Consciousness Recovery Induced by Intrathecal Baclofen Administration After Subarachnoid Hemorrhage

—Two Case Reports—

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Abstract

Two patients with subarachnoid hemorrhage recovered consciousness after intrathecal baclofen administration using an implanted intrathecal baclofen pump delivering 50 μ g per day using a simple infusion mode. Intrathecal baclofen resulted in significant reduction of spasticity 3 months after the implantation. Case 1 was reduced to a completely bedridden state with spasticity and could slightly move her fingers following commands. However, the patient could eat food and wash her face with minimal assistance at 3 months after the implantation, and could stand up in the parallel bars with assistance and speak several words at 8 months. Case 2 was in a completely bedridden state at 10 months after onset and could neither drink water nor follow instructions. However, the patient became oriented and could eat by herself within 3 to 4 weeks of implantation. She could walk with a cane and use the stairs with minimal assistance at 2 and 3 months after implantation. The patient could speak fluently within 6 months of implantation. Flatulence and dysuria happened during the screening test, but these symptoms were not repeated after implantation of a pump-catheter-system and continuous intrathecal baclofen infusion. Continuous intrathecal baclofen infusion caused both improvement in muscle tone and spasms and consciousness recovery from the vegetative state. This therapy is a strong candidate treatment for patients with spasticity and consciousness disturbance.

Key words: intrathecal baclofen, subarachnoid hemorrhage, spasticity, consciousness recovery, gamma-aminobutyric acid

Introduction

Baclofen, an agonist of the gamma-aminobutyric acid (GABA)-B receptor, induces the outflow of potassium and suppresses postsynaptic excitation.^{22,24,25)} Baclofen has been known for many years to be useful in the treatment of spasticity.²²⁾ Oral administration of baclofen often fails to alleviate severe spasticity adequately, but intrathecal administration has been reported as effective in reducing spasticity and safe in microgram doses.²²⁾ Therefore, intrathecal baclofen has been successfully used for the control of severe spasticity in patients with several diseases such as spinal cord injury, multiple sclerosis, brain injury, cerebral palsy, degenerative diseases, and cerebrovascular diseases including subarachnoid hemorrhage (SAH).^{1,3,6-11,13,14,16,17,23-27)} Baclofen also has additional beneficial effects in other conditions such as chronic pain, dystonia, tetanus, and vegetative state.^{15,21,22,25,26)}

We treated two patients with SAH who recovered consciousness triggered and maintained by intrathecal baclofen administration.

Case Reports

Two patients with SAH received treatment with intrathecal baclofen after inadequate response to other previous treatment modalities. Each patient initially received intrathecal baclofen bolus injection of 50 to 100 μ g to test its efficacy. After the efficacy was verified, the patients underwent implantation of an intrathecal baclofen pump to deliver 50 μ g baclofen per day by a simple infusion mode. Pump refills were required every 3 months. At each follow-up visit, spasticity in the upper and lower extremities was evaluated by Ashworth scores.

Case 1: A 43-year-old woman presented with SAH in Hunt and Kosnik grade IV (Fig. 1A), and underwent immediate clipping operation for an anterior communicating artery aneurysm. External decompression was performed for brain swelling 2 days after onset. Tracheostomy, left ventriculo-peritoneal shunting with cranioplasty, and percutaneous endoscopic gastrostomy were also performed. Two months after the operation, the patient was reduced to a completely bedridden state with spasticity unresponsive to treatment with oral baclofen, dantrolene, and levodopa (Fig. 1B). The patient could slightly move her fin-

gers following commands and phonation was sometimes possible with a faint voice (Fig. 2A). The patient initially received percutaneous intrathecal baclofen injection of 50 μ g to test its efficacy. Ashworth score decreased significantly from 2.9/3 (upper limb/lower limb) to 1.8/2.5. After positive evaluation, the patient underwent implantation of a pump-catheter system for continuous intrathecal baclofen application. The catheter tip was placed at T9 level and the daily dosage continued to be 50 μ g per day. Administration of intrathecal baclofen resulted in significant reduction of spasticity 3 months after the implantation (Fig. 2B). Ashworth score further decreased to 1.5/1.4 8 months after treatment. The patient became wheelchair dependent and could eat a pudding, brush her teeth, and write her daughter's name with moderate assistance one month after pump implantation. The patient could eat food and wash her face with minimal assistance at 3 months after pump implantation. Rehabilitation using

parallel bars started at 4 months and she could stand up in the parallel bars with assistance and speak several words after 8 months (Fig. 2C). Flatulence occurred during the screening test, but this symptom was not repeated.

Case 2: A 67-year-old woman presented with SAH in Hunt and Kosnik grade III (Fig. 3A). She underwent clipping operation for a right middle cerebral artery aneurysm on the next day. External and internal decompression was performed for increasing brain swelling causing anisocoria 4 days after onset. Barbiturate coma therapy was induced for 3 days. Thereafter, left ventriculo-peritoneal shunting and cranioplasty were performed. The patient was wheelchair dependent and could eat food and say some words at 3 months after onset. After discharge, the patient learned to brush her teeth, have a conversation, recognize the faces of her family, and maintain the upright position. However, tremor and rigid spasticity were ex-

Fig. 1 Case 1. A: Preoperative computed tomography (CT) scan showing subarachnoid hemorrhage from a ruptured anterior communicating artery aneurysm. B: CT scan taken 2 months after onset showing atrophy of the frontal lobes caused by the hematoma.

Fig. 3 Case 2. A: Preoperative computed tomography (CT) scan showing subarachnoid hemorrhage caused by a ruptured right middle cerebral artery aneurysm. B: CT scan taken 7 months after onset showing multiple cerebral infarctions caused by vasospasm.

