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Original article

NERIDRONIC ACID: ADVANCEMENTS AND CLINICAL POTENTIAL IN REFLEX SYMPATHETIC DYSTROPHY

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ABSTRACT

Bisphosphonates are widely used for the treatment of Complex Regional Pain Syndrome type 1 (CRPS-1). Despite their clinical potential, their indication for this disease remains a subject of debate. The purpose of this manuscript was to evaluate the efficacy and benefits of making use of neridronic acid in CRPS-1. Sixteen patients with CRPS-1 were evaluated before and after treatment with intravenous infusion of neridronic acid. All patients underwent the same treatment schedule and for all of them the VAS pain scale was used, integrated with functional assessment before and after treatment. The diagnosis of CRPS-1 was made using the Budapest Criteria. The onset of symptoms varied from 1 to 90 days, with an average of 50 days. All patients fulfilled the Budapest Criteria with pain present in 100% of cases, edema in 87.50%, hyperthermia in 62.50%, hyperhidrosis in 37.50%, skin redness in 56.25%, hypothermia in 12.50%, soft tissue retraction in 6.25% and joint mobility limitation in 87.50% of cases. The mean healing time was 40 days. Most of these patients (93.75%) had no sequelae. The use of neridronic acid has shown promising results in the treatment of CRPS-1. Results of the study suggested that its application, following a specific and standardized treatment schedule, could reduce pain and improve the quality of patients' life. Certainly, further studies on the real etiopathogenesis of this pathology will help to better establish indications in treatment and clinical practice.

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1. Introduction

Neridronic acid (6-amino-1-hydroxyhexylidene-1, 1-bisphosphonate) is an amino-bisphosphonate widely used in the treatment of bone diseases, with specific therapeutic indications for osteogenesis imperfecta (OI) [1] and Paget's disease (PDB) in Italy [2, 3]. Unlike other bisphosphonates, neridronic acid can be administered intravenously or intramuscularly [4]. Recent studies in literature suggest that neridronic acid may have potential clinical uses in various related bone and metastatic diseases [5,6].

Bisphosphonates (BPs) are derived from pyrophosphate, in which the P-O-P bridge is replaced with a non-hydrolysable P-C-P one. Two side chains are attached to this bridge: the long chain determines the chemical properties, mode of action and potency of the drug, while the short chain is responsible for chemical properties and pharmacokinetic characteristics of the compounds.

It is important to classify bisphosphonates from a chemical point of view, according to the presence or absence of a nitrogen atom in their molecular structure. Amino-bisphosphonates, which contain a nitrogen atom, have a different structure and consequently a different three-dimensional conformation of the side chains that determine the bisphosphonate's biological activity: thus, they have higher chemical power than non-amino bisphosphonates. Amino-bisphosphonates inhibit the enzyme farnesyl pyrophosphate synthase, a key enzyme involved in the mevalonate pathway, playing a role in the intracellular signaling pathway that regulates fundamental processes for osteoclasts.

Belonging to the amino-bisphosphonates, neridronic acid stands out for its intramuscular or intravenous formulations that prevent a series of complications that would arise from the oral assumption of bisphosphonates.

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Although oral bisphosphonates are the first-line treatment for a significant number of bone diseases, their administration creates significant discomfort for patients, with inevitable consequences for therapy compliance. Indeed, oral bisphosphonates can cause local irritation and ulceration in the esophagus and stomach. Pharmacokinetic investigations have demonstrated that bisphosphonates exhibit limited absorption in the gastrointestinal tract. The oral bioavailability of bisphosphonates is less than 1%, necessitating their administration on an empty stomach, with a time interval from meals and other medications [7]. These challenges, associated with oral intake, have prompted the development of parenteral formulations of bisphosphonates.

Throughout the years, various terms have been used to describe "complex regional pain syndrome" (CRPS). Up until the late 20th century the common names were "reflex sympathetic dystrophy" and "causalgia", worldwide [8]. However, the newer and more neutral term CRPS has gradually replaced these traditional terms in scientific literature [9]. CRPS can be divided into two types according to the absence (type I, much more common) or presence (type II) of a nerve branch or injury. The diagnostic distinction is important to discern the two types for the purpose of pharmacological/surgical treatment, which is different in the two cases. Since the underlying pathophysiology is still unclear and no treatment has been so effective as to obtain an indication for this disease, CRPS-1 remains a subject of debate. CRPS-1 is a severely disabling pain syndrome characterized by allodynia, hyperalgesia, edema, signs of vasomotor instability, movement disorders, joint stiffness and regional osteopenia [10]. Recent studies suggest that the onset and persistence of CRPS-I can follow a traumatic [11, 12, 13] or surgical event [14, 15, 16] and is mostly due to a neuropathy of small fibers. Tran et al [17], reviewing the published literature between 1950 and 2009, identified 41 randomized (controlled) trials that met their inclusion criteria; eighteen of these studies included the use of pharmacological therapies.

