

# Intravenous treatment with biphosphates in Complex Regional Pain Syndrome

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**Abstract.** *Background and aim of the work:* Complex Regional Pain Syndrome (CRPS) is a pathological persistence of spontaneous or evoked disproportionate pain after a tissue injury. Several drugs are employed, but only bisphosphonates seem to have good outcomes. Bone resorption is the responsible of the demineralization and pain. The purpose of our research is to analyze the characteristics of the cases victims of CRPS of upper extremity and study the beneficial effect of the intravenous neridronic acid sodium salt (Nerixia®), in an attempt to improve the results in this disabling disease. *Materials and methods:* We retrospectively examined 30 cases of CRPS that had undergone intravenous neridronic acid sodium salt therapy in our center. The patients were contacted after 12 months from the start of therapy and their clinical situation was assessed with Quick- Disability of the Arm, Shoulder and Hand (DASH). *Results:* The average age of our group was 59,76 years (span, 42–78), and female subjects were 84% (p-value <0.05). 72% of all cases were complications of wrist fractures. There's no relation between the onset of symptoms and the kind of first treatment (conservative or surgical) (p-value >0.05). The DASH Score (19 points are the best result, 95 the worst outcome) average was 41,1 points. The values of differed significantly (p-value <0.001) according to the age of the patient: 100% of patients under the age of 40 years had obtained a score below compared to the general average (< 41,1 points). In addition, the DASH Score values were related to the sex of the patient (p-value <0.001). Male subjects have obtained a better score (> 41,1 points). After 12 months of intravenous therapy, 52% of cases reports that they still have joint stiffness. The DASH values differed significantly depending on the onset of intravenous treatment (p-value <0.001): 100% of the subjects who have had the treatment in lesser than 3 months from the onset of symptoms have obtained worse result than the average of all our population. The 68% of all sample reported to have obtained a subjective improvement of symptoms after the therapy with the neridronic acid (p-value < 0.05). *Conclusion:* Our study showed that the CRPS affects a population between 42 and 78 years, especially women. Treatment with intravenous bisphosphonates seems to lead to an improvement in CRPS symptoms, in particular administration between 3 and 6 months after the onset of the disease. In particular, women over 61 years of age seem to have a lower improvement in symptomatology after treatment. 52% of cases report that they still have joint stiffness. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Complex Regional Pain Syndrome, intravenous biphosphates.

## Background and aim of the work

Complex Regional Pain Syndrome (CRPS) is a pathological persistence of spontaneous or evoked disproportionate pain (1) after a tissue injury (2). This disease is more frequent in women (4:1) and in a range of age from 30 to 70 years old (3, 4). The upper limb is more affected than the lower one (60% and 40% respectively), especially distal radial fractures (36%) treated with tight cast, wrist injuries with nervous compression or distal radio-ulnar instability (2, 4-6). The course of the pathology can be characterized by three phases (1, 2, 7). The first phase presents inflammatory alterations and onsets within 3 months from the trigger event. Symptoms are erythema, swelling and hyperalgesia (1, 7). The second phase manifests from 3 to 6 months. It occurs with severe pain, skin alterations (discoloration, cyanosis, decrease hair growth), onset of negative sensory signs (hypoesthesia) and motor weakness. In 6 months, the CRPS can progress in the third irreversible phase. It is represented by skin atrophy, motor dysfunction (muscles clones or dystonia) and muscles contractures. Chronic stage is also characterized by bone resorption and regional osteopenia (1, 2).

The diagnosis is difficult. The “Budapest diagnostic criteria” are the last clinical diagnostic criteria adopted (8). In the literature, five radiographic patterns were described: metaphyseal trabecular bone resorption, subperiosteal, intracortical, endosteal and surface bone resorption (9). In early-stage magnetic resonance can show bone marrow edema due to high bone turnover (8, 10). Treatment consists in multidisciplinary approach and the physical therapy (11). Several drugs are employed, but only bisphosphonates seem to have good outcomes (12). In fact, bone resorption is the responsible of the demineralization and pain. Bisphosphonates (BPs) can inhibit osteoclasts activity, providing pain relief and increasing bone density (10, 12). Clinical trials studied BPs effects compared with placebo. They reported positive results of intravenous alendronate, clodronate, pamidronate (14, 15).

