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Novel Treatment of Radicular Pain With a Multi-Mechanistic Combination Topical Agent: A Case Series and Literature Review

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Abstract

Introduction: Pharmacologic treatment of radicular pain with oral medications is limited by adverse effects and concern for dependence. While topical formulations have been explored in pain research, there is no published literature evaluating the efficacy in radicular pain. We present the first three cases of radicular pain successfully treated with a topical formulation of diclofenac, ibuprofen, baclofen, cyclobenzaprine, bupivacaine, gabapentin, and pentoxifylline (T7).
Case Presentation: Case series evaluating T7 for treatment of radicular pain in a single, outpatient pain center. Pain was rated on the numeric rating scale (NRS) on initial evaluation and follow up after a trial of T7. One to two grams of T7 was applied to the affected area 3 - 4 times daily in addition to the patient's baseline pharmacologic management. Three patients with median age of 50 (range, 39 to 65) and diagnosis of cervical and/or lumbosacral radicular pain participated. Two of the three had chronic radicular pain despite use of analgesic agents, spinal injections and failed spinal surgery syndrome. Each reported subjective improvement in radicular pain, function and sleep. There was an average decrease in NRS score consistent with 30% - 40% global improvement in symptoms, clinically significant based on the minimal clinically important difference for radicular pain. T7 was well tolerated without adverse reactions. Surgery was prevented or delayed in all cases.
Conclusions: This is the first report of the successful treatment of radicular pain with a topical agent. This highlights the need for randomized, prospective study of both single and compounded topical agents for treatment of radicular pain.

Keywords: Radiculopathy, Neuralgia, Anesthetics, Administration, Topical

1. Introduction

Radicular pain is a challenging clinical problem causing significant disability and is a major source of health care costs (1-5). Conservative treatment involves physical therapy, oral analgesic or neuropathic medication, and possibly epidural steroid injections (6, 7). It is caused by compression or irritation of spinal nerve roots as they exit the spinal column and characterized by dysesthesias occurring in a dermatomal or sclerotomal distribution (8). Traditional pharmacologic treatment has focused predominantly on oral medications (9). However, this approach is frequently ineffective due to its poly-mechanistic etiology, including inflammatory, mechanical/compression related, and neuropathic pain. Furthermore, there are limitations in creating a potentially effective oral regimen due to pharmacologic interactions and potential for adverse effects with increasing doses and numbers of medications (1, 6, 7, 9). Multiple agent delivery via the topical route almost entirely eliminates the risks associated with poly-pharmacy given minimal systemic absorption. However, there is a paucity of such research (9-11) and there is no published literature addressing the treatment of radicular pain with topical medication.

Indeed, the possibility of treatment of complex pain via the topical route has become more relevant as support for the neuroimmunocutaneous system has developed and the role of the skin in nociception has been studied. Based on this hypothesis, topical medications penetrate through the epidermis and act as ligands that bind receptors found on nociceptors on the skin, ultimately increasing action potential thresholds for signal transmission through pain fibers (10, 12-14).

While topical medications can have potential side effects such as skin irritation and erythema, they are generally well tolerated with little risk of toxicity (15, 16). Advantages include pain relief when oral medications are not appropriate, either temporarily (as in post-operative nausea), or chronically (post-stroke dysphagia). In some

circumstances, the topical formulation can be used when an oral form is contraindicated; for instance, the use of systemic non-steroidal anti-inflammatory drugs (NSAIDs) in a patient with chronic kidney disease (CKD), or osteoporotic and diabetic patients in which corticosteroids carry a higher risk of adverse effects.

One commonly used medication is the lidocaine 5% patch, which produces a local anesthetic effect by decreasing neuronal membrane permeability to sodium ions thus inhibiting depolarization (17). It may be considered for treatment of pain associated with diabetic neuropathy. The study found that application of the 5% patch significantly improved pain and quality of life in patients with painful diabetic neuropathy. Additionally, it has been effective in treating neuropathic pain of various forms as monotherapy and adjunctive therapy (18-25).