Different bisphosphonates and therapeutic schemes [18, 19] have been used to obtain positive results in controlling pain, edema and functional limitations in CRPS-1 patients. A Cochrane review, that was published in 2013 [20], found that the evidence supporting the effectiveness of bisphosphonates for pain relief was of low quality in CRPS-1. It emphasized the need for further studies to determine their efficacy. Recently, a meta-analysis was conducted to evaluate the effectiveness of treatments with bisphosphonates for CRPS-1, including four trials with a total of 181 participants. The bisphosphonate regimens used in these trials included oral alendronate (40 mg on day 1 for 8 weeks), intravenous pamidronate (60 mg once), intravenous clodronate (300 mg on day 1 for 10 days) and intravenous neridronate (100 mg on days 1, 4, 7, and 10). The analysis revealed that the bisphosphonate group had a statistically significant reduction in pain scores compared to the placebo group at 30-40 days, as measured by the Visual Analog Scale (VAS). The reduction in VAS pain scores was recorded at 2-3 months [21].

A multicenter, randomized, placebo-controlled, double-blind study tested the efficacy of neridronate in patients with CRPS-1 [22]. The study involved 82 patients with CRPS-1 in their hands or feet who were randomly assigned to receive intravenous infusions of 100 mg of neridronate every three days for four times, starting from day 0 (first infusion) and ending on day 9 (fourth infusion) or placebo.

After 50 days, the placebo group was treated with the same neridronate regimen. Within the first 20 days, the VAS score significantly decreased in the group that received neridronate compared to baseline. In the following 20 days, the VAS index remained unchanged in the placebo group and further decreased in the treated group.

There was also a significant improvement in functional indices. These results provide evidence that the use of neridronate is associated with clinically relevant and persistent benefits, representing the treatment of choice for CRPS-1 [23]. The aim of the present study was to evaluate the efficacy and benefits of the intravenous infusion on neridronic acid, comparing the obtained data with other studies in the literature.

2. Methods

The study includes a total of 16 patients with a diagnosis of CRPS-1 and all of them met the Budapest Criteria [24], which are the most recent and commonly used criteria in clinical trials and diagnostic frameworks [25]. Indeed, the diagnosis can be made when a series of factors and clinical features are met, as described in Table 1. Four criteria are listed, indicated with letters A), B), C), and D), and both A) and D) must be met to diagnose CRPS. Criteria B) and C) are satisfied by considering the categories of signs and symptoms that must be present in a number of at least one symptom in 3 or more categories and at least one sign in 2 or more categories. The signs and symptoms are grouped into four categories (sensory, vasomotor, sweating-edema, and motility-tissue trophism), listed in the second part of the table.

The study population included 10 females (age range: 31-65 years, mean age: 50,10 years) and 6 males (age range: 42-63 years, mean age: 52,17 years).

Inclusion criteria of the study were: a spontaneous pain intensity in the affected limb ≥ 5 in a Visual Analog Score (VAS) from 0 (no pain) to 10 (maximum pain), prior treatment with BPs, all patients aged ≥ 18 years, no nerve damage suggesting CRPS-2. None of the patients had ever taken any other drugs prescribed for CRPS-1 when they were enrolled.

Exclusion criteria consisted of patients with renal diseases, diabetes, autoimmune diseases and pregnant women.

DIAGNOSTIC CRITERIA FOR CRPS (Budapest criteria) - (A–D must apply)

A) The patient has continuing pain which is disproportionate to any inciting event ☐
B) The patient has at least one sign in two or more of the categories ☐
C) The patient reports at least one symptom in three or more of the categories ☐
D) No other diagnosis can better explain the signs and symptoms ☐

N°	CATEGORY	SIGNS (you can see or feel a problem)	SYMPTOMS (the patient reports a problem)
1	SENSOSRY	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) ☐	Reports of hyperesthesia and/or allodynia ☐
2	VASOMOTOR	Evidence of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry ☐	Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry ☐
3	SUDOMOTOR /OEDEMA	Evidence of oedema and/or sweating changes and/or sweating asymmetry ☐	Reports of oedema and/or sweating changes and/or sweating asymmetry ☐
4	MOTOR / TROPHIC	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) ☐	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) ☐

Table 1. New IASP diagnostic criteria for complex regional pain syndrome ("Budapest criteria") [25], (A–D must apply).

The affected areas were ankle and foot in 6 cases (4 females and 2 males); hip in 4 cases (1 female and 3 males); knee in 1 case (1 male); wrist and hand in 5 cases (3 females and 2 males).

