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LETTER TO THE EDITOR

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Successful Pain Management with Epidural Oxytocin

Miguel Condés-Lara,[1] Héctor Zayas-González,[1,2] Alfredo Manzano-García,[1] Estefanía Córdova-Quiroz,[2] Juan Granados-Mortera,[2] Marco García-Cuevas,[2] Julio Morales-Gómez[2] & Abimael González-Hernández[1]

1 Departamento de Neurobiología del Desarrollo y Neurofisiología, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Querétaro, México

2 Hospital Regional de Petróleos Mexicanos, Salamanca, Guanajuato, México

Correspondence
A. González-Hernández, Departamento de Neurobiología del Desarrollo y Neurofisiología, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Boulevard Juriquilla 3001, Querétaro 76230, México.
Tel/Fax: +52-442-238-1042;
E-mail: abimaelgh@gmail.com
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Pain is a prevalent symptom experienced by more than 70% of patients with advanced cancer. Although opioid analgesics are recognized as the first-line treatment in moderate to severe cancer pain, patients can develop intolerable adverse effects (e.g., respiratory depression). In this context, the discovery of new compounds to treat pain remains as a key challenge. Recently, oxytocin has emerged as an interesting molecule to induce analgesia [1–4]. Basic research in rodents shows that spinal oxytocin (endogenous or exogenous) induces antinociception [5,6]. Therefore, although a recent Phase I study showed that intrathecal oxytocin failed to modify the pain score to noxious stimuli [3], the potential analgesic effect of this peptide in hypersensitivity states remains unclear. Here, we report two cases of intense chronic pain and its responses to epidural oxytocin-based treatment. Both cases were reviewed and approved by our institutional ethic committee following the ethical standards established in the Declaration of Helsinki and the patients gave their informed consent.

Patient 1

A 72-year-old female, with a diagnosis of refractory cancer pain secondary to: (1) terminal phase, metastatic uterine cancer, (2) pathological pelvis, and (3) right hip fractures, was admitted to the Emergency Room (ER) at the Hospital. Previously, she had been treated with transdermal buprenorphine (52.5 μg/h) with poor results for pain relief. Physical examination showed a painful palpable mass in the lower abdomen, a shortened left lower limb with external rotation and pain with mobilization. Using the visual analogue scale (VAS), the pain score was 8–9. An epidural catheter was inserted, and a bolus (4 mL) of 0.1% ropivacaine plus 500 μg morphine was given every 12 h. Along with reduction in pain (VAS: 2), a fall in the alert state was elicited (Richmond Agitation Sedation Scale, RASS: −2). The patient was discharged, and transdermal buprenorphine (52.5 μg/h) was prescribed. Also, as rescue treatment, epidural 0.1% ropivacaine plus 300 μg morphine was prescribed.

One week later, the patient was re-admitted showing signs of generalized deterioration accompanied by data indicating the onset of agonic stage. At this point, we started the pain management with a continuous intravenous (i.v.) infusion of morphine (100 μg/kg). An increase of sedation (RASS −2, −3) and poor analgesic response (VAS: 6–7) was achieved (see Table 1). Under these conditions, 2 international units (1 IU ~ 2 μg) of oxytocin (oxitopisa®, PiSA® Farmaceutica, Guadalajara, México) plus 0.1% ropivacaine were given (4 mL every 12 h for 24 h). After epidural administration of oxytocin (~20 min), the pain score decreased (VAS: 2) without alterations in the consciousness state (RASS: 0), whereas the cardiovascular parameters were not modified (data not shown). Interestingly, her appetite and interaction with her family was improved. The following day, the patient received epidural morphine (500 μg) plus 0.1% ropivacaine; a similar level of analgesia (VAS: 1–2) accompanied with sedation (RASS: −2, −3) was observed. On the fourth day, the patient was subjected to epidural oxytocin (2 IU); an adequate level of analgesia (VAS: 1–2) without sedation (RASS: 0) was achieved. Social interaction and appetite were also observed. The patient quietly passed away without pain in her home, with her family in attendance.

