61 – 96.41			

Table 7: Meta-analysis for adverse events. (Q: Total variance for heterogeneity; I^2: Observed variance for heterogeneity; CI: Confidence interval (LL: Lower limit–UL: Upper Limit).

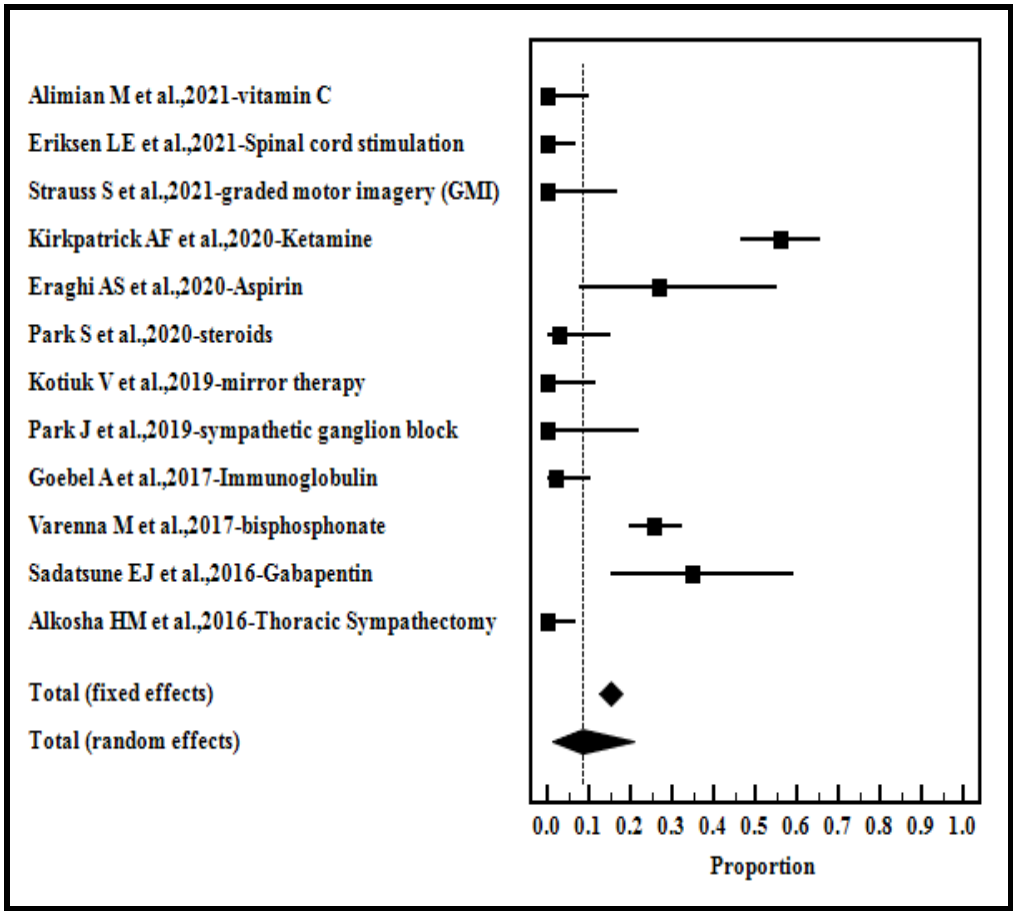

Fig 3: Forest plot for adverse events.

DISCUSSION

The treatment for CRPS is mainly dealt symptomatically with a combination of physical/occupational therapies, psychological therapy, neuropathic pain medications, anti-inflammatories and interventional procedures.[37]

Karri et al., [18] published a systematic study in 2021 that focuses on CRPS in children and explores neuromodulation, a well-known therapy option for adults, for pediatric patients. In the pediatric population, the key aims of CRPS therapy are pain reduction and improvement in all areas of functioning to enhance the patient's life quality. Intensive physical treatment is used in conjunction with cognitive-behavioral therapy. Pediatric patients may be assessed for neuromodulation procedures like spinal cord stimulation (SCS) in addition to dorsal root ganglion stimulus (DRG) devices, among other therapies under the standard of care approach. [19]

A total of 12 studies were included showing complicated regional pain syndrome treatment modalities following hand surgery. Among included 12 studies 6 were retrospective and 6 were RCT. A total of 633 cases were included with male\female was 214\387, mean age 50.015 years.