Another commonly prescribed topical medication is capsaicin, which, with repeated application depletes substance P from the terminals of afferent C fibers (26). Capsaicin, available in both a cream (0.025% or 0.075%) and an 8% transdermal patch, has demonstrated moderate analgesic effects in neuropathic pain (27). Capsaicin has been used in patients with PHN, HIV neuropathy, and diabetic neuropathy (28). In one study examining its effects on PHN, capsaicin cream applied four times daily resulted in a 21% reduction in pain compared to 6% with placebo (29). Furthermore, a 2013 systematic review identified four randomized controlled trials that evaluated 1,272 subjects with PHN treated with one application of either high-concentration capsaicin patch or standard concentration capsaicin. All four trials, noted a $\geq$ 30% reduction in pain at eight weeks compared to baseline; this was significantly greater for the high-concentration patch (43% versus 34%) (30).

While there is some research on topical analgesic agents used in the treatment of neuropathic pain, there is minimal literature addressing the effects of combination topical agents. Given the complex pathophysiology of pain, treatment using multiple agents with differing but complementary mechanisms of action can be beneficial (31). In an open label prospective study by Lynch et al. the use of combination topical amitriptyline and ketamine for refractory peripheral neuropathic pain was associated with significant reduction in pain and moderate to complete satisfaction at 6 to 12 months (32). In another study, McCleane et al. performed a randomized, double blind, placebo controlled trial using either an application of doxepin, capsaicin, or a combination of the two for chronic neuropathic pain. Results showed that while all three arms provided significant pain reduction of similar magnitude when compared to placebo, the combination cream provided more rapid onset of analgesia (33).

The potential benefit of compounded agents, through multiple mechanisms of action, may be useful for treatment of radicular neuropathic pain. Our literature review revealed no study addressing the treatment of radicular pain with a topical agent, or furthermore, with a combination of compounded topical agents.

This case series of three patients describes the successful use of a combination compounded agent, including Diclofenac 5%, Ibuprofen 3%, Baclofen 2%, Cyclobenzaprine 2%, Bupivacaine 1%, Gabapentin 6% and Pentoxifylline 1% which we will refer to subsequently as "T7" for the treatment of radicular pain. One to two grams of the cream was applied in the dermatomal region of pain (thus the doses were not exact). Each of these components as described below has a role in the treatment of pain via a different mechanism of action. The topical compound was prepared by one of two established compounding pharmacies.

2. Case Presentation

2.1. Case 1

A 39-year-old male without significant past medical history presented with three weeks of neck pain with radiation into the left upper extremity and into all of the digits. The pain was initially attributed to mal positioning during sleep then worsened a few days later following a competitive soccer game. The patient reported 10/10 pain in severity on a numerical rating scale (NRS), and had subjective complaints of weakness, numbness and tingling in the left upper extremity. His symptoms were exacerbated by walking and lying down. He felt that his sleep was affected. Medications included hydrocodone-acetaminophen 5 - 325 mg as needed (up to every 8 hours) which did not relieve his pain.

Physical examination demonstrated 5/5 strength in the C5-T1 myotomes bilaterally, and intact sensation to light touch and pinprick. The muscle stretch reflex exam was remarkable for symmetric 1 + reflexes at the biceps, brachioradialis and triceps tendons bilaterally. Cervical extension and right rotation both provoked a typical distribution of radiating pain and Spurling's test was positive on the left. Provocative maneuvers of the bilateral shoulders did not cause significant pain. An MRI revealed severe stenosis at the left C6-7 neural foramen and a small C5-6 central disc protrusion. The patient was diagnosed with left C6-7 radicular pain.