Patients were observed before and after the treatment with 100 mg of neridronic acid in a 500 ml isotonic saline solution administered over 3 hours for four consecutive days (0-3-6-9 schedule). The VAS pain scale was integrated with functional assessment, before and after the treatment.

This study was performed in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants.

3. Results

The onset of symptoms varied from 1 to 90 days, with an average mean of 50 days. Symptoms were generally progressive in 14 patients (87.50% of all cases), with a moderate pain intensity in 12 cases (75%) and a type of referred pain mechanical and/or persistent at rest in 13 patients (81,25%).
All fulfilled Budapest Criteria for diagnosis are shown in Table 2. Edema was present in 14 patients (87.50% of cases), mainly in distal forms (foot/ankle n°5/83.3%, wrist/hand n°5/100%, knee n°1/100% and hip n°3/75%). Hyperthermia was detected in 10 cases 62.50% of patients, hyperhidrosis in 6 patients (37.50%) and skin redness in 9 cases (56.25).
Hypothermia was detected in 2 cases (12.50%) and soft tissue retraction in 1 case (6.25%) localized in wrist/hand. Joint mobility limitation was present in 14 cases (87.50%), in all cases (100%) of wrist/hand, hip/knee districts and to a lesser extent in foot/ankle in 4 cases (66,67%).
The diagnosis of reflex sympathetic dystrophy was monotopical in 14 cases (87.50%) and polytopical in 2 patients (12.50%).
In these 2 cases (12.50%), it was additive (one focus extinguished and another started) and migratory (once the focus extinguished, another one appeared in a different and distant location).
The hips resulted the most affected joint with a subsequent involvement of the knee, and from the knee migration to the ankle; moreover, data showed a slight tendency towards the right side found in 9 patients (56.25%) and a clear predominance of the lower limbs for 11 cases (68.25%).

SYMPTOMS	N° PATIENTS / (%)*	LOCALIZATION	N° PATIENTS / (%)**
EDEMA	n° 14 / (87.50%)	Foot-Ankle Wrist-Hand Knee Hip	n° 5 / (83.33%) n° 5 / (100%) n° 1 / (100%) n° 3 / (75%)
HYPERTERMIA	n°10 / (62.50%)	Foot-Ankle Wrist-Hand Knee	n° 4 / (66.70%) n° 5 / (100%) n° 1 / (100%)
HYPERHIDROSIS	n° 6 / (37.50%)	Foot-Ankle Wrist-Hand	n° 4 / (66.67%) n° 2 / (40%)
SKIN REDNESS	n° 9 / (56.25%)	Foot-Ankle Wrist-Hand Knee	n° 5 / (83.33%) n° 3 / (60%) n° 1 / (100%)
HYPOTHERMIA	n° 2 / (12.50%)	Wrist-Hand	n° 2 / (40%)
SOFT TISSUE RETRACTION	n° 1 / (6.25%)	Wrist-Hand	n° 1 / (20%)
JOINT MOBILITY LIMITATION	n° 14 / (87.50%)	Foot-Ankle Wrist-Hand Knee Hip	n° 4 / (66.67%) n° 5 / (100%) n° 1 / (100%) n° 4 / (100%)

Table 2. Summary of symptoms satisfying Budapest criteria and their localization recorded in our experience (*% of cases on total number of patients included in the study; **% of patients out of the total number of cases involving that specific district).

All patients had a significant decrease in VAS ($p<0.05$), between before and after the treatment schedule based on subsequent intravenous infusions of neridronic acid. The VAS score decreased from scores close to 8 (VAS range: 7.4 – 9.2) to an average of 1 (VAS range: 0 – 2.4) at the end of all four infusions.
The average healing time of all symptoms was 40 days (range: 25-70 days), with the wrist and hand requiring a longer period (70 days), whereas the ankle required a shorter period (25 days).
Most of patients, in number of 15 (93.75%) had no sequelae, while one patient (6.25%), during the follow-up, reported functional limitations of the wrist likely due to the pre-treatment immobilization