In comparison with the systematic review of Tran et al., [20] in which the search criteria turned in 41 RCTs, each with an average of 31.7 participants. In 70.7 percent and 19.5 percent of RCTs, respectively, blinded evaluation and sample size rationale were given, the best treatment results were with bisphosphonate treatment.

Another research by Eraghi et al. [21] was done at Rasoul Akram Hospital in Tehran, Iran, from August 2016 to September 2017. It was a double-blind, randomized controlled experiment. CONSORT (Consolidated Standards of Reporting Trials) criteria were followed by the authors. A total of 179 individuals were investigated, with each fracture being analyzed separately. There was no variance in gender between patients with CRPS and non-CRPS patients. Patients with CRPS had a substantially greater average age (P=0.008).

Symptomatic management for CRPS involves a mix of physical/occupational treatments, psychosocial counseling, neuropathic pain medicines, anti-inflammatories, and surgical intervention. [22] The efficacy of many of the drugs used to treat CRPS is predicated on their efficacy in treating neuropathic pain. The number of medications that have undergone CRPS trials is small, and the data is presented in this review. This review also covers the results of neuromodulation trials including spinal cord stimulating (SCS) and dorsal root ganglion (DRG) stimulus. Many of the treatment methods for CRPS have insufficient evidence to support their usefulness, and further study is needed. [23]

In the current metanalysis; there were several methods of treatments in included studies vitamin C, Spinal cord stimulation, graded motor imagery (GMI), Ketamine, Aspirin, steroids, mirror therapy, sympathetic ganglion block, Immunoglobulin, bisphosphonate, Gabapentin, and Thoracic Sympathectomy.

On the other hand; Duong et al., [24] in which There were 41 RCTs found using the original criteria. Five of them were eliminated because they mentioned non-anesthesia providers (such as acupuncturists) or utilized procedures that were not widely used (e.g., Low-level laser treatment, TMS stimulation, and manual lymphatic drainage). Another experiment was eliminated because the data from the placebo group was not analyzed. 14 RCTs looked into pharmacologic therapies, four looked into neuraxial blocks, and three looked into spinal cord/dorsal root ganglion stimulation. Eight and six research, respectively, looked at intravenous/peripheral sympathetic blocks and adjuvant therapy.

In research by Eraghi et al.,[21] a total of 103 patients with unilateral, extra-articular distal radius fractures took part in the research for 14 months. Fifty-one individuals were given aspirin and the other fifty-two were given placebos.

In a Cochrane review of Smart et al.,[25] 18 randomized controlled trials (RCTs) on physiotherapy-based therapies (n=739) were investigated. The majority of the studies looked at were of 'poor' quality or had a 'high' risk of bias. Despite these flaws, the Cochrane review identified two medicines with the greatest available evidence that might help CRPS I patients improve their pain and function. Graded motor imagery (GMI) and mirror therapy are two extremely comparable treatments.

In terms of the afflicted side, we discovered that the affected side was right in 48 cases and left in 36 cases, with a mean illness duration of 30.3 months.

In comparison with the study of Bean et al., [26] which reported that the majority of the patients were women, and most of them had upper-limb problems. The average illness duration was 62.75 (24.3) days.

In another retrospective study by Massimo et al., [27] in which the average age at CRPS-I identification was 57.1 ± 12.9 years, with a higher percentage of females (122, 62.9%) and no difference in average age at detection between men and females (P = 0.28). The median duration of the disorder was four months (IQR= 2–6). The lower extremity (foot) was more often afflicted than the upper limb (hand), with 119 patients (61.3%) having foot disease and 75 having hand illness (38.7 percent). Thirteen patients (6.7%) had previously been diagnosed with CRPS-I, which had more typically included another location (10 cases).

In addition to the above findings, the current review reported that the disease subtype was warm (237), cold (52), NA (21) as regard localization was Upper limb in (158) cases and Lower limb in (119) cases, as regard Predisposing event was either due to distal radius fractures, wrist fracture, other surgery, carpal

tunnel surgical intervention, cervical spine, extra-articular distal radius fractures, Ischemic cerebral infarction, Hemorrhagic cerebral infarction, Traumatic brain injury, Carpal tunnel syndrome surgery, In this research, crushing injuries were the most prevalent kind of injury, followed by clean-cut injuries, traction injuries, and gunshot injuries.

