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PERINEURAL BOTULINUM TOXIN INJECTION FOR CANCER-RELATED PAIN: CASE REPORT OF TWO PATIENT

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Background: Management of cancer-related pain is an important public health issue, with significant impacts on patient quality of life. Interventional techniques for pain relief, such as perineural catheters, are widespread in clinical practice, allowing the reduction of reliance on morphine. However, their use can result in difficulties, such as catheter dislodgement, leading to a loss of efficacy. Alternative techniques may therefore be advantageous. One such technique is the perineural injection of botulinum toxin (BoNT), a neurotoxin with motor blocking properties, which is reported to exert long-term analgesic effects.

Case Report: Herein, we describe 2 cases of patients with refractory cancer-related pain, of differing origin, treated by perineural BoNT injection. In both cases, medium-term analgesic effects were achieved from a single injection.

Conclusion: These case reports add to the growing literature on the use of BoNT for cancer-related pain relief, and support calls for future randomized clinical trials in this area.

Key words: Botulinum toxin, cancer-related pain, perineural block, interventional pain management.

BACKGROUND

The management of chronic cancer-related pain is a major public health issue (1). The underlying pain-generating mechanisms are most often a combination of nociceptive and neuropathic in origin, in connection with the consequences of compression or tumor invasion, or secondary to treatment (chemotherapy, radiotherapy, surgery) (2).

Usually, drug management of cancer pain, and particularly opioid treatment, is complicated by the rapid development of side effects and limited efficacy, restricting its use (3). In accordance with the fourth step of the World Health Organization scale, the use of interventional techniques can be proposed, in particular continuous perineural block in the case of tumoral plexus or truncal invasion (4). These blocks have an analgesic effect, which allows the reduction of the patient's dose of morphine. Despite the fact that most current knowledge is based on case reports or series, these techniques are routinely used in clinical practice (5). However, the use of a continuous perineural catheter, as is required for these techniques, has disadvantages, including the risk of infection during prolonged use and the dislodgement of the catheter (6,7).

Botulinum toxin (BoNT) is a neurotoxin whose action involves blocking the exocytosis of neurotransmitters and inflammation mediators at the neuronal level by binding to the synaptosomal-associated protein (SNAP-25). Historically, intramuscular injection of BoNT has been used for its motor blocking properties

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in the treatment of spasticity in common neurological disorders (8). BoNT is also a recommended treatment for the management of localized neuropathic pain (9). Subcutaneous injection in the painful area improves localized neuropathic symptoms. Other studies have described perineural administration of BoNT as offering a significantly long-lasting therapeutic effect, especially around the greater occipital nerve or the trigeminal nerve (10). In recent years, several studies have highlighted the interest of BoNT in cancer-related pain syndromes (11), with the majority of studies reporting its use against painful scar tissue or local muscle spasms following surgery or radiotherapy (12).

For the first time, we report a medium term analgesic effect following a single perineural injection of BoNT in 2 cases of refractory cancer pain; one patient presenting femoral compression by a sarcoma and the other presenting with Pancoast's syndrome in the context of lung adenocarcinoma.

CASE PRESENTATION

Case 1

We report a 56-year-old man diagnosed with a sarcoma after reporting pain and swelling at the root of the right thigh. Magnetic resonance imaging revealed a mass surrounding the neurovascular bundle at the femoral level. Primary chemotherapy was initiated with doxorubicin and ifosfamide (3 rounds), switched by radiotherapy (50 Gy in 25 fractions) due to the tumoral progression. Clinically, the patient presented with a pain in the right lower limb, characterized by a mixed component, nociceptive and neuropathic, due to nerve compression at the root of the thigh and likely associated with radiotherapy of the tumor in the region of the femoral nerve. An intravenous morphine treatment was rapidly initiated (up to 100 mg per day), associated with a continuous infusion of ketamine (100 mg per day) and antineuropathic treatments, such as gabapentin (2,400 mg per day) and amitriptyline (50 mg per day). Despite the treatment, pain fluctuated from 7 to 9 on a visual analog scale (VAS) ranging from 0–10. Moreover, the increase in dose was also limited by the appearance of side effects, such as confusion, constipation, and nausea. A femoral catheter was then placed, connected to a subcutaneous implantable injection system, in order to reduce the risk of infection. The analgesic effectiveness of the femoral block was rapidly observable, however, after one week, a zone of cutaneous necrosis appeared next to the implantable port, thus requiring its removal (Fig. 1).

In order to achieve sustained pain relief, we proposed a perineural infiltration of BoNT to the patient, next to the right femoral nerve. After obtaining the patient's agreement, we carried out a hydrodissection using ropivacaine (2 mg/mL, 4 mL in total), followed by a perineural injection of BoNT type A (100 units, Xeomin®, 50 units/mL of saline) around the femoral nerve guided by sonography. At one week of follow-up, the patient reported significantly reduced levels of pain, with scores ranging from 3–4 out of 10 on the VAS. This represented a reduction of up to 50% of the initial pain score, allowing to stop the ketamine treatment and decrease the dose of intravenous morphine. However, a progression of the oncological disease was noted despite chemotherapy and radiotherapy. A surgical intervention was thus carried out one month after the BoNT injection. Interestingly, the duration of analgesia was effective up to the time of surgery. During the intervention, the tumor was removed, as well as the femoral neurovascular bundle.