Fig. 2 Case 1. A: Photograph taken before the test injection showing the patient was reduced to a completely bedridden state, with the spastic extremities held in flexion. B: Photograph taken one week after pump implantation showing intrathecal baclofen administration had resulted in significant reduction of spasticity and the lower limbs in the relaxed position. C: Photograph taken 6 months after pump implantation showing the patient could raise her hands with minimal assistance.

Fig. 4 Case 2. A: Photograph taken before the test injection showing the patient was in a completely bedridden state because of the tremor and rigid spasticity, and could not follow instructions. B: Photograph taken several days after pump implantation when the patient could follow a simple command of “Raise your hand.” C: Photograph taken 6 months after pump implantation showing the patient could walk with a cane without assistance and speak fluently.

acerbated at 7 months after onset (Fig. 3B). She failed to respond adequately to conservative treatment with oral amantadine and levodopa, so she was rehospitalized in a completely bedridden state at 10 months after onset. The rigid spasticity was causing significant nursing care problems with decreased level of consciousness. The patient moved her left extremities spontaneously, but she could not drink water or follow instructions (Fig. 4A). The spasticity was reduced after a percutaneous intrathecal injection of 100 μ g baclofen to test its efficacy. Ashworth score decreased significantly from 2.8/2.5 (upper limb/lower limb) to 1.9/1.8. The patient was treated with continuous infusion of intrathecal baclofen delivered via an implanted pump. The catheter tip was placed midway between T9 and T10 levels and the daily dosage continued to be 50 μ g per day. Spasticity in both upper and lower extremities decreased significantly 3 months later and Ashworth score decreased to 1.3/1.5 at 6 months after implantation. The patient could nod her head and follow simple commands several days later (Fig. 4B). The patient could swallow liquid food and ask about the date and place 2 weeks after implantation. She became oriented and ate by herself within 3 to 4 weeks of implantation. The patient could walk with a cane and use the stairs with minimal assistance at 2 and 3 months after implantation. The patient could speak fluently within 6 months of implantation (Fig. 4C). Dysuria occurred during the screening test, but this symptom was not repeated.

Discussion

Baclofen has other potential effects on the recovery from coma besides reducing spasticity. Sporadic episodes of dramatic recovery from the persistent vegetative state have been reported after intrathecal administration of baclofen.^{20–22,24–26} Our cases also show recovery of consciousness from persistent severe disability after intrathe-

cal baclofen administration. The improvement of consciousness was more prominent than estimated from the ameliorated movement. The mechanism of the effectiveness of intrathecal baclofen remains unclear. However, several hypotheses have been proposed as follows.

Similarities between intrathecal baclofen and spinal cord stimulation in consciousness recovery are interesting because both involve the spinal GABAergic system.²⁵ Recently, GABAergic neurotransmission in the pontine reticular formation was observed to promote wakefulness.²⁸ Baclofen may modulate the amount of information reaching the cortex by influencing the GABA-related gating systems within the spinal circuits, and dysregulated sleep-wake cycles which interfere with alertness and awareness might be stabilized by the GABAergic effect of intrathecal baclofen.²⁰ However, many general anesthetics such as propofol, pentobarbital, chloral hydrate, muscimol, and ethanol are also thought to cause loss of wakefulness, in part by enhancing GABA type A receptor-mediated neurotransmission.^{12,28,30}

Baclofen tends to cause side effects of worsening of the psychiatric condition with irritability, assaultiveness, and prominent auditory hallucinations.^{4,18} The activation of dopaminergic neurons might be involved in the recovery of consciousness, so causing this side effect under certain circumstances.² Low dose baclofen induces dopamine receptor hypersensitivity,¹⁹ and also acts as a beta-phenylethylamine agonist, enhancing the action of dopamine through endogenous amphetamine-like effects.^{4,29}

Fifteen minutes after application of the GABA agonist zolpidem, one patient awoke from the semi-comatose condition and remained awake for the next 3–4 hours,⁵ but returned to the semi-comatose state after the drug action subsided. We have not tried the discontinuation of baclofen after consciousness recovery was verified, because the anti-spastic effect is transient and continuous intrathecal infusion of baclofen is necessary for the treat-

ment of the spasticity. However, the efficacy of baclofen in the consciousness recovery is supposed to be transient.

Patient selection is very difficult for such treatment. We have implanted pump-catheter-systems in another two patients with massive cerebral infarction, but consciousness level did not improve. Therefore, the degree of the brain damage might be related to the recovery of consciousness. Furthermore, no screening test for consciousness recovery has been developed. In our patients, the consciousness level did not change even after the test injection of baclofen. The consciousness level tended to improve only slightly several days after the implantation and continuous intrathecal baclofen infusion.

The risks of intrathecal baclofen infusion are symptoms related to overdose such as hypotonia, lethargy, vertigo, and psychological disturbances,⁶⁾ but are responsive to rapid decrease of dosage. The other risks are related to withdrawal such as seizures, psychic symptoms, and hyperthermia, which may occur after catheter disconnection, migration, kink, obstruction, development of fibrosis, disconnection of pump reservoir, porosity of pump membrane, unexplained pump dysfunction, and leakage.¹⁴⁾ These symptoms improve after the reintroduction of baclofen, usually without sequelae. In our patients, flatulence and dysuria happened during the screening test, and were thought to be caused by the abrupt increase of intrathecal baclofen concentration after the one-shot injection. However, these symptoms did not recur after implantation of the pump-catheter-system and continuous intrathecal baclofen infusion.

The benefits of continuous intrathecal baclofen infusion are both the improvement in tone and spasms but also the possibility of the consciousness recovery from the vegetative state. Since the adverse consequences do not exceed the benefits of intrathecal baclofen, this therapy seems to be a strong candidate treatment for patients with spasticity and consciousness disturbance.

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