Jankovic, [28] was conducted and reported that the average age of CRPS patients is 36 to 46 years old, with women accounting for 60% to 80% of cases. A fracture (16 percent–46 percent), strain or sprain (10 percent–29 percent), post-surgery (3 percent–24 percent), and contusion or crush damage (8 percent–18 percent) are the most common causes. Pain, edema, and autonomic malfunction, like changes in temperature or color in the affected limbs, motor impairment, and psychological disorders, such as depression, are common clinical characteristics of CRPS. Sidawy, [29] CRPS spreads in three phases, according to the study. Early on, CRPS usually affects just one limb, causing discomfort, mild edema, and a rise in skin temperature. CRPS has the potential to spread from one limb to the other. In its latter stages, CRPS may affect the whole body as well as the four extremities, causing extreme pain, edema, cold and cyanotic limbs, joint rigidity, and muscle and bone atrophy.

In the current metanalysis; we found that adverse event showed in 127 cases mostly with Ketamine and bisphosphonate and was in form of stomach upset in 47 cases, respiratory depression in 9 cases, Headache in 10 cases, moderate hypocalcemia in 1 case, acute phase reaction in 48 cases, acute anterior uveitis in 1 case, dizziness in 3 cases, drowsiness in2 cases, tinnitus in 2 cases and pin tract infections in 4 cases. Moreover; 12 studies were included 6 studies showed adverse events with highly significant heterogeneity p-value <0.0001.

Bisphosphonates are extensively utilized in the treatment of CRPS, according to data from several modest RCTs that have shown considerable benefits. [30]. Bisphosphonates are thought to have a role in controlling inflammatory mediators, as well as the proliferation and migration of bone marrow cells, while the specific mechanism is unknown[22]. Young et al., 19 compared the use of three 60 mg intravenous pamidronate infusions to oral prednisolone in 21 post-stroke CRPS patients and showed that pamidronate was equally as efficacious for pain management.

Chevreau et al., [32] published a meta-analysis in which four RCTs with a total of 181 patients found that bisphosphonates significantly reduced pain in patients with CRPS-1 when compared to placebo, confirming the effectiveness and safety of bisphosphonates in the management of CRPS.

In addition to the above findings, 10 studies showed responders with a high event in bisphosphonate then in Ketamine study with highly significant heterogeneity among included studies p-value 0.0005.

The meta-analysis results of Zhao et al., [33] revealed that in comparison to the self-controlled baseline, the Ketamine therapy resulted in a lower average pain score (p <0.000001). However, between-study heterogeneity has statistical significance. The occurrence rate for immediate pain alleviation was 69 percent (95 percent confidence interval (CI) 53 percent, 84 percent). The pain alleviation event rate was 58 percent at the 1–3-month follow-ups (95 percent CI 41 percent, 75 percent). The currently available research on ketamine infusion for CRPS was evaluated, and meta-analyses were undertaken to assess ketamine infusion's effectiveness in the treating of CRPS. Their results showed that ketamine infusion may give clinically efficient pain-relieving for less than three months in the short term.

Bisphosphonates have also been studied in two further RCTs for CRPS. Varenna et al., [34] found that a ten-day intravenous infusion (100 mg qid every third day) of neridronate, an amino-bisphosphonate chemically identical to alendronate and pamidronate, resulted in decreased pain ratings at 20 and 40 days when compared to placebo. Moreover, at day 40, the neridronate group had a higher percentage of patients with a pain reduction of ≥ 50% (73.2 percent vs 32.5 percent, respectively; P = 0.0003), lower edema, less pain with passive motion, and a lower incidence of both allodynia (15 percent vs 50 percent; P < 0.0001) and hyperalgesia (12.5 percent vs 61.1 percent; P = 0.0027) than the placebo group. Young et al. [31] In the second research, hemiplegic stroke patients with CRPS were compared to a two-week tapering course of oral prednisolone vs six-day intravenous pamidronate (60 mg TID every other day) regimen. These researchers discovered that prednisolone reduced wrist circumference more than palmidronate did at one, two, and four weeks, while palmidronate reduced pain ratings more at one and two weeks.

Finally, we found that 6 studies comparing Average baseline pain score pre and post-treatment show highly significant heterogeneity p-value <0.0001

Fischer et al. [35] randomized 56 CRPS patients to a five-day regimen of intravenous magnesium (70 $mg.kg^{-1}$ over four hours each day) or saline in 2013. At one, three, six, and twelve weeks following the commencement of therapy, no intergroup variations in Impaired Level Sum Scores or pain (11-point BOX scale) were identified. Van der Plas et al., [36] looked at the advantages of injectable magnesium in individuals with CRPS-related dystonia. The subjects were given either injectable magnesium (escalating daily dosages of 1,000 to 2,000 mg) or saline for three weeks. They received the other medication after a one-week washout period; no intergroup variations in dystonia were identified. However, these findings should be taken with care since van der Plas et al., [36] abruptly ended the experiment (after enrolling only 22 out of a planned 40 patients) due to recruiting difficulties.