Case 2

We also report a 55-year-old woman, recovering from an addiction to heroin and under methadone treatment, with right upper limb and back pain. Chest computed tomography revealed a mass, located at the apex of the right lung and different secondary metastasis along the spine. A bone biopsy confirmed a lung adenocarcinoma. Physical examination indicated Pancoast's syndrome and Horner's syndrome (myosis, mild ptosis of the right eyelid). The patient described a pain score of 10 out of 10 on the VAS in the territories of ulnar and median nerve, associated with a functional impotence of the right upper limb due to the pain generated by the compression of the tumoral mass on the right brachial plexus. Despite increasing the patient's medication with methadone (60 mg per day), rivotril (5 mg per day), and antineuropathic treatment, such as gabapentin (1200 mg per day) or venlafaxine (150 mg per day), the patient presented with painful paresthesias and major mechanical allodynia in the area of the median and ulnar nerve from the upper right arm down to the right hand. The patient also presented a motor impairment in relation to the pain. After obtaining the patient's agreement, we performed perineural BoNT type A infiltration, (75 units around the median nerve and 75 units around the ulnar nerve, Xeomin®, 25 units/mL of

saline), via the axillary approach guided by sonography. The patient reported a decreased intensity of pain (3–4 out of 10 on the VAS) after 5 days. After 3 months, the patient described persistent analgesia (2 out of 10 on the VAS) associated with partial functional recovery of the upper limb. However, the patient reported ongoing paraesthesia next to the fifth finger. Unfortunately, the patient's oncological disease had an unfavorable progression, with the appearance of diffuse metastatic lesions, ultimately leading to the death of the patient.

DISCUSSION

In these case reports, a single perineural injection of BoNT resulted in significant medium-term analgesia. Due to the presence of progressive oncological disease, patient follow-up could not be longer than a few months. However, owing to the 3–6 month duration of action that is reported in the literature, it should be noted that BoNT may be used for long-term neuromodulation (13).

The use of BoNT is particularly interesting as an alternative to continuous perineural catheters. The perineural use of BoNT seems to bring 2 major advantages compared to the perineural catheter. First, we can highlight its safety and its ease of use. Although catheter complications, such as infection or hematoma are rare, the use of a single BoNT injection would allow the avoidance of these risks completely. Moreover, nerve block failure may result from technical complications, such as displacement, obstruction or disconnection. Such complications are often described during the patient's follow-up at home and lead to a loss of efficacy (14). Few side effects are linked to BoNT injection, especially with intramuscular or subcutaneous injection (9,11). Perineural administration, especially on the face, can cause transient muscle weakness lasting a few months (10). A clinical study in patients with peripheral neuropathic pain reported transient muscle weakness in patients after perineural injection of BoNT to the upper limb, however, this only concerned 2 patients having received truncular radial injection and was without functional incapacity (15). Second, and perhaps of most interest, is that the use of BoNT provides the possibility to maintain patient autonomy, as it requires much less care management than a perineural catheter. Indeed, the perineural catheter requires a significant amount of monitoring, including daily visits from a nurse to check the entry point and the wound dressing. In contrast, BoNT requires a single injection and limited follow-up, ensuring that the patient's daily life is minimally impacted.

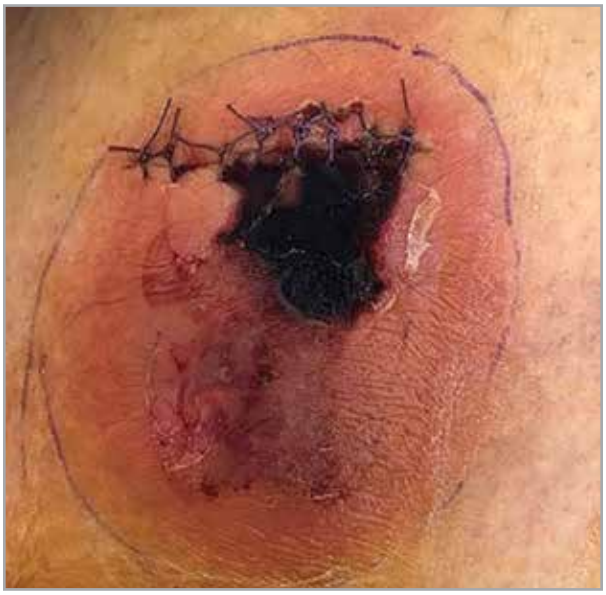

Fig. 1. Necrotic zone visible at the site of subcutaneous implantable injection system.
The implantable port was ablated after one week due to the presence of cutaneous necrosis. The suture was carried out in sterile conditions and the patient took a 7-day course of antibiotic therapy (amoxicillin).

CONCLUSION

The use of perineural BoNT for cancer-related pain can provide long-lasting pain relief, of at least a few months. It appears to be an effective and safe alternative to continuous peripheral block. Randomized clinical trials are now necessary to investigate the use of perineural BoNT for cancer-related pain, to determine an effective dose, and to confirm its place in the therapeutic arsenal of cancer pain management.

Author Contributions

YB reviewed the literature, wrote and revised the manuscript and approved the final version to be published. DT critically revised the manuscript and approved the final version to be published.

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