In our clinical practice, we have highlighted that patients who have been affected by CRPS have had important consequences and limitations in their lifestyle. Taking into account the reduced literature on the

use of intravenous bisphosphonate, the purpose of our research is to analyze the characteristics of the cases victims of the CRPS of upper extremity and study the beneficial effect of the intravenous neridronic acid sodium salt (Nerixia®), in an attempt to improve the results in this disabling disease.

## Methods

We retrospectively examined all consecutive cases of CPRS that had undergone intravenous neridronic acid sodium salt (2 mg per kg divided into 4 intravenous doses, diluting the drug with saline 0,9% for 4 in day hospital treatment) therapy in our center (between January 2016 and December 2019). The patients were reviewed in terms of the following variables: gender, age, kind of injury (fracture, nervous compression), type of surgical or conservative treatment (fracture osteosynthesis, neurolysis, immobilization with cast), days after the injury of the onset of complications and of the starting of intravenous therapy, telephone contact with clinical condition assessment with Quick- Disability of the Arm, Shoulder and Hand (DASH) (Italian translation of Institute for Work and Health I.W.H 2003), evaluation of residual stiffness and of subjective improvement after intravenous therapy. This research is based on the data provided by the clinical reports available on our web database and telephone follow up evaluation. Our Data Platform revealed 30 records. We excluded patients without upper limb injury, followed for less than 1 year, with CRPS diagnosis not associated with radiographic imaging and without complete and exhaustive data. Our patients did not begin a specific rehabilitation protocol during intravenous treatment. We do not have a precise rehabilitation protocol for this type of pathology, so this parameter has not been examined. Statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, TX). We studied two level categorical variables, multi-level categorical variables and ordinal continuous variables using a two-tailed *t* test, Kruskal-Wallis Test, Chi squared and logistic regression test, as appropriate. Before entering in ward before entering the ward, it is the hospital policy to seek consent for the use of the data for scientific studies from all patients.

## Results

We analyzed 30 cases that having suffered from CRPS. Of these cases, 3 patients (10%) were excluded because they did not meet the inclusion criteria and complete data were not present in our database. 2 cases (6.7%) were lost during the follow up. Of the rest 25 patients, 18 (72%) were complications of wrist fractures (45% treated with surgery), 4 (16%) fracture of metacarpal (Figures. 1-3) or phalanges bones (all treated with immobilization), 2 (8%) outcomes of surgery of median nerve decompression and 1 (4%) result of a surgical procedure in rhizoartrosis' diagnosis (Table 1).

We didn't find a relation between the onset of symptoms and the kind of first treatment (conservative or surgical) ( $p$ -value  $>0.05$ ). The average age of the group was 59,76 years (span, 42–78). The number of female subjects (84%) was higher than male (16%)



**Figure 1.** Post traumatic X-Ray of a patient's right hand. In the antero- posterior view it's possible to diagnose a fracture of the head of the fifth metacarpal bone.

( $p$ -value  $<0.05$ ). Considering the first lesion as time 0, the diagnosis of CRPS was done in an average of time from 3 to 6 month in 18 patients (72%); in lesser than 3 months in 5 cases (20%), and in the rest (8%) in more than 6 months ( $p$ -value  $<0.05$ ). In 19 patients (76%) intravenous therapy with nerindronic acid was administered in lesser then 6 months from the onset of the pathological pain, in 5 cases (20%) in lesser



**Figure 2.** After 3 months from the trauma, in the same view (antero-posterior of right hand) it's possible to see bone reabsorption of the fifth metacarpal bone. With the help of clinical evaluation, we can diagnose the CRPS.



