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Brandon P Staub

Gianna P Casini

*Parkview Health*, [gianna.casini@parkview.com](mailto:gianna.casini@parkview.com)

Edward A Monaco

Raymond F Sekula

Trent D Emerick

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# Near-resolution of persistent idiopathic facial pain with low-dose lumbar intrathecal ziconotide: a case report

Brandon P Staub<sup>1</sup>  
Gianna P Casini<sup>2</sup>  
Edward A Monaco III<sup>3,4</sup>  
Raymond F Sekula Jr<sup>3,4</sup>  
Trent D Emerick<sup>4,5</sup>

<sup>1</sup>Department of Anesthesiology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; <sup>2</sup>Pain Management, Parkview Health, Fort Wayne, IN, USA; <sup>3</sup>Department of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; <sup>4</sup>University of Pittsburgh Physicians, Pittsburgh, PA, USA; <sup>5</sup>Division of Chronic Pain, Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

**Purpose:** Persistent idiopathic facial pain (PIFP) is a poorly defined and debilitating chronic pain state with a challenging and often inadequate treatment course. This is the first case report identifying the novel use of low-dose lumbar intrathecal ziconotide to successfully treat PIFP with nearly complete resolution of pain and minimal to no side effects.

**Methods:** The patient was a 37 year-old female whose PIFP was refractory to multimodal medication management and multiple neurovascular surgical interventions. A single-shot lumbar intrathecal trial of ziconotide (2.5 mL, equivalent 2.5 µg) was injected when she was at her baseline pain level — VAS 7/10. She received complete resolution of her pain for about 9 hours, concordant with ziconotide's half-life. She was subsequently implanted with a lumbar intrathecal delivery system.

**Results:** The patient experienced complete resolution of her facial pain with a single-shot intrathecal trial of ziconotide. The intrathecal pump system has provided nearly complete (VAS 1/10) pain relief. Two flares of pain occurred 10 and 18 months after pump placement, which subsequently resolved after increasing the ziconotide dose by 0.5 µg/day on each occasion. The patient is currently maintained on a dose of 2.0 µg/day and is pain-free.

**Conclusion:** This is the first case report describing the use of a single-shot lumbar intrathecal trial of ziconotide and subsequent placement of lumbar (as opposed to thoracic) intrathecal ziconotide pump for PIFP. A single-injection intrathecal trial is a low-risk, viable option for patients with this debilitating and frustrating pain condition. Successful trials and subsequent intrathecal pump placement with ziconotide may supplant multimodal medication management and/or invasive orofacial surgical intervention for PIFP.

**Keywords:** allodynia, chronic pain, neuropathic pain, pain disorder, pain management, persistent pain

## Introduction

Persistent idiopathic facial pain (PIFP), often previously referred to as atypical FP, is a form of excruciating and debilitating neuropathic FP. It is likely an underdiagnosed condition and has a poor prognosis.<sup>1</sup> The estimated lifetime prevalence of PIFP is approximately 0.03%, incidence 4.4 per 100,000 person years, and women in their 40s are most likely to suffer from the condition.<sup>1-3</sup> Patients with PIFP may represent approximately 10%–21% of the population of orofacial pain clinics.<sup>4,5</sup>

The International Headache Society has described PIFP as “persistent facial and/or oral pain, with varying presentations but recurring daily for more than 2 hours per day over more than 3 months, in the absence of clinical neurological deficit.”<sup>6</sup> The guidelines describe the pain as primarily dull, aching, or nagging, and the pain does

Correspondence: Trent D Emerick  
Division of Chronic Pain, Department of Anesthesiology, University of Pittsburgh School of Medicine, UPMC Montefiore Hospital, 3459 Fifth Avenue, Suite NE 570, Pittsburgh, PA 15213, USA  
Tel +1 412 692 2234  
Fax +1 412 692 2235  
Email emericktd@upmc.edu

not follow a peripheral nerve distribution. Most patients present with poorly localizable, debilitating pain along the distribution of the trigeminal nerve that does not follow a dermatomal distribution and is typically without periods of remission.<sup>1</sup> The pain ranges from dull to sharp, can be bilateral or unilateral, and engages various locations on the face.

