Spinal Myoclonus Responding to Continuous Intrathecal Morphine Pump

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ABSTRACT

Spinal myoclonus is a sudden, brief, and involuntary movement of segmental or propriospinal muscle groups. Spinal myoclonus has occasionally been reported in patients undergoing opioid therapy, but the pathophysiology of opioid-induced myoclonus has not been elucidated yet. Here, we present two patients with spinal segmental myoclonus secondary to ischemic and radiation myelopathy. Conventional medications did not help treat persistent myoclonus in both legs. Continuous intrathecal morphine infusion was implanted for pain control in one patient, which relieved spinal myoclonus entirely. This experience led to the application of this method with a second patient, leading to the same gratifying result. Spinal myoclonus reemerged as soon as the morphine pumps were off, which confirmed the therapeutic role of opioids. In contrast to the opioid-induced myoclonus, these cases show a benefit of opioids on spinal myoclonus, which could be explained by synaptic reorganization after pathologic insults in the spinal cord.

Key Words  Myoclonus; spinal myoclonus; opioid; treatment.

CASE REPORT

Myoclonus is a sudden, brief, and shock-like involuntary jerk caused by muscle contractions (called positive myoclonus) or inhibition of muscle activities (called negative myoclonus).1 Based on suspected anatomical origin, myoclonus is practically classified as a cortical, subcortical, spinal, or peripheral myoclonus. Spinal myoclonus could be segmental or propriospinal depending on the distribution of the involuntary muscle groups. Most spinal segmental myoclonus is etiologically secondary to structural lesions, such as syringomyelia, trauma, tumor, myelitis, or ischemic myelopathy. Toxic or metabolic causes may also induce spinal myoclonus, including iatrogenic opioid administration.

The pathophysiology of myoclonus was first postulated by Swanson et al.,2 who suggested that myoclonus may be the result of spontaneous firing of cell groups due to removal of an inhibitory mechanism, direct irritation of neurons, or mixed process. Davis et al.3 reported two autopsy cases of secondary spinal myoclonus in which large anterior horn cells in the spinal cord were spared, in contrast to considerable loss of small and medium sized interneurons. The pathologic findings supported the indirect loss-of-inhibition hypothesis, such that inhibitory interneuronal damage releases anterior horn cells to discharge spontaneously.

Opioid-related myoclonus has been reported in patients with systemic or local administration. Systemic opioid treatment is associated with chronic administration of opioids in cancer patients for pain control, and local injection is applied to provide spinal anesthesia for operations as well as analgesia.4 Chronic and high-dose opioids appear to be risk factors of myoclonus, in which accumulated excitatory metabolites, diamorphine or...
hydromorphone, may be responsible for myoclonus development. Switching the opioid type and reducing the dosage are useful methods for avoiding adverse opioid effects.

Here, we report two cases in which medically intractable spinal segmental myoclonus completely vanished during low-dose continuous intrathecal morphine infusion.

CASE REPORT

Case 1
A 73-year-old farmer developed transverse myelopathy in 1976 with sensory at the T12 level manifesting as mild spastic paraparesis, bilateral Babinski sign, neurogenic bladder, and severe dysesthetic pains in the hips and flanks. He also had severe non-painful irregular myoclonic jerks in the legs, which further impaired his ability to ambulate. Clonazepam, valproic acid, and baclofen failed to improve myoclonus. The exact cause of myelopathy was not determined, but it was thought to be attributed to possible ischemic infarction.

He was referred to the University of Minnesota Hospital in 1984 for pain control. Continuous intrathecal morphine administration via infusion pump resulted in complete control of myoclonic jerks. Morphine dosage remained unchanged at 3 mg/day over six-year period. Discontinuation of morphine resulted in prompt return of myoclonus.

Case 2
A 38-year-old man with transverse myelopathy at the T10 level by undetermined cause, possibly radiation-induced, developed severe myoclonic jerks in April 1990. His past medical history was significant for stage III-A Hodgkin’s lymphoma which was first diagnosed in 1989. He underwent staging laparotomy, splenectomy, and radiotherapy from neck to paraaortic region with a maximum 4,500 rad dose between April and May, resulting in complete remission of lymphoma. His stimulus-sensitive myoclonus showed a violent first jerk which was uncommonly followed by much smaller jerks at irregular time intervals. At times, myoclonus appeared in both legs more severely than painful flexor spasm, and he suffered from bilateral acetabular fracture due to these jerks.