A trial of mechanical diagnosis and treatment ("McKenzie-method physical therapy") and oral gabapentin were prescribed. Pain medication was continued at the current dose. One to two grams of T7 with application to the neck 3 - 4 times daily, was prescribed. At

four month follow up, the patient admitted that he had not attended physical therapy or used the oral gabapentin. He did, however, use T7 as prescribed and reported that it was helpful in reducing pain to an NRS score of 6/10, a 30% - 40% global improvement in symptoms. He reported better sleep and subjective improvement of activities of daily living.

2.2. Case 2

A 47-year-old obese female with past medical history of chronic low back pain with an L5-S1 central disc extrusion and right L4-5 foraminal disc protrusion, status post remote laminectomy and lumbar fusion, presented with complaints of acute on chronic low back pain radiating into the buttocks and posterior thighs. She rated the severity at 10/10 on the NRS. Symptoms were exacerbated by walking, sitting and standing. Medications included hydromorphone 2 mg as needed (up to every 6 hours), a transdermal fentanyl 25 mcg/h patch every three days, Cyclobenezprine 10mg as needed (up to every 8 hours), diazepam 5mg nightly and gabapentin 400mg three times daily. These medications did not significantly reduce her pain or improve her daily functioning.

Physical examination demonstrated 5/5 motor strength in the bilateral L2-S2 myotomes. Muscle stretch reflexes were symmetrically trace in the bilateral Achilles tendons, unobtainable in the medial hamstring tendons and 1 + at the patellar tendons. Bilateral slump sit and straight leg raise did not provoke symptoms. Provocative maneuvers of the bilateral hips did not cause significant pain. Reimaging of the lumbar spine by MRI showed stable appearance of the L5-S1 laminectomy and fusion without new foraminal or central canal stenosis. The patient was diagnosed with bilateral L5/SI lumbosacral radicular pain.

Physical therapy and 1-2 grams of T7 with application to the neck and low back 3 - 4 times daily, were prescribed. She was instructed to continue her other medications with the goal of decreasing use. At 3 month follow up, she reported 7/10 pain on the NRS, and 30% improvement in her symptoms with the use of T7 topical formulation.

2.3. Case 3

A 65-year-old male with a past medical history of chronic low back and radicular pain status post remote partial L4 laminectomy, presented with his typical long-standing bilateral hip pain radiating to the anterior thighs. He rated his pain as 5/10 at baseline with exacerbation and associated numbness and paresthesia during standing and walking. Medications included Meloxicam 7.5 mg daily and Tramadol 50mg twice daily. Past pharmacologic treatments included ibuprofen, naproxen, celecoxib, nortriptyline, pregabalin and gabapentin. He had previously completed a 3 month course of physical therapy and continued a home exercise program. One year ago he received bilateral L4-5 transforaminal epidural steroid injections (TFESIs) that provided ongoing 30-40% pain relief and bilateral L4-5 and L5-S1 zygapophyseal joint injections with no pain relief. One month prior to presentation, the patient received a left L3-4 TFESI resulting in 1 week of 60% pain relief.

Physical examination demonstrated 5/5 strength in the L1-S2 myotomes of the bilateral lower extremities. Low back and radiating leg pain was exacerbated with lumbar extension. Bilateral slump sit and straight leg raise did not provoke symptoms. Muscle stretch reflexes were 1 + and symmetric in the bilateral lower extremities. Provocative maneuvers of bilateral hips did not cause significant pain. An EMG completed 1 year prior to presentation was consistent with bilateral L3-L4 radiculopathy. An MRI revealed disc bulges at multiple levels and a grade 2 anterolisthesis of L4 on L5 resulting in moderate to severe foraminal and central canal stenosis, as well as a stable appearance of the L4 partial laminectomy. Bilateral hip x-rays showed only mild OA of the left hip.

He was prescribed one to two grams of T7 applied to the low back 3 - 4 times daily. He was instructed to continue his other medications with the goal of decreasing use. At 4 month follow up, the patient rated his pain as 3/10, a subjective 50% reduction in symptoms, with concurrent improvement in sleep and function during daily activities.