4. Discussion

Complex Regional Pain Syndrome 1 (CRPS-1) is a condition that presents diagnostic, clinical and therapeutic challenges. The symptoms are varied, affecting multiple systems. Since there are no clear and objective diagnostic criteria, attempts to classify the condition for epidemiological and therapeutic purposes rely on diagnostic algorithms or criteria, only based on clinical and anamnestic data.
There are almost as many diagnostic criteria for complex regional pain syndrome as there are names to this disorder [26, 27, 28]. The diagnosis of CRPS-1 is based on clinical examination, which often requires a multidisciplinary approach. Persistent joint swelling, functional limitation, disproportionate and persistent pain compared to the triggering event are considered "red flags" that should raise suspicion of CRPS-1 [29].
The severity of pain and secondary joint stiffness can cause significant functional limitations and psychological instability in patients. Trauma, immobilization in a cast, surgery and other triggers are usually reflected in most studies on the subject. However, the timing of symptom onset is typically within a month from a trauma event [30] or limb immobilization [31], making it one of the most common triggers. Moretti et al. [32], in a narrative review of the literature, reported a series of cases of CRPS-1 after surgery or other invasive procedures in non-orthopedic settings. Although these types of triggers are rare or probably underestimated, they are a further example of how the pathogenic mechanism at the base of CRPS-1 is complex and of multidisciplinary interest.
Spontaneous onsets, which present with a similar clinical picture, are uncommon (<10% of cases) [33].
Factors that favor the development of CRPS-1 include tight casting, immobilization in an unnatural position, prolonged immobilization and lack of loading [34, 35].
Fractures (>40% of cases) [36], sprains, contusions, surgical procedures and bone bruise [37] are the main trigger factors for the development of CRPS-1. Nearly everyone experiences tissue trauma, yet few develop CRPS-1 and the severity of trauma does not relate to the development of CRPS-1. Clearly then, some individuals are more susceptible than others and for this reason, systems are being developed for an increasingly personalized treatment of the patient [38]. Although it is the most common trigger of CRPS-1, fracture is associated with a more favorable course than soft tissue injury is [39].
Furthermore, we found that the inciting event did not particularly influence the right, left or bilateral position of CRPS-1, except for surgery, which favored a more pronounced bilateralism.
The presence of common triggers varies depending on the study and circumstances. For instance, in the study population, CRPS-1 affected the hip without any other factors. When considering sex and body district, women showed a preference for the ankle (40%), hand/wrist (20%), knee (10%) and hip (30%), while men showed a preference for the hand/wrist (50%), ankle (33.33%) and hip (16.67%). Other studies have found a predilection for the other side and a greater preference for the upper limbs in women [40].
The healing time varied between 25 and 70 days, with a mean of 40. On average, the wrist and hand required a longer period to heal, while the ankle required a shorter period. Most patients (93.75%) did not have sequelae, and only 6.25% had functional limitation of the wrist, likely due to pre-treatment immobilization.
A relevant result of the present study, in line with other works [41] in literature, is that almost all patients (93.7%) did not report the presence of symptoms at the 12-month follow-up, in this case patients reported the

same results at 24 and 36 months follow up [42]. Athletes exhibiting disproportionate pain post sports-related injury should be promptly evaluated and managed via a multidimensional approach to avert the long-term consequences of algodystrophy [43].

Visual analog scale (VAS) pain scores were obtained from all evaluation points before and after treatment showing us that all patients reported pain relief at the end of the four neridronic acid infusions.

The results did not show any differences in terms of prognosis when genders are compared and this is also found in the literature [44]. However, the study showed significant disparity in results depending on the affected body district and group studied. It is possible that the multifarious characteristics of the observed population influenced these data.

An accurate analysis of symptoms is essential for an early diagnosis and the subsequent prognosis of patients.

Timely diagnosis and treatment are the best practices to avoid permanent functional limitations in the affected limb that would affect a patient's quality of life [45]. Approximately a 15% of patients may experience continuous pain and reduced functionality up to two years after symptom onset when the diagnosis is delayed [46].

Unfortunately, CRPS-1 is still poorly understood, particularly in its early clinical expressions, and its symptoms can simulate a wide range of other possible pathologies that requires the attention of different specialists. This varies depending on where patients are recruited and the organization of the healthcare system, among other factors. Often there is a lack of knowledge regarding CRPS (Complex Regional Pain Syndrome) among primary and secondary health care professionals, and this fact can cause delays in diagnosis and treatment. It is fundamental to perform an adequate differential diagnosis by evaluating the different clinical picture that may present itself, as in the case of infections [47, 48].

Recent studies have found that CRPS-1 could be related to a dysfunction of the immune system, suggesting that it may be a systemic disease rather than just a regional one [49, 50]. Future research should focus on this aspect and explore new diagnostic and therapeutic approaches to improve patient outcomes.

5. Conclusions

The use of neridronic acid has shown promising results in the treatment of CRPS-1. While currently indicated for osteogenesis imperfecta and Paget's disease, this study suggests that its application in a 100 mg dose with 500 ml of saline solution over a 3-hour period can effectively reduce pain and improve the functional capacity of patients suffering from this debilitating condition. The 0-3-6-9 pattern of administration over a four-dose treatment cycle has shown efficacy in the authors' experience. This breakthrough treatment could change the lives of those affected by CRPS-1 and provide hope for a better quality of life.

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