



# Colombian Journal of Anesthesiology

*Revista Colombiana de Anestesiología*

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Wolters Kluwer

## Multimodal intrathecal therapy for phantom limb pain: a report of 2 cases

### Terapia intratecal multimodal para tratamiento de dolor de miembro fantasma: Reporte de dos casos

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**Keywords:** Pain Management, Phantom Limb, Infusion Pumps, Infusions, Spinal, Case Reports

**Palabras clave:** Manejo del Dolor, Miembro Fantasma, Bombas de Infusión, Infusión Espinal, Informes de Casos

#### Abstract

**Introduction:** Phantom limb pain (PLP) is a chronic debilitating condition, frequently observed in amputees. At present, there is no standard treatment, and its optimal management requires a multidisciplinary approach in which minimally invasive treatment should be considered in more complex cases.

**Objective:** To report successful treatment of 2 cases of PLP treated with ziconotide as part of multimodal intrathecal management.

**Materials and methods:** Descriptive, retrospective case report developed in a multimodal pain treatment unit.

**Results:** A total of 2 cases of patients with diagnosis of PLP refractory to medical therapy, treated with intrathecal multimodal therapy, are presented. Their favorable course, with 50% pain reduction, is described.

**Conclusion:** Implantation of infusion systems for administration of intrathecal analgesia with ziconotide at the cervical and supraspinal level proved to be effective in the described cases; this technique should be evaluated in specific trials for the treatment of PLP refractory to other therapies.

#### Resumen

**Introducción:** El dolor de miembro fantasma es una condición crónica debilitante, frecuentemente observada en pacientes amputados. En la actualidad carece de un estándar de tratamiento. Su óptimo manejo requiere un abordaje multidisciplinario en el que el tratamiento mínimamente invasivo debe ser considerado en los casos más complejos.

**Objetivo:** Reportar el éxito obtenido en dos casos de dolor de miembro fantasma tratados mediante ziconotida, como parte del manejo multimodal intratecal.

**Materiales y métodos:** Se trata de un reporte de casos, descriptivo y retrospectivo, desarrollado en una unidad de tratamiento integral del dolor.

**Resultados:** Se presentan dos casos de pacientes con diagnóstico de dolor de miembro fantasma refractario a tratamiento médico, tratados con terapia multimodal intratecal; se describe su evolución favorable después del inicio de la terapia, con una reducción de dolor del 50 %.

**Conclusiones:** La implantación de sistemas de infusión para administración de analgesia intratecal con ziconotida a nivel cervical y supraespinal demostró ser eficaz en los casos descritos;

How to cite this article: Carvajal G, Rocha A, Dupoirion D. Multimodal intrathecal therapy for phantom limb pain: a report of 2 cases. Colombian Journal of Anesthesiology. 2019;47:198–201.

Read the Spanish version of this article at: <http://links.lww.com/RCA/A858>.

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Colombian Journal of Anesthesiology (2019) 47:3

<http://dx.doi.org/10.1097/CJ9.0000000000000106>

esta técnica debe ser evaluada en ensayos específicos para el tratamiento del dolor de miembro fantasma en miembros superiores, refractario a otras terapias.

## Introduction

Phantom limb pain (PLP) is a neuropathic-type pain secondary to the presence of painful sensation in an absent limb, and dependent on central factors such as spinal plasticity and cortical reorganization, usually difficult to manage.<sup>1,2</sup> PLP occurs in 50% to 80% of amputees,<sup>3</sup> and it is also associated with psychological and peripheral nervous system factors.<sup>3-6</sup>

At present, there is no standard treatment, and evidence is limited.<sup>7-9</sup> Few clinical trials have evaluated a specific pharmacological therapy for this intervention, and those that exist are of low methodological quality.<sup>9,10</sup>

Intrathecal analgesia is indicated for somatic and neuropathic pain associated or not with cancer.<sup>11</sup> Ziconotide is a conotoxin originally isolated from the *Conus magus* mollusk and is currently the only non-opioid analgesic for intrathecal use approved both by the European Medicines Agency and the United States Food and Drug Administration (FDA). The objective of this work is to present the use of this drug as part of multimodal intrathecal management in patients with PLP.<sup>11</sup>

## Materials and methods

Once the approval of the bioethics committee (Approval No. 2013 72) and patient informed consents were obtained, 2 cases of chronic PLP refractory to pharmacological treatment were selected in the pain department of the *Institut de Cancérologie de l'Ouest* in France, and treated by means of an implantable delivery system for intrathecal analgesia. The information was gathered from the patients' electronic clinical records.