CONCLUSION

In conclusion, although there has yet to be good therapy for CRPS, years of study have taught us a lot about the disorder, and our knowledge of it is still growing. A CRPS population is varied, with various subgroups presenting different clinical and biochemical traits, resulting in a wide range of therapeutic responses. Furthermore, in comparison to CRPS type I, the evidentiary foundation for CRPS type II is limited. As a result, further research is required to determine which patient subgroups might benefit the most from presently available treatments. Because of the syndrome's complexity, focusing on a single mechanism is unlikely to be beneficial. Combination therapy, like with other chronic disorders, maybe the future of CRPS management, and research into this will be required.

Conflict of interest : none

REFERENCES

1. Bruehl S. Complex regional pain syndrome. *BMJ*. 2015; 351:2730.

2. Harden RN, Oaklander AL, Burton AW, et al. Reflex sympathetic dystrophy syndrome association. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med*. 2013; 14:180–229.

3. Ortiz-Romero J, Bermudez-Soto I, and Torres-Gonzalez R. Factors associated with complex regional pain syndrome in surgically treated distal radius fracture. *Acta. Ortop. Bras.* 2017; 25:194–6.

4. HAMZA F., Salem A., Nassar L, et al. CLINICAL PICTURE OF CRPS, In; Type II Complex Regional Pain Syndrome: The Possible Role of Mast Cells , PHD plastic surgery thesis, AL-Azhar University library, Cairo, Egypt. 2016; 10.

5. Stanton-Hicks M, Baron R, Boas R, et al. Complex Regional Pain Syndromes: guidelines for therapy. *Clin J Pain*. 1998; 14(2): 155-66.

6. Alimian M, Eraghi AS, Chavoshizadeh SA, et al. Regional vitamin C in Bier block reduces the incidence of CRPS-1 following distal radius fracture surgery. *European Journal of Orthopaedic Surgery & Traumatology*. 2021; 31:689–93

7. Eriksen LE, Terkelsen AJ, Blichfeldt-Eckhardt MR, et al. Spinal cord stimulation in severe cases of complex regional pain syndrome: A retrospective cohort study with long-term follow-up. *Eur J Pain.* 2021;00:1–14.

8. Strauss S, Barby S, Hartner J, et al. Modifications in FMRI Representation of Mental Rotation Following a 6 Week Graded Motor Imagery Training in Chronic CRPS Patients. *The Journal of Pain.* 2021; 6: 680−91

9. Kirkpatrick AF, Saghafi A, Yang K, et al. Optimizing the Treatment of CRPS With Ketamine. *Clin J Pain*. 2020; 36(7):516-23.

10. Eraghi AS, Khazanchin A, Hosseinzadeh N, et al. A randomized controlled trial on Aspirin and complex regional pain syndrome after radius fractures. *Eur J Transl Myol*. 2020;30 (1): 1-8

11. Park S, Kim HJ, Kim DK, et al. Use of Oral Prednisolone and a 3-Phase Bone Scintigraphy in Patients with Complex Regional Pain Syndrome Type I. *Healthcare*. 2020; 8:16

12. Kotiuk V, Burianov O, Kostrub O, et al. The impact of mirror therapy on body schema perception in patients with complex regional pain syndrome after distal radius fractures. *Br J Pain.* 2019;13(1):35-42.

13. Park J, Lee YJ, Kim ED, et al. Clinical effects of pulsed radiofrequency to the thoracic sympathetic ganglion versus the cervical sympathetic chain in patients with upper extremity complex regional pain syndrome. A retrospective analysis. *Medicine*. 2019; 98: 14282.

14. Goebel A, Bisla J, Carganillo R, et al. Low Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome. *Ann Intern Med*. 2017;167:476-83.

15. Varenna M, Manara M, Rovelli F, et al. Predictors of Responsiveness to Bisphosphonate Treatment in Patients with Complex Regional Pain Syndrome Type I: A Retrospective Chart Analysis. *Pain Medicine*. 2017; 18: 1131–8

16. Sadatsune EJ, Leal PDC, Cossetti RJD, et al. Effect of preoperative gabapentin on pain intensity and development of chronic pain after carpal tunnel syndrome surgical treatment in women: a randomized, double-blind, placebo-controlled study. *Sao Paulo Med J.* 2016; 134(4): 285-91

17. Alkosha HM, Elkiran YM. Predictors of long-term outcome of thoracic sympathectomy in patients with complex regional pain syndrome type 2. *World Neurosurgery*. 2016; 92:74-82.

