The Effectiveness of Nifedipine for Vasomotor Instability Associated with Chronic Regional Pain Syndrome in a Young, Female Patient

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Purpose

Chronic regional pain syndrome (CRPS) can be difficult for a physician to diagnose as well as manage. Symptoms may be variable, vague, and unclear. Once a diagnosis has been established, treating this disorder may be even more difficult. A diagnosis does not always equate to a reduction of symptoms. We report the complete resolution of pain and vasomotor instability of a young, female patient with CRPS using oral Nifedipine (Procardia).

Literature Review

Chronic regional pain syndrome (CRPS) is a disabling condition manifested by hyperalgesia, allodynia, trophic changes, and vasomotor disturbances (1). It can be a challenging problem for physicians as there are a variety of treatment options (2). Two classifications exist: CRPS 1, once termed reflex sympathetic dystrophy (RSD), and CRPS II, previously *causalgia.* The only delineating factor is that frank nerve injury is associated with CRPS II (3). A civil war surgeon, Silas Weir Mitchell, first described the term *causalgia* in 1872 with nerve-associated injuries. The term has a Greek origin from words meaning pain and burning. Other terms once used to describe this disease state include *sympathetically maintained pain* and *sympathetically independent pain*. It was not until 1994 that the International Association for the Study of Pain (IASP) established criteria and terminology for CRPS (4).

CRPS is subdivided into three stages. Stage I occurs shortly after to three months post-injury and is defined by marked swelling, discoloration, hyperhidrosis, and pain. Stage II occurs 3 to 9 months following the injury. While pain continues, motor changes begin to take place and vasomotor instability is apparent. Radiographs at this time may show signs of decreased bone density. Stage III occurs 9-18 months from the initial injury. The involved limb is cold, dry, and stiff. Though pain decreases, functionality of the patient is reduced as muscle wasting occurs and joints become relatively fixed. Radiographs show severe osteopenia (5).

The exact etiology remains unclear. Various mechanisms have been proposed but most of the literature supports multiple pathways. The underlying cause differs from person to person and can even change over time in the same individual. Proposed mechanisms include central and peripheral sensitization where the person's own body mistakes normally non-painful stimuli as a painful response; altered cutaneous innervation; low norepinephrine levels; an impaired sympathetic nervous system; increased inflammatory markers; genetic influences; and psychological factors (6).

Symptoms vary which make a diagnosis difficult. The triad of motor, sensory, and autonomic dysfunction is a classic finding, as patients will typically present with pain out of proportion and marked temperature differences between involved extremities(6). Advanced imaging can also be useful. Increased peri-articular uptake is the most common finding on a tri-phasic bone scan. Electrodiagnostic studies may assist in making a diagnosis as well especially in CRPS II patients. Once a diagnosis has been made treatment may be even more problematic as individual responses differ between patients (5).

Regardless of treatment a multidisciplinary approach is necessary with pain reduction, physical rehabilitation, and restoring function as the primary goals (4). Potential treatment modalities include pharmacologic regimens, nerve blocks, neurolysis, opioids, bisphosphonates, corticosteroids, Vitamin C, topicals, and physical/occupational therapy (3). Physical therapy is considered to be the mainstay of treatment (6). There is also a small amount of literature on the use of calcium channel blockers (i.e.. Nifedipine) for treatment of CRPS (7,8). We report the case of a 14-year-old female who had complete resolution of vasomotor instability and pain associated with CRPS with the use of oral Nifedipine.

Case Study

A 14-year-old female presented to our outpatient clinic with the chief complaint of pain localized to the first metatarsophalangeal and hallux interphalangeal joint left foot for five days duration. She described the pain as tingling and numbness in nature. She denied any injury at the time. Her past medical history was significant for juvenile rheumatoid arthritis for which she took Methotrexate but was otherwise unremarkable. Review of systems was non-contributory. Physical exam revealed palpable pedal pulses. The left lower extremity displayed blanching erythema with increased warmth noted in comparison to the contralateral limb. Areas of maximum pain were noted (Figure 1). Clinically, there was pain with plantar palpation to the hallux interphalangeal joint and 1st metatarsophalangeal joint left foot. All other exam findings were normal. She was treated conservatively for sesamoiditis with offloading and anti-inflammatory medications. At her follow-up examination, her pain had not improved with activity modification and offloading. Clinically the patient's digits had a dusky hue particularly the left foot. Radiographs were taken which revealed a decreased bone density with a "washed-out" appearance (Figure 2). No fractures were noted. Patient was advised to again limit her activities and non-invasive vascular studies with cold immersion stress testing were ordered. Vascular studies revealed vasospastic disease.

At her next 10 week follow-up, vascular studies were discussed. The left foot was cool to the touch with a pale appearance in comparison to the right (Figure 3). The right foot was beginning to become painful similar to the left. The patient's pain did not seem to be improving despite appropriate activity modification. An MRI was ordered which was consistent with suspected sesamoiditis. The patient was cast immobilized however her pain worsened. A tri-phasic bone scan was ordered which was consistent with CRPS (Figure 4). Therefore, after consult with her primary care physician, the patient was started on Nifedipine 10mg TID. Physical therapy was recommended but the patient could not tolerate range of motion exercises or weight-bearing at the time. Over the course of several weeks, her symptoms of pain and vasomotor instability gradually resolved and her normal skin color returned (Figure 5). She is currently close to two years out from her initial visit and has had complete resolution of her symptoms. She continues to take a maintenance dose of Nifedipine on a regular basis.

