

Novel Epidural Baclofen Infusion Trial for Intractable Spasticity with Long-Term Follow-Up Observation and a Focused Review of the Literature

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Abstract

Background: Intrathecal baclofen (ITB) infusion has been increasingly used in patients with intractable spasticity. Prior to the implantation of the permanent pump, a trial is usually conducted to document efficacy. Intrathecal bolus injection of baclofen, followed by serial evaluations to confirm the improvement of spasticity, has been most commonly used during such trials. However, for patients who refused to undergo ITB trial injection due to previous untoward complications such as intractable headache, there has been no other alternatives.

Objective: To report the first case of a successful epidural baclofen infusion trial, conducted as outpatient in a lady with severe spasticity due to multiple sclerosis; to report the long term follow-up observation (3 years) following the permanent intrathecal pump placement; and to conduct a focused review of the literature pertaining to epidural baclofen.

Design: Case report.

Setting: Tertiary-care pain clinic.

Case Report: A 62-year-old female with progressive spasticity of bilateral lower extremities and left upper extremity due to multiple sclerosis, not responding to multiple oral antispasticity drugs, was referred to clinic for ITB therapy. The patient adamantly declined ITB bolus trial due to previous episode of severe headache following lumbar puncture. Thus an outpatient epidural baclofen infusion was performed and was successful. Based on the positive response from the epidural infusion trial, a permanent IT pump was subsequently placed and the patient has had sustained reduction of her spasticity since pump implantation 3 years ago.

Limitation: Single center case report.

Conclusion: In patients who are reluctant to the ITB bolus trial due to previous complication such as headache, an outpatient epidural baclofen infusion trial, when done properly, can serve as an alternative approach to the ITB trial and provides needed information.

Keywords: Baclofen; Intrathecal; Epidural; Outpatient; Spasticity; Multiples sclerosis

Introduction

Baclofen, a lipophilic derivative of gamma-aminobutyric acid (GABA), has been utilized to treat spasticity due to upper motor neuron syndromes such as brain injury (BI), spinal cord injury (SCI), multiple sclerosis (MS) [1-3]. Although the exact mechanism is unknown, baclofen appears to inhibit the monosynaptic and polysynaptic reflexes at the spinal level [1,3]. In cases of severe spasticity not responding to high doses of oral baclofen or when patients experience intolerable side effects due to oral baclofen, ITB may be more beneficial [4].

It is well accepted that prior to the permanent ITB pump placement, a trial should be performed to document efficacy of spinal baclofen. Usually, the patient is admitted inpatient to the hospital, an intrathecal bolus injection of a dose of baclofen between 50 mcg and 100 mcg is given [5], a physician or physical therapist performs focused serial neuromuscular examinations, using commonly accepted spasticity rating scale, i.e., the Ashworth Scale, or the Modified Ashworth Scale [6,7] to assess the reduction of spasticity, following the IT baclofen bolus. It was not until recently that Harned et al. reported a novel trialing method with the utilization of short term indwelling IT catheter in 3 patients with complex hemiparetic spasticity, who failed to respond to the traditional IT bolus trialing method, but were "captured" with the more sophisticated IT catheter trialing method, which allowed wider dosage range than the traditional IT bolus protocol [8]. Our case patient, however, had previously experienced severe spinal headache following lumbar puncture and therefore firmly

refused any ITB trial. Epidural baclofen infusion was the only option in our case patient. However, to the best of our knowledge, there has been no report on using epidural baclofen infusion trial performed in an outpatient setting. We performed a focused literature search and did find some pertinent data that supported the idea of epidural baclofen trial for intractable spasticity [9].

Case Report

An otherwise healthy, 62-year-old female with history of MS diagnosed 8 years prior to her initial visit, was referred to our pain clinic by her neurologist for ITB therapy for her progressive spasticity. The patient had been experiencing intractable spasticity involving bilateral lower extremities (LE) and left upper extremity (LUE) un-responding to oral antispasticity medications. She had been wheel chair bound over the past 2 years. Upon her presentation to our clinic, she was on baclofen 60 mg three times a day, tizantidine 4 mg three times a day,

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amphetamine 20 mg am and noon (for excessive sleepiness), gabapentin 300 mg three times a day, Prempro 0.625 mg daily, Synthroid 75 mcg daily, fluoxetine 20 mg daily, and glatiramer injection daily. She had had multiple sessions of IVIG and oral/IV steroid previously. She had also tried on cyclopenzaprine 10 mg twice a day, and diazepam 10 mg three times a day as needed without efficacy, and with excessive daytime drowsiness. She had undergone physical therapy and occupational therapy previously without sustained success. Her previous medical history was significant only for hypothyroidism and depression. Her previous surgical history was noncontributory. She had no history of alcohol, cigarette, or illicit drug usage. Her family history was significant for MS in her brother. The striking physical findings during her exam were the rigid extension of bilateral LE and the adducted, internally rotated, and flexed LUE. Following a pre-implantation psychological evaluation confirming her candidacy, she consented to the placement of tunneled epidural baclofen infusion catheter. Her oral tizantidine was gradually weaned off because of her excessive sleepiness with no observed benefit with continued usage of tizantidine.