18. Karri J, Palmer JS, and Charnay A. Utility of electrical neuromodulation for treating chronic pain syndromes in the pediatric setting: a systematic review. *Neuromodulation.* 2021.

19. Taylor SS, Noor N, and Urits I. Complex Regional Pain Syndrome: A Comprehensive Review. *Pain Ther*. 2021; 10: 875–892.

20. Tran DH, Duong S, and Bertini P. Treatment of complex regional pain syndrome: a review of the evidence. *Can J Anesth/J Can Anesth*. 2010; 57: 149–66.

21. Eraghi AS, Khazanchin A, Hosseinzadeh N, et al. A randomized controlled trial on Aspirin and complex regional pain syndrome after radius fractures. *Eur J Transl Myol*. 2020; 30(1): 8643.

22. Urits I, Shen AH, Jones MR, et al. Complex regional pain syndrome, current concepts, and treatment options. *Curr Pain Headache Rep*. 2018; 22:10.

23. Vas L, and Pai R. Musculoskeletal ultrasonography to distinguish muscle changes in complex regional pain syndrome type 1 from those of neuropathic pain: an observational study. *Pain Pract*. 2016; 16: 1–13.

24. Duong S, Bravo D, and Todd KJ. Treatment of complex regional pain syndrome: an updated systematic review and narrative synthesis. *Can J Anesth/J Can Anesth*. 2018; 65: 658–684.

25. Smart KM, Wand BM, and O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. *Cochrane Database Syst Rev.* 2016; 2: 10853.

26. Bean DJ, Johnson MH, Heiss-Dunlop W, et al. Extent of recovery in the first 12 months of complex regional pain syndrome type-1: A prospective study. *Eur J Pain*. 2016; 20(6): 884-94.

27. Massimo V, Maria M, Francesca R, et al. Predictors of Responsiveness to Bisphosphonate Treatment in Patients with Complex Regional Pain Syndrome Type I: A Retrospective Chart Analysis, *Pain Medicine*. 2017; 18 (6): 1131–8.

28. Jankovic J, Mazziotta JC, Newman NJ, et al. Diagnosis of neurological disease. *Bradley and Daroff's Neurology in Clinical Practice. 8th ed. Philadelphia, PA: Elsevier*. 2022.

29. Sidawy AP, and Perler BA. Rutherford's vascular surgery and endovascular therapy. *Elsevier health sciences*. 2018; Apr 3

30. Żyluk A, and Puchalski P. Effectiveness of complex regional pain syndrome treatment: a systematic review. *Neurol Neurochir Pol*. 2018; 52(3): 326–33.

31. Young HE, Hyeyun K, and Hee IS. Pamidronate effect compared with a steroid on complex regional pain syndrome type I: pilot randomised trial. *Neth J Med*. 2016; 74(1): 30–5.

32. Chevreau M, Romand X, Gaudin P, et al. Bisphosphonates for treatment of Complex Regional Pain Syndrome type 1: a systematic literature review and meta-analysis of randomized controlled trials versus placebo. *Jt Bone Spine*. 2017; 84(4): 393–9.

33. Zhao J, Wang Y, and Wang D. The Effect of Ketamine Infusion in the Treatment of Complex Regional Pain Syndrome: a Systemic Review and Meta-analysis. *Curr Pain Headache Rep.* 2018; 22(2): 12.

34. Varenna M, Adami S, Rossini M. Treatment of complex regional pain syndrome type 1 with neridronate: a randomized, double-blind, placebo-controlled study. *Rheumatology (Oxford)*. 2013; 52: 534-42.

35. Fischer SG, Collins S, Boogaard S, et al. Intravenous magnesium for chronic complex regional pain syndrome type 1 (CRPS-1). *Pain Med*. 2013; 14: 1388-99.

36. van der Plas AA, Schilder JC, Marinus J, et al. An explanatory study evaluating the muscle relaxant effects of intramuscular magnesium sulfate for dystonia in complex regional pain syndrome. *J Pain*. 2013; 14: 1341-8.

37. Urits I, Shen AH, Jones MR, et al. Complex regional pain syndrome, current concepts and treatment options. *Curr Pain Headache Rep*. 2018; 22:10.