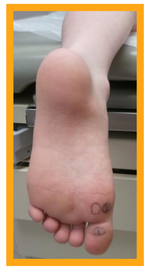

Figure 1. Initial office visit.

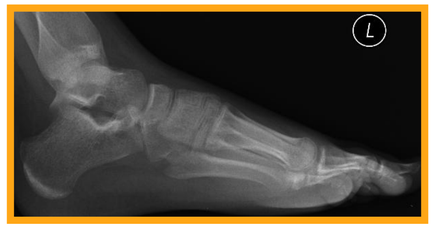

Figure 2. Initial radiograph. Notice the decreased bone density.

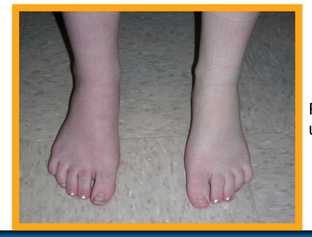

Figure 3. Ten week follow-up. Pre-Nifedipine treatment

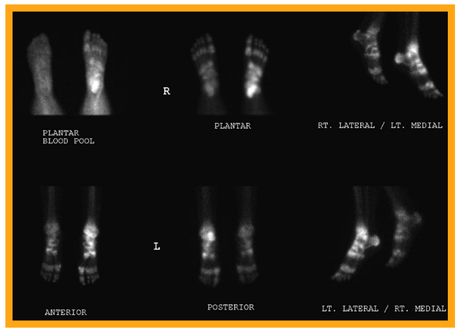

Figure 4. Triphasic bone scan: delayed uptake.

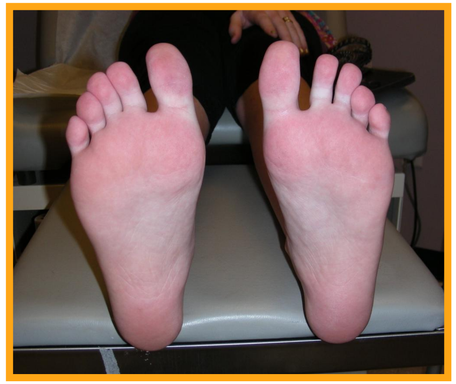

Figure 5. Post-Nifedipine treatment.

Discussion

The literature regarding the use of oral Nifedipine for treatment of CRPS patients is sparse with most data obtained from two moderate sized studies. Muizelaar et al. treated 59 patients with acute and chronic CRPS (41 type I; 18 type II) with either Nifedipine and/or Phenoxybenzamine. Only 20% of patients had lower extremity CRPS where the other 80% involved the upper extremity. There was a cure rate of 60% in acute CRPS patients treated with oral Nifedipine, however, there were only five patients treated in this group. In the chronic stage of CRPS, there was a cure rate of 33% with 10/30 responding to treatment. One interesting note was that physical therapy was not implemented in the acute stages. The authors noted that while Nifedipine appears to be an effective alternative alone, it may have been even more beneficial when used as adjunct with functional rehabilitation (7).

Secondly, Prough et al. treated 13 patients with CRPS with titrated doses of Nifedipine from 10mg to 30mg depending on the response to the initial 10mg dose. Only three patients had CRPS involving the lower extremity. Results showed that seven patients had a complete response, two had partial relief, three withdrew due to headache, and one patient showed no response to treatment. Cold immersion stress testing performed prior to therapy displayed vasomotor instability in 9/12 patients with five patients showing an improvement in testing after treatment. The authors concluded that Nifedipine may not only improve pain but also vasomotor instability as was evident with improved cold stress testing post-treatment (8). Most common side effects of Nifedipine treatment included headaches and orthostatic dizziness in both studies (7,8).

Recent guidelines published on CRPS suggest that, though the literature is lacking, (Level IV), there is a "strong mechanistic rationale for managing vasoconstriction" with oral Nifedipine (9). Moreover, Groeneweg et al. suggests that given Nifedipine's potent vasodilator activity and minimal cardiac risk profile it may be an effective treatment in chronic cold CRPS (10). Nifedipine has been used successfully in other vasospastic conditions such as Raynaud's phenomenon which confirms the rationale for using it in CRPS patients (11,12). Oral calcium channel blockers negate vasoconstriction mediated by sympathetic control by relaxing smooth muscle of the vessel lumen therefore increasing blood flow to the area. In the case report presented, we believe the patient responded well to treatment since the vasospastic component of her CRPS seemed to be the driving force behind her symptoms.

While much literature has been published on the management of CRPS, there has also been recent data published on prophylaxis. Adapted from wrist fracture literature, a daily dose of 500mg of Vitamin C daily has been shown to be effective in preventing CRPS in foot and ankle trauma/surgery patients (13).

As stated, the literature is sparse regarding the treatment of acute and chronic CRPS with oral Nifedipine. Ultimately, we do not advocate that Nifedipine should be used alone but rather as option in conjunction with physical therapy and functional rehabilitation. It appears that calcium channel blockers have a role in the management of chronic, cold CRPS when vasoconstriction persists, however, higher-level studies are needed.

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