**Figure 3.** After 3 months from the intravenous therapy and after 6 months from the trauma, in the same antero- posterior view of the right hand of this patient, we can see a normal apposition of the bone in the head of the fifth metacarpal. The CRPS symptoms are clinically and radiographically disappeared.

than 3 months and in only 1 (4%) case in more than 6 months. The telephone follows up was carried out 12 months after the first intravenous administration. Patients' symptoms and the ability to perform certain activities have been analyzed with the Quick DASH Score (19 points are the best result, 95 the worst outcome). In our sample the average was 41,1 points. The values of DASH Score\_differed significantly (p-value <0.001) according to the age of the patient. In fact, 50% of cases over 61 years old had achieved a worse

**Table 1.** Details of the orthopedic lesions affected by CRPS.

Cases	N° (%)
Wrist fractures	18 (72%)
Metacarpal or phalange bones fractures	4 (16%)
Surgical procedure in median nerve compression	2 (8%)
Surgical procedure in rhizoartritis	1 (4%)

result than the general sample. 100% of patients under the age of 40 years had obtained a score below compared to the general average (< 41,1 points). In addition, the DASH Score values were related to the sex of the patient (p-value <0.001). In particular, male subjects obtained a mean of 38.75 points, compared than 42.43 points achieved by the female cases. After 12 months of intravenous therapy, 52% of cases reports that they still have joint stiffness; we have not shown meaningful relationship between stiffness and the age of the patients (p-value > 0.05). Instead, the DASH values differed significantly depending on the onset of intravenous treatment (p-value <0.001): 100% of the subjects who have had the treatment in lesser than 3 months from the onset of symptoms have obtained an average of 54.7 points, worse result than the average of all our population which is worse than the average score of study sample (> 41,1 points). The 68% of all sample reported to have obtained a subjective improvement of symptoms after the therapy with the nerindronic acid (p-value < 0.05). There were no high-lighted side effects.

## Discussion

CRPS is a painful and progressive condition following major or minor traumatic triggering event (1, 2). As described in the literature, our study showed that the CRPS interest a population between 42 and 78 years old, especially women. We found a majority (72%) of cases resulting from a wrist fracture, but we didn't find relation between the onset of CRPS and kind of first treatment (conservative or surgical) (p-value >0.05) (4). Some authors suggested that severity of the fracture increases the risk of disease onset (5, 6). In wrist fracture CRPS must be suspected when delayed healing, persistent joint stiffness and inappropriate intensive neuropathic pain (16).



In our study, the diagnosis of CRPS was done in an average of time from 3 to 6 month ( $p$ -value  $< 0.05$ ). The first phase presents inflammatory alterations and onsets within 3 months from the trigger event (8,10). The second or dystrophic phase manifests from 3 to 6 months from disease onset and shows progressive reduction of inflammatory symptoms, in this phase we found that intravenous treatment with bisphosphonate has a greater success ( $p$ -value  $< 0.05$ ) than its use in the first 3 months. The disease progression can evolve over 6 months in the third irreversible phase, called atrophic stage (5). This disease is characterized by bone resorption and high bone turnover, with demineralization, regional osteopenia and pain. Bisphosphonates can provide pain relief and increase bone density by inhibiting osteoclasts formation and activation (10, 12, 17). Oral administration of BPs is possible but characterized by low bioavailability ( $>1\%$ ) and side effects. They can also give as parenteral formulations (13). Clinical trials studied BPs effects compared with placebo and reported positive results of intravenous treatment (14, 15, 18). The neridronic acid inhibits farnesyl-pyrophosphate synthase, an enzyme that regulate osteoclasts function (13, 19, 20). In our research, 68% of our group reported subjective improvement after the administration of intravenous therapy with Nerixia® (2 mg per kg divided into 4 intravenous doses, diluting the drug with saline 0,9% for 4 in day hospital treatment) ( $p$ -value  $< 0.05$ ). In particular, women over 61 years of age seem to have a lower improvement in symptomatology after treatment ( $p$ -value  $< 0.001$ ). 52% of cases reports that they still have joint stiffness, without relation with the age of the cases ( $p$ -value  $>0.05$ ). The mobilization and rehabilitation in addition to medication has a crucial role in the treatment of CRPS. However, in our study the rehabilitative component was not taken into account for lack of a standardized protocol. This study could be influenced by the small number of samples examined, the absence of a control group, the lack of a blind study, the retrospective nature, the comorbidities of patients not examined.

## Conclusion

In conclusion, treatment with intravenous bisphosphonates seems to lead to an improvement of CRPS

symptoms, especially the administration between 3 and 6 months from the onset of the disease. The best outcomes were achieved in patients under 40 years and male. The best outcomes were achieved in male patients and younger than 40 years old. However, the joint stiffness is a common problem despite the disappearance of the pain.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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