The diagnosis of PIFP is challenging to make. Diagnosis is often one of exclusion. Due to the debilitating nature of the disorder and absence of effective treatments, patients with PIFP often seek treatment from clinicians of multiple disciplines, most commonly including pain specialists, otolaryngologists, dentists, neurologists, neurosurgeons, and psychiatrists.<sup>7</sup>

At this point, there are no curative therapies for PIFP. A relatively limited number of pharmacological, nonpharmacological, and interventional treatment modalities have been found to be moderately effective in the treatment of PIFP. Pharmacologic treatments include topical analgesics (lidocaine cream, capsaicin), botulinum-toxin injections, low-dose tricyclic antidepressants, selective serotonin-reuptake inhibitors, serotonin–norepinephrine-reuptake inhibitors, anticonvulsants, and opioids (tramadol or oxycodone). Nonpharmacological treatment regimens include cognitive behavior therapy (as an adjunct to antidepressant therapy), pulsed-radiofrequency treatment, and peripheral nerve stimulators.<sup>1</sup>

Ziconotide (Prialt; Jazz Pharmaceuticals, Dublin, Ireland), is a 25-amino-acid polybasic peptide present in the venom of *Conus magus*, a marine snail.<sup>8</sup> It selectively binds to N-type voltage-gated calcium channels on neurons, which are of particularly high density in the presynaptic terminals of primary afferent neurons that ultimately terminate in the dorsal horn of the spinal cord.<sup>9</sup> Calcium influx is subsequently disrupted and prevents release of neurotransmitters (such as glutamate) and neuropeptides that are involved in pain transmission.<sup>10–15</sup>

Intrathecal ziconotide has been used for chronic-pain control in patients suffering from malignant and nonmalignant and AIDS-associated pain, and has had notable success as a first-line monotherapy for intrathecal pump delivery.<sup>16–18</sup> In this report, we describe the first case of using low-dose lumbar administration of intrathecal ziconotide specifically for PIFP.

## Case report

Written informed consent was provided by the patient to have this case published. Institutional approval was not required to publish these case details. A 37-year-old woman was referred

to the University of Pittsburgh Medical Center's Center for Brainstem and Cranial Nerve Disorders with bilateral FP having failed multiple treatments. The pain began as left-sided dental pain in 2013. Although an etiology for her pain could not be determined, she was given a diagnosis of "atypical trigeminal neuralgia". In 2016, she developed right-sided FP of a similar quality and nature as her left-sided FP. She described the pain as starting at her left ear and radiating across her forehead, maxilla, and mandible.

The pain was exacerbated by "everything", but specifically included snow, rain, wind, cold, hot liquids, spicy food and crunchy food. The patient described her FP as starting at her left ear with radiation across her forehead, maxilla, and mandible and she rated it as 7/10 on a VAS. She did not permit palpation of her face secondarily to the pain. She trialed and failed medical management, including pregabalin, gabapentin, carbamazepine, phenytoin, levetiracetam, and nortriptyline. She had undergone two prior microvascular decompression surgeries that eliminated her pain for <2 weeks each time. She also underwent two glycerol rhizotomies with only short-lived relief. The patient denied a history of oral surgeries or procedures other than a remote history of wisdom-tooth extraction approximately 16 years prior to the onset of pain.

After evaluation at our institution, a diagnosis of PIFP was made. After discussion of all options with the patient, including repeat injections, medication management, and cervicomedullary stimulator placement, the decision was made to attempt a trial of intrathecal ziconotide in the lumbar spine as a precursor to intrathecal pump placement. The patient was evaluated by a psychologist and felt to be a reasonable candidate for intrathecal pump treatment prior to the trial.

The patient's medical history was unremarkable, other than the FP and frontal headaches that occurred approximately three times weekly and were treated with hydrocodone/acetaminophen. She is a nonsmoker. Of note, she had suffered post-dural puncture headaches with previous labor epidurals.

## Ziconotide trial

The patient was then given a single injection of 2.5 mL (2.5 µg at 1 µg per mL) of intrathecal ziconotide at the L3–L4 level. She remained in the recovery area following the injection for observation. Within approximately 2 hours of the trial, the patient had significant improvement in her VAS pain scores, down from 7/10 prior to the injection to 2/10. Classic triggers of her pain, such as drinking coffee or an ice pack on her face, did not cause any worsening of her pain. No medication side

effects, such as paranoia or hallucinations, were observed. She was monitored for 6 hours after the injection, and her pain remained approximately 2/10. The patient experienced complete resolution of her pain for approximately 9 hours. By postprocedure day 2, her FP had returned to her baseline 7/10 VAS. She developed transient symptoms of post-dural puncture headache following discharge. The patient was very satisfied with the trial and very interested in pursuing an intrathecal pump of ziconotide.