## Results

### Case 1

A 79-year-old female patient with recurrent renal cancer presented with a pathological right humeral fracture that required osteosynthesis; however, amputation was warranted because of an infectious complication. Postoperatively, the patient developed PLP in the thoracic limb, accompanied by a sensation of an uncomfortably positioned limb, with pain of 9/10 on the Numerical Rating Scale (NRS). Despite treatment with gabapentin 1200 mg/d, amitriptyline 10 mg/d and transdermal fentanyl 25 µg/h, there was no adequate pain relief, and added sedation was considered unacceptable by the patient.

A Synchronomed II (Medtronic, U.S.A.) intrathecal infusion system was then implanted with a percutaneous tech-

nique using a puncture at L2 under fluoroscopic guidance. The tip of the catheter was placed at the level of C1 (cervical), and treatment was initiated with morphine 0.5 mg, ropivacaine 6 mg, and ziconotide 0.2 µg per day. Systemic opioids were interrupted during the postoperative period, and gabapentin and amitriptyline were gradually discontinued over a 1-week period. Side effects diminished over a 6-month follow-up period and the score on the NRS dropped to 2/10, with the patient reporting only phantom limb sensation.

### Case 2

A 60-year-old male patient with a history of 3 decades of pain: in 1983 he sustained a traumatic amputation of the right upper limb with brachial plexus avulsion, and ensuing PLP. The patient received several treatments unsuccessfully, the most recent including transdermal fentanyl 100 µg/h and transmucosal rescue fentanyl 200 µg 3 times a day, carbamazepine 400 mg/d and amitriptyline 25 mg/d. He had undergone sympathetic nerve blocks, placement of a spinal stimulation system (removed due to epidural abscess) and implantation of an additional cervical electrode (removed due to breakage). A lesional procedure was performed in the dorsal root entry area, interscalene block, and even motor cortex stimulator which led to a good, though short-lived, clinical response (50% pain reduction). The device was inactive because, when the therapeutic effect was lost, the patient demanded discontinuation of the therapy.

At the time of assessment, he complained of PLP with a score of 6/10 on the NRS. The option of implanting a Synchronomed II (Medtronic, U.S.A.) intrathecal infusion delivery system was selected. An Ascenda (Medtronic, U.S.A.) catheter was passed under fluoroscopic guidance beyond the cervical level (cisterna magna), through a puncture at L3 (Fig. 1). Treatment was initiated with morphine 1.7 mg, ropivacaine 9.9 mg and ziconotide 1.1 µg. A period of 2 months after the intervention, the patient reported 50% pain reduction with adequate tolerance.

## Discussion

Intrathecal analgesia is a validated technique for the treatment of chronic pain refractory to conventional medical therapy. This route of administration has shown superiority when compared to systemic management.<sup>12</sup>

Multiple drugs have been described in the treatment of complex pain cases, including local anesthetics, opioids, ziconotide, baclofen, clonidine, and midazolam; however, only morphine, baclofen, and ziconotide have FDA approval.<sup>11</sup>

Ziconotide depends on presynaptic blockade of N-type spinal and cortical calcium channels and, as calcium influx diminishes, there is a drop in the release of pain neurotransmitters.<sup>13,14</sup> The polyanalgesia consensus rec-