A tunneled lumbar epidural catheter was placed at L2-L3 with catheter tip advanced to T12 under fluoroscopic guidance. Satisfactory catheter placement was confirmed by epidurogram. The proximal tip of the catheter was then tunneled, subcutaneously and connected to a Microject™ PCEA pump (Codman, Raynham, MA, USA) and reservoir bag containing preservative free baclofen 100 mcg/ml. The pump was programmed to deliver a basal rate of 0.4 ml/hr. The bolus dose was 0.2 ml with 30 minute lock-out interval. The patient was instructed to taper off her oral baclofen by decreasing 20 mg/day with initiation of epidural baclofen infusion (she was on 60 mg three times a day at the beginning of the trial). She was instructed how to operate the infusion pump before discharging home. The patient was again seen in the clinic for follow-up at days #3, #6, #9 and #12 post placement of epidural infusion catheter, and for infusion dosage adjustment. By day #12, her epidural baclofen infusion setting was at 1.3 ml/hr (basal), 0.6 ml (bolus), and with 30 minute lock-out. The patient only had to push the on-demand bolus button twice in the last 24 hours of the trial. She was completely off her oral baclofen. Both the patient and her husband were excited to see the near complete resolution of her LE rigid extension together with much improved ease of transfer in her activities of daily living (ADL). The patient also reported some improved range of motion of her LUE as well. The trial was then terminated, and the patient was restarted on her previous oral baclofen regimen. She subsequently consented for the permanent ITB pump placement.

A non-programmable Codman 3000 constant flow rate implantable pump was used in our patient. The needle entry level was at L2-L3 and the final IT catheter tip was at T12. Satisfactory IT catheter needle placement was confirmed by positive CSF flow and by performing an intraoperative myelogram. The patient did receive a lumbar epidural blood patch with 8 ml autologous blood, immediately after the satisfactory placement of the IT catheter to lessen the chance of post-puncture spinal headache. The whole procedure of ITB pump placement was uneventful. The patient did report moderate headache after the procedure, but it resolved within 24 hours.

Her initial ITB infusion was started at 100 mcg/day, and over the following 6 months, the daily dose was gradually titrated up to 350 mcg/day. She has been on the same ITB dose for over 3 years now. Her oral baclofen was tapered off over 2 months following IT pump placement. She has not been on any oral baclofen for about 3 years. The patient has been very satisfied with the result of her ITB therapy.

Discussion

Intrathecal baclofen (ITB) therapy has evolved into a standard

treatment for severe spasticity, especially in patients with spinal cord injury and multiple sclerosis [10-14].

Although the exact mechanism is unknown, baclofen, a gamma-aminobutyric acid (GABA) agonist, appears to inhibit the monosynaptic and polysynaptic reflexes at the spinal level [1,3], through the interaction with GABA_B receptors on the spinal cord, resulting in decreased calcium influx at the pre-synaptic terminal and thus reduced release of endogenous excitatory transmitters [15-18].

Traditionally, ITB trial is done either as inpatient or as outpatient, by injecting a bolus of baclofen dose between 50 mcg to 100 mcg into intrathecal space [5], and then the patient is observed for improvement in spasticity using Ashworth Scale (AS) or Modified Ashworth Scale (MAS) [6,7]. A reduction of 2 point in MAS in spasticity due to spinal origin is considered significant [8].

However, ITB bolus trialing method certainly has a few limitations. First, single bolus baclofen injection does not achieve steady-state pharmacokinetics and is associated with side effects such as nausea, drowsiness and vertigo [19]. Second, in patients with complex spasticity involving both upper and lower extremities, a single bolus trial approach may fail to capture those responders subsequently identified when trialing with using indwelling IT infusion catheter [8]. Perplexed by the dilemma, Harned et al. recently introduced their novel approach of trialing with indwelling IT catheter for complex spasticity problems with promising results. Third, although there was scarce of literature on post-dural puncture headache (PDPH) following ITB bolus injection, it is likely it happens more often considering that the incidence of PDPH following diagnostic lumbar puncture is around 33% [8,20]. For those who did develop PDPH after ITB bolus, it is conceivable that the trial outcome could be compromised by the intractable headache.

Fourth, the ITB bolus trial generally requires oral baclofen weaned off prior to ITB bolus injection [19], this could be extremely difficult to achieve when patients were experiencing severe spasticity while on oral baclofen, weaning off their oral baclofen could predispose them to complications such as skin breakdown and serious withdrawal effects [19].