## Pump placement and follow-up

After the successful trial, the patient opted to proceed with intrathecal pump placement. The epidural space was entered in the lumbar cistern at approximately the L4–L5 level and the intrathecal catheter advanced to 17 cm from the skin. The patient's recovery was significant for likely post-dural puncture headache on postoperative day 3, as she described a global headache that improved when she assumed the supine position. She noted that this headache was different from her baseline frontal headaches. She further noted resolution of her FP to 0/10 VAS, as she had no baseline base and no pain with activities that historically had exacerbated her pain. The positional headache resolved on its own within approximately 1 week. About 1 month postoperatively, the patient went to an outside hospital (given that she lived approximately 6 hours from the University of Pittsburgh Medical Center), due to swelling at her left-lower-quadrant pump pocket-insertion site. The patient subsequently underwent surgical reexploration with laminectomy to repair a cerebrospinal fluid leak and pseudomeningocele, and was discharged home shortly thereafter.

It has been approximately 22 months since intrathecal pump placement. The patient was pain-free for approximately 10 months at a dose of 1.0 µg/day. She then experienced an acute exacerbation of her pain, and the dose was increased to 1.5 µg/day. After the dose increase, she had little (VAS 1/10) to no pain for approximately 8 additional months. She then again had an acute worsening of her pain. The daily dose of ziconotide was increased to 2.0 µg/day, and since then she has remained pain-free with no notable side effects.

## Discussion

The diagnosis of PIFP is appropriate when neuropathic FP does not align with more common causes.<sup>1</sup> Differential diagnosis is extensive and spans a variety of organ systems: musculoskeletal (temporomandibular disorder), odontogenic (dental caries), neurovascular (trigeminal autonomic cephalgias), dermatological (Sjögren's syndrome), neurological

(varicella zoster/postherpetic neuralgia), and other etiologies. Symptoms can be equally as vast and confusing, ranging from hyperalgesia to hypoalgesia, allodynia to dysesthesia to anesthesia, and intermittent to continuous pain, often with no correlating image findings or causal agent.

Treatments for PIFP are increasingly promising with modalities such as pulsed-radiofrequency ablation of the sphenopalatine ganglion, peripheral nerve-field stimulators, and botulinum toxin injections.<sup>1</sup> Ziconotide, a 25-amino-acid polybasic peptide made from the venom of *Conus magus*, a marine snail, selectively binds to N-type voltage-gated calcium channels on neurons that block neurotransmission from primary afferent nociceptors.<sup>8</sup> Intrathecal administration of ziconotide has had some efficacy in chronic-pain patients, ranging from pain secondary to nonmalignant conditions to cancer pain to refractory pain in AIDS patients. There has also been some documentation of its use for neuropathically mediated FP, including trigeminal neuralgia<sup>19,20</sup> and a case series of three patients with PIFP.<sup>21</sup>

The patient featured in this case report experienced temporary complete resolution of her FP with a single-injection intrathecal trial and nearly complete resolution of pain with intrathecal monotherapy via intrathecal pump administration. Ziconotide and morphine are the only two agents US Food and Drug Administration-approved for intrathecal pain management. Ziconotide is a hydrophilic molecule. This accounts for the ability to administer it in the lumbar region, yet patients are able to experience relief for FP without the need for catheter-tip placement at the cervicomedullary junction.<sup>22</sup> The exact mechanism by which intrathecal ziconotide results in relief of idiopathic FP is not entirely clear. It has been hypothesized that ziconotide can also exert some action centrally in regions of the cerebrospinal fluid aqueduct, eg, the caudate nucleus of the trigeminal nerve, with resultant relief of trigeminal neuralgia.<sup>19</sup>

The 2017 Polyanalgesic Consensus Conference stated that ziconotide was the first-line treatment for intrathecal analgesia for chronic refractory pain.<sup>23</sup> Additionally, current data suggest that intrathecal ziconotide demonstrates greater efficacy when ziconotide is the first monotherapy trialed.<sup>24</sup> Pruzik et al were able to treat chronic pain effectively in 53% of patients with intrathecal monotherapy of ziconotide as a first-line intrathecal agent.<sup>18</sup> The study utilized a low dose and slow titration of ziconotide. Unlike morphine, intrathecal ziconotide can be stopped abruptly without concern for withdrawal and is not associated with risk of respiratory depression. Pruzik et al did not note any withdrawal

symptoms in their patients upon stopping the ziconotide after 3 months of use.

