・病例報告・

Pain control with Methadone and Ketamine in Morphine nonresponsive terminal cancer pain

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Introduction

Pain management remains one of the major challenges in the practice of palliative medicine. Approximately 80%-90% of pain due to cancer can be relieved relatively simply with oral analgesics and adjuvant drugs in accordance with the WHO guidelines. Nevertheless, there remains a small percentage of patients who experience severe pain despite rapid upward titration of opioid analgesics in their last days. Therefore, a comprehensive assessment and specialized management are needed in such cases. Methadone and ketamine in these cases with intractable neuropathic pain proved their efficacy.

CASE REPORT

Case 1. A 67-year-old woman with advanced cervical cancer was diagnosed in July 2016. External Beam radiotherapy to the pelvis 40 Gy/20 Fr with concurrent weekly Cispalatin was given. Chemoradiotherapy was completed in October 2016.

The patient was admitted with progressive low back pain accompanied by weakness of the lower limbs for 2 months. Metastasis to the spine (T3, T4) and pelvic lymph nodes was found 2 months ago. The patient and her family refused further radiotherapy despite the paraplegia from mailignant spinal cord compression. Corticosteroids were started since then but were not very effective. Before admission, she was taking Arcoxia60 mgqd and tramadol 50 mg q8 h for her pain. When admitted, she complained of stabbing pain on her low back (6/10 on VAS scale), with radiation to her legs and exacerbation by movement. Moreover, weakness in the legs (the muscle power only 3) and urinary retention and constipation had already started. Then, Foley was inserted.

First, we titrated tramadol to 100 mg q8 h. Neurontin 300 mgqN and paracetamol 500 mg q8 h were added. During the first three days, her pain was not controlled very well, and she always required 10 mg/5 ml morphine or Voren IM for breakthrough pain after movement. Morphine was required 2-3 times per day, but the pain score only decreased to 4-5/10, and she presented vomiting because of morphine even though we prescribed antiemetics.

Therefore, after 3 days, we decided to switch from tramadol and morphine to methadone because of her neuropathic pain and intractable adverse side effects of morphine. We started methadone with a low dose of 5 mg q8 h for the patients. The pain control was quite good for the first week (down to 2/10 on the VAS scale). After one week, her pain continued to be alleviated again, with allodynia over the low back and pelvic region and numbness of the lower limbs. and the scale up to 8/10. We titrated the methadone dose to 20 mg q8 h slowly for 15days, and her pain was controlled well (the scale down to 1-2/10). Unfortunately, after good pain control for one week, she presented vomiting again, and we rechecked that there were no electrolyte abnormalities or bowel obstructions. We considered the side effects of opioids, and we prescribed the antiemetics again but not effectively. She could not take any oral drugs, and the pain resolved. There are only oral preparations of methadone in Macao. Therefore, we changed to another NMDA receptor antagonist - ketamine. We used CSCI ketamine with Primperan in a syringe driver and stopped the oral medications. We started ketamine at 150 mg q24 h, then up to 300 mg q24 h in three days and obtained good pain control (VAS 1/10) and no more vomiting. The patient's general condition deteriorated then, and she died after 2 weeks peacefully.

Case 2. A 33-year-old woman with advanced colon cancer with metastasis to the liver,lungs and peritoneum was diagnosed in May 2016.

Repeated operations, chemotherapy and radiotherapy were given. Chemotherapy was stopped on Nov 2020.