Patient 2

An 85-year-old male patient, with diagnosis of refractory cancer pain secondary to: (1) prostate cancer and (2) pathological vertebral and pelvis fractures caused by metastatic bone cancer, was admitted to the ER at the Hospital. The patient presented intense

Table 1 Values of the visual analogue scale, Richmond Agitation Sedation Scale, Lattinen Index, and the Karnofsky Score in patient 1 obtained before and after intravenous or epidural administration of morphine or oxytocin. Note that after epidural morphine or oxytocin administration, the pain was relieved (measured with VAS and Lattinen Index). It is interesting to note that after oxytocin, the values of VAS and Lattinen Index were similar to treatment with morphine, whereas the RASS score was improved, suggesting that epidural oxytocin exerts an analgesic action without sedation, as observed with morphine

	Schedule treatment/day				
	Day 1 morphine (i.v.)	Day 2 oxytocin (epidural)	Day 3 morphine (epidural)	Day 4 oxytocin (epidural)	Day 5 morphine (epidural)
VAS					
Before	8–9	6–7	5–6	6	5
After	6–7	1–2	1–2	1–2	1–2
RASS					
Before	−1	−2	0	−2	−3
After	−2, −3	0	−2	0	−3
Lattinen index					
Before	18	18	16	16	16
After	16	10	10	10	10
Karnofsky score	40	40	40	30	10

i.v., intravenous; RASS, Richmond Agitation Sedation Scale; VAS, Visual Analogue Scale.

low back pain (VAS: 9) accompanied by motor impairment of limbs. Hyperalgesia in the inguinal area (measured with Von Frey filaments) was referred. An epidural catheter was inserted, and treatment was given as follows: the first, third, fifth, and sixth week of treatment, the patient received 2 IU of oxytocin plus 0.1% ropivacaine in 4 mL every 12 h. To track the quality of the analgesia, the patient and his family were instructed to keep a pain diary. The weeks the patient received oxytocin, he reported no pain (VAS: 1–2; RASS: 0). At the weekly follow-up consultations, the relatives reported a good level of social interaction and appetite, with no changes in the vital signs. The hyperalgesia in the inguinal area stayed low. The second and fourth week, the patient received epidural morphine (500 μg) plus 0.1% ropivacaine; a similar level of analgesia (VAS: 1–2) was obtained, but was accompanied by sedation (RASS: −1, −2). From the fifth week, the patient's general condition deteriorated leading to his death at the end of the sixth week of treatment.

Together, these cases suggest that epidural oxytocin is able to induce analgesia in patients with intense chronic pain. Considering that: (1) previous report in dogs showed no substantial neurotoxic effect after intrathecal bolus of oxytocin (11–550 μg) [7]; and (2) recent human phase I preclinical study established the safety of intrathecal administration of this neuropeptide [3], we decided to treat our patients with epidural oxytocin. As oxytocin receptors are expressed at the spinal dorsal horn levels in monkeys [8] and rodents [9], the analgesic effect observed in our patients may be mediated by spinal segmental mechanisms. Nevertheless, the possible involvement of supraspinal mechanisms (due to the leaking in the cerebrospinal fluid) cannot be excluded [10]. While the cellular mechanisms to induce analgesia are still being investigated, the overall oxytocin-induced analgesia was undeniable.

Notably, our patients were more conscious and had better interactions with their relatives and more appetite on the days they received oxytocin. These responses suggest that their mood was improved. Remarkably, although the performance status (Karnofsky score) in the first patient was not modified, this report constitutes the first evidence in humans showing that epidural oxytocin has a potent analgesic action similar to morphine without its adverse effects. In addition, it is interesting to note that the dose used (2 IU/12 h) was much lower than the one estimated in the Phase I study [3], but the analgesia achieved was similar to that with morphine. These data reinforce the idea that this peptide could play a key role in pain modulation in hypersensitivity states. Furthermore, although we used a commercial oxytocin pharmaceutical formulation instead of oxytocin formulated in preservative-free solution, the risk-to-benefit ratio seemed acceptable. Indeed, as stated in article 37 (Unproven Intervention in Clinical Practice) of the Declaration of Helsinki, we judged that epidural oxytocin could offer our patients the alleviation of their suffering.

To the best of our knowledge, these cases provide the first evidence for the efficacy of spinal oxytocin alleviating intense pain. Certainly, more detailed studies are required to establish unequivocally the analgesic properties of epidural oxytocin, but this report suggests that in addition to analgesia, oxytocin improves the life quality of patients. Undeniably, oxytocin emerges as an outstanding potential medicine for pain management.

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Conflict of Interests

The authors declare no conflict of interest. The sponsors had no further role in (1) study design, (2) collection, analysis and interpretation of data, (3) the writing of the report, and (4) the decision to submit the article for publication.

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