Various dosing strategies of intrathecal ziconotide continue to be studied, but ziconotide has yet to be used as a mainstream intrathecal medication for chronic pain, despite not causing granulomas at the catheter site and providing opioid-sparing treatment.<sup>25</sup> The maximum daily dose of intrathecal ziconotide has been described as 19.2 µg/day.<sup>26</sup> Ziconotide is often cited for having a narrow therapeutic window that can incite a number of adverse effects, including nausea, dizziness, diarrhea, peripheral edema, memory impairment, asthenia, balance disorder, ataxia, abnormal gait, fatigue, somnolence, urinary tract infection, headache, vomiting, pain, increased creatine kinase, and pruritus.<sup>24,27</sup> Psychiatric symptoms associated with ziconotide include confusion (33%), memory impairment (22%), speech disorder (14%), hallucinations (12%), paranoid reactions (3%), hostility (2%), delirium (2%), psychosis (1%), manic reactions (0.4%), aphasia (12%), abnormal thinking (8%), and amnesia (1%).<sup>28</sup> There are also data to support suicidality being increased with ziconotide.<sup>29,30</sup> To that end, it is contraindicated in patients with psychosis history. Adverse events and serious adverse events were reported in 71.0% and 21.5% of patients in an interim analysis of data from the PRIZM study.<sup>24</sup> Other studies have reported rates of adverse events of 57%–92.9%.<sup>31–33</sup> Our patient did not experience any negative side effects during either the ziconotide trial or since placement of the intrathecal pump. Despite its side-effect profile, ziconotide appears to have great potential for the treatment of chronic pain, including PIFP.

Ziconotide has been shown to have a volume of distribution equivalent to the total estimated cerebrospinal fluid volume of approximately 140 mL.<sup>26</sup> Therefore, even low intrathecal infusion dosing strategies likely circulate ziconotide from the lumbar intrathecal space to the cerebrospinal fluid surrounding brain and brain-stem tissue. In a study of continuous intrathecal infusion rates of 0.1–7.0 µg/h in patients with chronic pain, a majority did not have detectable plasma levels of ziconotide.<sup>26</sup> No specific dose has been delineated for when side effects become more likely. The general tendency is to start with low infusion rates of around 1.2 µg/day and up-titrate very slowly.<sup>18</sup>

To date, only one case series has documented the use of intrathecal ziconotide specifically for PIFP.<sup>21</sup> Lux and Rasche documented doses of 2.4, 3.9, and 6.0 µg/day for three patients that they treated for PIFP.<sup>21</sup> Treatment was stopped in one patient (2.4 µg/day dose) due to side effects. The other two patients experienced reduction in their pain

scores from numeric rating scale (NRS) 10 to NRS 4 and NRS 9 to NRS 6.<sup>21</sup> Our case study is different from Lux and Rasche in a number of ways. We utilized a single-injection trial instead of an external pump infusion trial, which has a lower risk profile with regard to potential adverse effects. Our patient's intrathecal catheter was much lower in the spinal column (lumbar cistern), rather than in the mid-thoracic region, and finally our patient experienced complete resolution of her pain, both during the single-injection trial and for approximately 10 months after pump placement at a low dose (1.0 µg/day) of ziconotide. Our patient has required two separate dose increases (0.5 µg/day each time), and at the current dose (2.0 µg/day) remains pain- and side effect-free.

The patient has required two dose increases of ziconotide since the placement of her intrathecal ziconotide pump. This may raise the question of whether the patient is developing a tolerance to ziconotide. This seems unlikely, as data from other large registries and an open-label trial suggest the absence of a tolerance effect.<sup>23,34,35</sup> For example, Raffaelli et al noted that patients that stayed in their study >6 months were receiving stable doses of ziconotide, which may suggest the absence of a tolerance effect.<sup>34</sup> Deer et al documented mean doses of 3.2 µg/day at 12 weeks and 1.9 µg/day at 12 months, further supporting the assertion that patients do not develop tolerance.<sup>23</sup>

## Conclusion

This is the first case report describing the use of a single-shot lumbar intrathecal trial of ziconotide and subsequent placement of a lumbar intrathecal ziconotide pump for PIFP with a protracted pain-free period after pump placement. A single-injection intrathecal trial is a low-risk, viable option for patients with this debilitating and frustrating pain condition. Successful trials and subsequent intrathecal pump placement with use of ziconotide may supplant multimodal medication management and/or invasive orofacial surgical intervention for PIFP.

## Disclosure

The authors report no conflicts of interest in this work.

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