In our patient, she was on baclofen 60 mg three times a day while still having spasm with bilateral LE in rigid extension on physical examination, we discarded the idea trying to wean off her oral baclofen as we did not believe it feasible. Because of her previous experience of “monster headache” following her lumbar puncture, she refused considering any ITB bolus trial. Faced with no other options, we considered epidural baclofen infusion trial.

We performed a focused literature search and did find a pertinent report of epidural baclofen bolus injection for intractable spasticity by Jones et al. [9]. The authors also hypothesized that baclofen could cross the dura to act directly in the spinal canal just like morphine, as high morphine concentration had been found in IT space after epidural morphine injection [21], in spite of lacking an assay to measure IT baclofen concentration [9]. Interestingly, the hypothesis by Jones et al was subsequently confirmed by the novel research work of Bree et al., who demonstrated that baclofen transport across the blood brain barrier (BBB) was through a carrier-mediated transport system, rather than passive diffusion [22]. Moreover, Bree et al. also demonstrated that the transport of baclofen across BBB was stereoselective [23].

Over the past decade, we have successfully performed hundreds of epidural morphine infusion trials in the outpatient setting, in patients with intractable chronic pain who failed conventional pain management. Enlightened by the pioneering work of Jones et al. [9]

and faced with no other alternative, we decided on an epidural baclofen infusion trial, to be done as outpatient instead of as inpatient, which were the cases with Jones at el. We were also concerned whether epidural baclofen infusion could be done safely, in a similar manner as we have with epidural morphine infusion.

Unlike baclofen, epidural opioid administrations for analgesia have been investigated previously by others [21] including Bernards [24-28], who demonstrated that lipid solubility played a significant role in the epidural pharmacokinetics of epidurally administered opioids. He hypothesized the more lipid soluble opioids are, the longer time they tend to stay in the epidural space, i.e., mean residence time (MRT), without reaching the intrathecal space, and therefore, epidurally administered morphine more readily reached intrathecal space than more lipid soluble opioids. This concept contrasts commonly held belief that drugs of hydrophilic nature cannot pass BBB. Research work by Bernards further demonstrated that the only mechanism by which drugs redistribute from the epidural space to spinal cord is diffusion through the spinal meninges [24-28].

We believed the epidurally administered baclofen would distribute into intrathecal space. The outpatient epidural baclofen infusion trial of our patient was successful in controlling her spasticity. Both the patient and her husband were very pleased with the trial result. They were able to see how much she was able to do with ease functionally during the infusion trial. She was without any complications or the need to wean off her oral baclofen prior to initiation of her trial.

Recall that she was on an extremely high oral baclofen dosage (60 mg three times day) at the start of her epidural baclofen infusion trial. Following the beginning of the infusion, she was started on gradual tapering her oral baclofen. On day #12, she was off oral baclofen, while receiving epidural baclofen infusion at 1.3 ml/hr (concentration 100 mcg/ml), plus bolus of 0.6 ml (she only used the bolus dose twice on day #12). Her overall daily epidural infusion dose was 3240 mcg or 3.24mg (1.3 ml×24×100 mcg/ml + 0.6 ml ×2×100 mcg/ml). So, in this case, we can calculate the ratio of oral baclofen vs epidural baclofen to be ~55.6 (180 mg/ 3.24 mg), although this ratio may not accurately reflect the total amount of baclofen remaining inside her body due to the simultaneous oral baclofen tapering.

To this day, she is still doing well on ITB 350 mcg/day with sustained efficacy without significant side effects. The ratio of her epidural dose at the end of epidural infusion trial vs current intrathecal dose is ~9.3 (3240 mcg/ 350 mcg). These numbers are within the same orders of magnitude to the previous study by Loubser et al. in which the IT dose requirement was found to be 100-250 fold less than the oral dose [19].

Lastly, we believe an outpatient epidural infusion trial offers the patients and their caregivers the opportunity to experience and observe the therapeutic change from a functional point of view, i.e., how they perform with their activities of daily living (ADL). There were reported cases of worsening ambulation or transfers following permanent ITB pump placement following ITB bolus trial, as some of the tonicity were used by patients to perform pivot transfer or assist ambulation, when their lower extremities became totally flaccid with ITB infusion, they lost their ambulating abilities [19,29,30]. This underscores the importance of performing a thorough evaluation including functional improvement during patients' ADL, rather than a mere reduction of Ashworth score.

Conclusion

In patients who are reluctant to the ITB bolus trial due to previous complication such as headache, an outpatient epidural baclofen

infusion trial can serve as an alternative approach to the ITB trial and provides needed information. Outpatient epidural baclofen infusion trial may facilitate weaning off patients' oral baclofen and provide practical information pertaining to how patients function in their ADLs.

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