Maximum therapeutic dosages of clonazepam, valproic acid, and dantrolene provided only moderate improvements to myoclonus. A trial of morphine via epidural catheter brought myoclonus under complete control in a dose-dependent manner. Subsequently, continuous intrathecal morphine administration (1.4 mg/day) was achieved via pump and reservoir. It became possible to treat fracture by closed reduction and skeletal traction. After these procedures, he was able to return to a gait rehabilitation program. Myoclonus continued to require the same morphine dosage for satisfactory control over a nine-month period. Clonazepam and valproic acid were slowly tapered off, and dantrolene was also discontinued. Discontinuation of infusion was associated with prompt return of myoclonus.

DISCUSSION

Myoclonus shows a broad spectrum of clinical presentation and relates to a number of underlying causes. Symptomatic or secondary myoclonus is the most common etiological category, which could be associated with apparent structural disorders or culprit drug administrations. Spinal myoclonus, one of the clinical subgroups, could also relate to underlying spinal cord lesions. Both presented cases had a history of precedent myelopathies due to ischemia and radiotherapy, which are known causes of spinal myoclonus.

Previous case reports on opioid-induced spinal myoclonus mostly occurred in neurologically intact patients. Postulated mechanisms of opioid-induced myoclonus include opioid induced local neurotoxicity responsible for abnormal hyperactivity of anterior horn cell groups, or imbalance of spinal and central opioid receptor activity triggering spinal reflex arc circuits. We hypothesize that the contradictory therapeutic role of opioids in this report might result from aberrant changes of neural substrates due to past pathologic insults of myelopathy. The nervous system experiences plasticity in response to injury through altered neuronal activation patterns, reorganization, and synaptic rearrangements. While neuronal plasticity is beneficial for functional recovery, maladaptive plasticity may lead to central pain, spasticity, and autonomic dysreflexia. Similarly, abnormal spinal cord circuitry may underlie spinal myoclonus after myelopathy. In addition, animal experiments have demonstrated that the
expression levels of different types of opioid receptors were altered after spinal cord insult. Therefore, it is an understandable result that local opioids showed an opposite effect due to synaptic reorganization and altered opioid receptor composition in these cases.

A comparable treatment using continuous intrathecal morphine infusion has been reported in a case of spasticity after spinal cord damage. Soni et al. tried low-dose intrathecal morphine pump treatment to alleviate spasticity in a patient with spinal cord injury, since the patient developed a tolerance to intrathecal baclofen. Alternative intrathecal morphine showed improvement of spasticity and maintained the therapeutic effect with a low dosage (300 µg/d). A possible explanation for the opioid effect on spasticity is based on previous electrophysiologic studies showing that intravenous morphine treatment depressed monosynaptic and polysynaptic reflexes in animals with chronic spinal transection. Similarly, opioids may have a therapeutic effect in pathologic spinal myoclonus by reducing abnormal hyperactivity of reflex arc.

Treatment of spinal myoclonus depends on resolving the underlying disease first before turning to symptomatic therapy. If the primary cause cannot be eliminated, symptomatic treatment may help. Clonazepam is considered the drug of choice in spinal myoclonus. Alternatively, levetiracetam, tetrabenzine, and targeted botulinum toxin injections have been reported to be effective. In this report, we present two experiences treating secondary spinal myoclonus with continuous intrathecal morphine, which has not been reported previously. After failure of conventional medications, we tried continuous intrathecal delivery of morphine sulfate via an implanted pump, which resulted in successful control of myoclonus in both legs. At 1–3 mg/day, no drug tolerance or untoward side effects developed during the follow-up periods (5 years and 9 months, respectively). Discontinuation of morphine infusion resulted in prompt return of myoclonus, establishing causality.

In conclusion, as far as we know, continuous intrathecal morphine infusion has not been reported to treat spinal myoclonus. The therapeutic effect of low-dose intrathecal morphine was sustained without tolerance or side effects during the follow-up period. Both patients, however, showed prompt return of spinal myoclonus as soon as the infusion pump was terminated, suggesting that the underlying therapeutic mechanism may be a reversible process. An excellent response to intrathecal morphine is a contradiction to previous reports of opioid-induced myoclonus. Synaptic reorganization, including opioid receptor systems in the spinal cord, may explain the responsiveness to morphine. A trial of intrathecal morphine could be considered in patients who suffer from symptomatic spinal myoclonus unresponsive to conventional medications.

Conflicts of Interest
The authors have no financial conflicts of interest.

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