The patient was admitted with abdominal pain and anal pain for three months (VAS 8-10/10). Before admission, she was taking rountined long-relased morphine 90 mg q12 h plus 10 mg for breakthrough pain, but this treatment was not effective. She was referred from CHCSJ and sat in the ambulance to our hospital that the transfer process may lead to overwhelming anal pain when admitted. Her general condition was poor. She was yelling at the ward. We gave her subcutaneous morphine 5 mg, but it did not work. We prescribed routine MST 60 MG Q12H and methadone 5 mg Q8H. Then, two hours later, we gave her another 10 mg morphine for the pain (VAS7), but the pain was alleviated to VAS 5. Two hours later, her husband required sedation because of her restlessness, and we gave her subcutaneous Dormicum5 mg; then, she had slept for 1 hour. However, she still felt pain all the night. On the second day, considering her intractable pain and terminal agitation, we prescribed 100 mg of CSCI Ketamine and 10 mg ofDormicum, and she remained calm. She was still alert but was very weak. She passed away two days later.

Discussion

Methadone is a lipophilic and highly protein-bound synthetic opioid with 50-80% oral bioavailability and a half-life of 72 hours. Not only does methadone have activity at the mu-opioid receptor, but it is also an inhibitor of serotonin reuptake and a moderate antagonist at the NMDA receptor.These actions may help account for using methadone for neuropathic pain as well as for opioid tolerance and opioid-induced hyperalgesics [1, 2].While morphine has long been the "gold standard" by which other opioid analgesics have been compared, methadone has been proposed as a suitable alternative because of its

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lower potential for opioid-induced neurotoxicity, absence of active metabolities, and NMDA-receptor-antagonist activity. Recent data support the conclusion that S-methadone(d-isomer), by virtue of its NMDA-receporter-antagonist activity, affects the development of morphine-induced tolerance and hyperalgesia.

Ketamine is a dissociative anesthetic agent commonly given for surgical anesthesia. In palliative care practice, ketamine has been administered as a coanalgesic, in addition to opioids and other coadjuvant drugs. Ketamine is now considered to be an essential adjuvant analgesic for refractory cancer pain and is on the WHO's Essential Drug List for patients who no longer respond to high doses of opioids [3]. There are a multitude of guidelines [4, 5] for the use of doses of ketamine in the management of intractable neuropathic pain in patients with terminal cancer illness. The mechanism of action of ketamine includes its features as an NMDA receptor antagonist and its dopaminergic, cholinergic, noradrenergic, serotoninergic, opiate and anti-inflammatory effects. We only performed a subcutaneous injection in our hospital. Psychomymetic side effects, as well as delirium, dizziness, blurred vision,hypertension, tachycardia, increased intracranial pressure and urinary tract symptoms. Prevention of psychomymetic side effects was made by using haloperidol (we useddroperidol and midazolam in this case).

The patient presented here highlights the complexity of pain management. Opioid irrelevant and opioid side effects appeared to play a significant role in pain management in these cases. Rotation to methadone and ketamine in these cases, we were able to achieve better pain control.

Conclusion

The management of neuropathic pain is a compelling clinical challenge, the outcome of which is often unsatisfactory. These case reports should encourage us to use methadone and ketamine for intractable neuropathic pain when indicated. The cases also highlight the emotional, professional, and personal challenges that palliative care teams face when looking for a patient who has intractable neuropathic pain.

References

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（本文編輯：彭洪泉）

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對老年患者血管擴張的程度較大，所以術中老年患者的循環波動較大，除了輸液量相對較多外，麻醉醫生必須適量使用血管活性藥物配合維持循環的穩定，注意輸液量過多造成術後循環系統的併發症及對腸吻合口水腫等影響。

麻醉手術期間的體溫是影響患者復甦的重要因素之一。老年患者的中樞核心溫度調節功能減弱；皮下組織鬆弛，麻醉後外周血管擴張程度大，散熱多；手術室溫度、氣腹、輸液溫度等因素都直接影響患者圍術期的體溫，影響患者的復甦及預後，所以圍術期的保溫意義重大，這也是ERAS麻醉管理的重要措施之一。

麻醉管理作為ERAS中重要的組成部份，隨着ERAS理念的不斷完善，更加要求不斷優化和完善圍術期的麻醉管理，這也是麻醉學走向圍術期醫學科發展的必經之路。

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（本文編輯：盧得健）