3. Discussion

This case series of three patients describes the successful use of T7, a combination compounded agent, including Diclofenac 5%, Ibuprofen 3%, Baclofen 2%, Cyclobenzaprine 2%, Bupivacaine 1%, Gabapentin 6% and Pentoxifylline 1% for the treatment of radicular pain. Below we review each component and their role in the treatment of pain via a different mechanism of action.

3.1. NSAIDs: Diclofenac and Ibuprofen

Both Diclofenac and Ibuprofen have antipyretic and anti-inflammatory properties due to the inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX) (34). Various studies have examined the use of the topical formulation in acute soft tissue injuries, arthritic disorders, neuropathic orofacial pain, and myofascial pain (35). One study on temporomandibular joint dysfunction found that when topical and oral NSAID formulations were compared, there was no significant difference in pain relief. It is important to note that 88% of those who received the oral formulation reported epigastric symptoms while

no adverse effects were observed with the topical formulation (35-37).

With regard to neuropathic pain, a recent randomized, placebo controlled, double blind, crossover trial evaluated the use of 1.5% topical diclofenac for neuropathic pain from PHN and complex regional pain syndrome. The authors found that after 2 weeks of topical application, subjects who received diclofenac had less pain compared to placebo on the visual analogue scale (VAS) (38).

Another study examined the role of chronic Ibuprofen administration following spinal cord injury in an animal model at a dose of 60 mg/kg twice daily. The authors reported reduction in neuropathic pain by reducing central hyperexcitability (39).

With regards to use in radiculopathy, while animal models of injury have been promising (40, 41) our literature review revealed no studies examining the use of Diclofenac or Ibuprofen (topical or oral) for the treatment of radicular pain.

3.2. Muscle Relaxants: Baclofen

Baclofen is a GABA b receptor agonist, traditionally been used to control spasticity of central or spinal cord origin, but also has intrinsic anti-nociceptive properties which have been harnessed for the treatment of neuropathic pain (42-49). As described above, baclofen, in combination with amitriptyline and ketamine has been used in the treatment of chemotherapy induced neuropathy with promising results (50). Topical baclofen was found to be effective for intractable vulvodynia and proctodynia (51), as well as for resolution of neuropathic pain from acromegaly (47) Another recently published study by Somberg and Molnar shows promising results from a combination topical formulation that includes baclofen, ketamine, gabapentin, amitriptyline, bupivacaine and clonidine for treatment of diabetic neuropathy and other chronic pain conditions (52).

Interestingly, there has been one previous study examining the analgesic effect of intrathecal baclofen in a series of six patients with lumbosacral radiculopathy, not associated with spinal cord injury, treated with one injection of 250 mcg baclofen. The authors reported that the effect lasted between 6 to 39 hours (53). Additionally, a series of case reports was published by Zuniga et al. examining the use of intrathecal continuous infusion of baclofen for analgesia in patients with chronic pain whether nociceptive, neuropathic or central in origin. The authors found that intrathecal baclofen provided ongoing pain relief for prolonged periods of time and in some cases was found to be effective in several patients who had become tolerant of intrathecal morphine (53).

We are unaware of studies examining the role of topical or oral formulations of baclofen in the treatment of radicular pain.

3.3. Muscle Relaxants: Cyclobenzaprine

Cyclobenzaprine is a skeletal muscle relaxant with a tricyclic-antidepressant-like structure and a mechanism of action that is not fully understood. It is postulated to act centrally to reduce tonic motor activity. It is also believed to act on both gamma and alpha motor neurons in the ventral horn of the spinal cord (54). Oral formulations have been used commonly in the treatment of acute back pain (34) but review of available literature finds no studies examining efficacy, topical or oral formulation, for treatment of neuropathic or radicular pain.