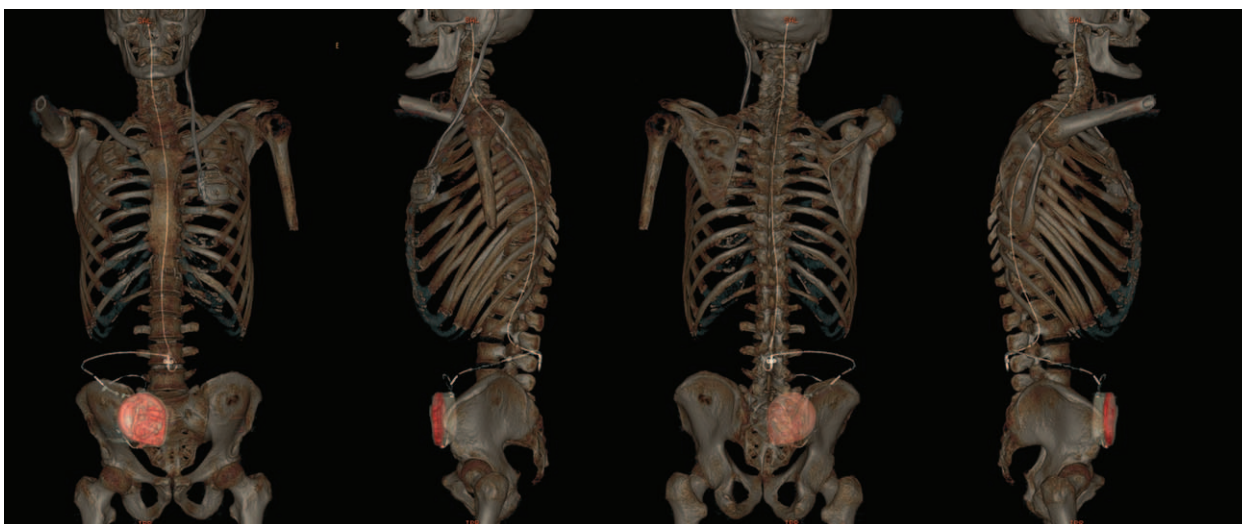


Figure 1. 3D high-resolution CT reconstruction with the system in place. The tip of the catheter is seen at the level of the cisterna magna. 3D=three dimensional, CT=computed tomography. Source: Author.

ommends this therapy as first-line in the management of neuropathic and nociceptive pain, associated or not with cancer.<sup>11</sup> It is administered intrathecally and its adverse effects may include visual hallucinations, ataxia, creatinine kinase elevation (CPK), and hypotension.<sup>15</sup> No undesirable adverse effects, particularly cognitive, were seen in either of these 2 cases, and there was no CPK elevation. Cerebral intraventricular analgesia has been described with good results, one of the first reports being that of a patient with a 23-history of pain due to brachial plexus avulsion.<sup>16</sup> The efficacy of ziconotide in the treatment of refractory pain has been demonstrated in several scenarios.<sup>17–20</sup> Intrathecal administration of opioids and local anaesthetics has been described exceptionally in cases of PLP of the lower extremity.<sup>21,22</sup>

Our report is consistent with prior publications like the trial by Staats et al<sup>19</sup> in a population of HIV-related pain, in which 5 patients received ziconotide, achieving complete pain relief, with response to treatment in 50% of all the patients, compared to 17.5% in the placebo group ( $P=0.001$ ).

Later, Wermeling and Berger<sup>18</sup> described patients with complex regional pain syndrome, lumbar radiculitis, and acquired immunodeficiency syndrome who achieved substantial persistent relief even after infusion discontinuation.

Staquet et al<sup>20</sup> reported cerebral intraventricular administration of a combination of ziconotide, morphine, and ropivacaine in patients with intractable cancer pain and central neuropathic pain, again with favorable results (reported pain score reduction from 9.5 to 3.5). The technique described in this work is particular because of the high cervical location in the 2 patients, given the presence of upper limb PLP.

The limitations of this study have to do with its descriptive nature and low recruitment, explained by the exceptional use of the technique; however, it opens the door to further studies with more weight that can provide evidence about the use of these drugs at the cervical and supraspinal level.

## Conclusion

The use of implantable drug delivery devices for the administration of intrathecal analgesia with ziconotide at the cervical and supraspinal level appears to be a promising strategy for the treatment of refractory upper PLP. It must be considered as a therapeutic option offered in expert pain centers, considering the complexity of the technique and the inherent risks.

This work was presented at the World Congress on Pain Medicine and Regional Anesthesia in April 2018, in New York.

## Ethical responsibility

**Human and animal protection.** The authors declare that no animal or human experiments were carried out for this research.

**Data confidentiality.** The authors declare having followed the protocols of their institution regarding patient data disclosure.

**Informed consent.** Informed consent was obtained from all the individual participants included in the study.

## Funding

None of the authors received external funding for the preparation of this work.

## Conflict of interest

The authors certify that neither they or any of their family members have any commercial association (consulting work, shares, equity participation, patent/license agreements, etc.) that may represent a conflict of interest in relation to the submitted manuscript. This work was presented at the World Congress on Pain Medicine and Regional Anesthesia in April 2018, in New York.

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