3.4. Anesthetics: Bupivacaine

Bupivacaine is a local anesthetic that binds to voltage gated sodium channels and blocks influx into cells, thus preventing depolarization of the membrane. A benefit of using Bupivacaine in place of more commonly used lidocaine may be the prolonged duration of action (55). The majority of studies have examined the use of the Lidocaine medicated patch as discussed above, which has repeatedly been reported as superior to placebo for use in patients with diabetic neuropathy and post herpetic neuralgia. One could extrapolate those results to the use of Bupivicaine for neuropathy. With regards to use in radiculopathy, this author is unaware of studies examining the role of Bupivicaine in treatment.

3.5. Anticonvulsant: Gabapentin

A drug with both antiepileptic and analgesic properties, its mechanism of action works by inhibiting voltage gated calcium channels to decrease glutamate release and potentiate GABA transmission. It is commonly used in the treatment of neuropathic pain, specifically as a first line treatment for diabetic neuropathy, post herpetic neuralgia, central neuropathic pain, and fibromyalgia (56-59).

Given the side effect potential of systemic Gabapentin, topical use has been gaining popularity. One study examining skin permeation and antinociceptive effects of gabapentin in an in vivo pain model found that topical 5% gabapentin produced a similar reduction in nociception as systemic subcutaneous gabapentin and that topical 1% gabapentin reduced nociceptive behaviors. These findings suggest that topical administration of gabapentin may produce local antinociception (60).

A study by Hiom et al. describes the use of topical 6% gabapentin in the treatment of 23 patients with diagnoses of one of the following, PHN, post-surgical pain, complex

regional pain syndrome, painful diabetic polyneuropathy, vulvovaginodynia, trigeminal neuralgia, autonomic cephalgia, pudendal neuralgia and coccydynia. While 6 patients withdrew from the study due to lack of efficacy, 11 patients achieved 30% reduction in pain. All patients who responded to treatment experienced pain relief within 1 hour of application. Four patients reduced their systemic analgesia and one discontinued all oral analgesics (61). The topical use of gabapentin was evaluated in another study (retrospective) of 35 patients with vulvadynia in which it was well tolerated and associated with greater than 50% reduction in pain within 8 weeks in 80% of patients (62).

With regards to use in radiculopathy, in one placebo controlled study of 50 patients with lumbosacral radiculopathy found that when compared to placebo, those who received Gabapentin had improved motor and sensory function, lumbar flexion range of motion, and pain (63). In a second study, the efficacy of oral Gabapentin in acute and chronic radiculopathy was evaluated in with noted decrease in VAS pain score and significantly increased walking distances at follow up; however, 8 patients discontinued the study due to the adverse effects experienced (64). Finally, a recent study by Cohen et al. compared epidural steroid injection to oral gabapentin for the treatment of lumbosacral radiculopathy. This multicenter study included 145 participants with lumbosacral radicular pain who received either epidural steroid injection plus placebo or sham injection plus gabapentin. The authors found that while the group receiving the epidural injection had greater benefit in some outcome measures, it was modest and transient. At three months there was no significant difference between groups (65).

3.6. Hemorrheologic Agents: Pentoxifylline

Traditionally used in the treatment of intermittent claudication, it is a phosphodiesterase inhibitor that inhibits tumor necrosis factor alpha (TNF α), (66) an inflammatory cytokine found to be elevated in radiculopathy from herniated discs when compared to other back pain. This leads to the potential use of medications that inhibit TNF α for the treatment of radicular pain (67). Limited studies are available regarding the use of Pentoxifylline for pain associated with radiculopathy, but there are case reports showing potential in epidural fibrosis from failed back syndrome and a separate study showing improvement in radiation induced lumbosacral polyradiculopathy using a combination agent which included Pentoxifylline (68, 69). No studies have examined the topical formulation.

Radicular pain is one of the most common neuropathic pain syndromes, caused by compression or irritation of spinal nerve roots as they exit the spinal column and characterized by paresthesias occurring in a dermatomal distribution (10). Standard treatment consists of oral analgesics such NSAIDs and anticonvulsants such as gabapentin, with the possible addition of TCAs or opioid agents for refractory symptoms. These medications may cause a number of adverse effects ranging from sedation, dizziness and constipation, to gastrointestinal bleeding, increased risk of myocardial infarction, cardiac arrhythmia, seizure, and respiratory depression, among others (5, 35). The problem of polypharmacy and potential for drug-drug interactions further limits use. These medications may be limited in certain populations like the elderly and frail where use may increase the risk of falls, in CKD who are precluded from use of nephrotoxic agents such as NSAIDs, and there is a dose limit on medications that rely primarily on renal clearance, such as gabapentin. Given the potential for common and serious adverse effects, the use of topical analgesics has been introduced for a number of acute and chronic pain conditions (9).

This is the first report of the successful treatment of radicular pain with a topical agent, moreover, with a combination agent. In this case series, three patients presented with uncontrolled cervical and/or lumbosacral radicular pain, despite the use of various medications. Each patient, following a trial of T7, reported subjective improvement in radicular pain, improvement in function, and sleep. While pain did not completely resolve in any of the three cases, all patients reported clinically significant reduction in symptoms based on the minimal clinically important difference in pain for radicular pain (70). Given that two of the three patients had chronic radicular pain and failed spinal surgery syndrome, despite prolonged management with oral analgesics and spinal injections, a clinically significant reduction in pain accompanied by improved sleep and function should be considered a successful outcome. In such patients with limited further options that might include a surgical revision, a spinal cord stimulator or intrathecal pain pump, a trial of topical compounded analgesic agents represents a potentially more cost-effective and lower-risk option, though a larger study may better provide determination of cost analysis.

These three cases highlight the need for randomized, prospective study of both single and compounded topical agents for the treatment of radicular pain. Given the lack of literature on the treatment of radiculopathy with a single topical agent, it is unclear from this case series whether patients would have benefited from a single agent rather than the combination. Without study of the individual components within T7, identifying a single component as the most effective would be purely speculative. Future study of individual topical agents and simplified topical compounds is warranted in order to determine

the value of individual agents for the treatment of radicular pain, and whether synergy is present when adding agents together. However, anecdotally, topical lidocaine, NSAIDs, Capsaicin, and opioids in isolation frequently fail to control pain in patients with significant (and typically chronic) radicular pain. Notably, a limiting factor in the use of combination topical agents is the higher cost associated with a compounded medication. With that in mind, the topical formulation was well tolerated in all cases without noted adverse reactions and surgery was either prevented or delayed in all three cases. Adverse reactions were recorded based on patient report at follow up visits. Thus, cost analysis comparing combination topical agents, single topical agents, and other means of managing radicular pain is needed.

3.7. Conclusions

The topical formulation of diclofenac, ibuprofen, baclofen, cyclobenzaprine, bupivacaine, gabapentin, and pentoxifylline addresses both neuropathic and inflammatory components of radicular pain. It was found to be well tolerated, to reduce radicular pain as well as improve function and sleep in this case series of three patients who had failed other conservative or surgical treatment. Further study of the use of both single and combination topical agents for the treatment of radicular pain is warranted.

Footnote

Authors' Contribution: Study concept and design: Zachary L. McCormick, Christopher T. Plastaras; acquisition of data: Pegah Safaeian, Ryan Mattie, Matthew Hahn, Zachary L. McCormick, Christopher T. Plastaras; analysis and interpretation of data: Pegah Safaeian, Ryan Mattie, Matthew Hahn, Zachary L. McCormick, Christopher T. Plastaras; drafting of the manuscript: Pegah Safaeian; critical revision of the manuscript for important intellectual content: Pegah Safaeian, Ryan Mattie, Matthew Hahn, Zachary L. McCormick, Christopher T. Plastaras; statistical analysis: Zachary L. McCormick; administrative, technical, and material support: Christopher T. Plastaras; study supervision: Zachary L. McCormick, Christopher T. Plastaras.

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