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Original Articles

Intrathecal Baclofen in Cerebral Palsied Children with Severe Spasticity: A Pilot Study and Review of the Literature

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Abstract Continuous intrathecal baclofen infusion (CIBI) is an effective treatment in patients with severe spinal spasticity. Its use in spastic cerebral palsy (CP) is less well established. In the present study, we aim to evaluate the efficacy and safety of intrathecal baclofen in children with cerebral spasticity. Four non-ambulatory children with severe mental retardation were recruited, including two patients with spastic CP and two mixed spastic and dyskinetic CP. Bolus intrathecal baclofen was instillated via an indwelling catheter in the lumbar subarachnoid space, starting at a dose of 25 μg and increased by 25 μg increments 24 hours apart, with a maximum dose of 100 μg. The muscle tone of the upper and lower extremities were recorded by the Ashworth score at 2-hour, 4-hour and 6-hour post-injection. The average Ashworth score of the lower extremities decreased from 2.1 to 1.5. The muscle tone started to decrease within two hours after injection, and remained low throughout the six hour observation period ($p<0.05$). Three children had their muscle tone reduced to nearly normal (Ashworth scores 1.0 to 1.3). The average muscle tone in the upper extremities was not significantly affected. Apart from mild drowsiness and skin infection, no severe adverse events were encountered. Our preliminary data suggests that intrathecal baclofen is effective in reducing the lower extremity hypertonicity in spastic CP children. Patients with severe spasticity refractory to conventional therapy may benefit from CIBI via subcutaneously placed programmable pumps.

Key words Baclofen; Cerebral palsy; Intrathecal drug infusion; Spasticity

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Introduction

Cerebral palsy (CP) is one of the major long-term complications in premature and asphyxiated babies. Despite of advances in neonatal care in the past two decades, CP still affects 1.5 to 2.5 per 1000 live births in the United States.[1] Two-third of the CP patients have spasticity of variable severity, leading to significant morbidity including gait disturbances, contractures, joint dislocations and decubitus ulcers. The care of spasticity poses major financial as well as psychosocial burden on the family. Traditionally, physiotherapy and splintage play a major role to treat the hypertonicity and prevent contractures. In severe cases, soft tissue surgeries and osteotomies are often required. It is not uncommon for children to undergo multiple operations to tackle the orthopaedic problems. The response to oral anti-spasticity agents such as diazepam, baclofen and dantrolene are often unsatisfactory. A high dose is often required to achieve tone reduction, which is accompanied by intolerable side effects on the central nervous system (CNS).

New treatment modalities, notably botulinum toxin and selective dorsal rhizotomy (SDR), have revolutionized the

management of spasticity.[2,3] SDR have been shown to reduce the lower limb spasticity and bring about long-term functional improvement.[4,5] Nonetheless, stringent patient selection is required for an optimal outcome; patients who utilize the spasticity to maintain upright postures against gravity are contraindicated to the operation.[3]

In 1984, Penn and Kroin[6] described the use of continuous intrathecal baclofen infusion (CIBI) to alleviate spasticity of spinal origin. Long-term studies revealed that CIBI via an implanted pump was highly effective in reducing the rigidity and muscle spasms in patients with spinal cord injury and multiple sclerosis.[7,8] Subsequent reports suggested that CIBI was also beneficial to supraspinal spasticity associated with cerebral palsy and acquired brain injuries.[9-12]

Baclofen acts as a gamma-aminobutyric acid (GABA) analogue. The active component of baclofen is β-(aminomethyl)-p-chlorohydrocinnamic acid. It binds to GABA-B receptors within the brainstem, dorsal horn of the spinal cord, and other CNS sites, resulting in inhibition of calcium reflux into presynaptic terminals and thus suppressing the release of excitatory neurotransmitters.[13] Orally administered baclofen has low lipid solublity and penetrates the blood-brain barrier poorly, leading to a low concentration of drug at the site of action even after large doses.[14] Lumber intrathecal administration of baclofen results in a ten-fold increase in cerebral spinal fluid (CSF) drug level with one percent equivalent of the oral dose.[15] The lumber CSF level is four times of the level in the cisterna magna.[16] In the CSF, baclofen has a half-life of about five hours and a duration of action of 10 to 12 hours, with very little drug returning to the systemic circulation.[17]

The delivery system consists of a subcutaneously implanted pump with a reservoir. The pump is programmed to deliver various rates of the drug via a catheter in the lumbar subarachnoid space. Direct delivery of the drug to its site of action increases its effectiveness. It allows a reduction in dosage and minimizes the systemic side effects, such as drowsiness, confusion and lethargy. By adjusting the infusion rate of the pump, the spasticity can be titrated to avoid excessive weakness.

In the present study, we aimed to evaluate the efficacy and safety of bolus intrathecal baclofen in a group of cerebral palsied children with severe spasticity. Patients were admitted for a screening trial to determine if single intrathecal baclofen doses reduced their spasticity. The effective dose to bring about tone reduction was determined for each child. Patients who responded to the trial dose might be suitable candidates for CIBI via programmable pumps in the future.

Methods

Patients

Four children, aged five years eight months to 12 years six months, were recruited into the study. All of them were long-term residents in the Developmental Disabilities Unit of our hospital. All were severely mentally retarded, non-ambulatory children with either spastic or mixed spastic and dyskinetic CP of cerebral origin. They were barely able to attain sitting postures in CP chairs. There were intermittent painful extensor spasms, and increasing difficulty was encountered to manage their perineal hygiene. The demographic data was shown in Table 2. The initial evaluation included a thorough history and neurological examination. The previous medical treatment for spasticity was reviewed. The muscle tone in the upper extremities (biceps and triceps) and lower extremities (hip adductors, quadriceps, hamstrings and gastrocnemius) was assessed by the 5-point Ashworth scale (Table 1)[18] by two designated physiotherapists.

The inclusion criteria to the study included: (1)

Table 1 Ashworth scale

Ashworth score	Degree of muscle tone
1	No increase in tone
2	Slight increase in tone, giving a "catch" when affected part is moved in flexion or extension
3	More marked increase in tone, but affected part easily flexed
4	Considerable increase in tone, passive movement difficult
5	Affected part rigid in flexion or extension

Table 2 Average lower extremity Ashworth score at different doses of intrathecal baclofen

Patient	Age (year)	Sex	CP	Baseline	25 μg	50 μg	75 μg	100 μg	Side effects
1	5.6	F	Mixed	2.4	1.8	1.7	1.1	ND	Drowsy, skin infection
2	12.5	F	Mixed	2.0	2.0	2.0	1.3	1.4	Drowsy
3	8.3	M	Spastic	1.6	1.3	1.0	ND	ND	Nil
4	7.6	F	Spastic	2.0	2.0	1.9	ND	ND	Drowsy

CP: cerebral palsy; M: male; F: female; ND: not done

Moderate to severe spasticity of cerebral origin that interfered with postural control or function, or those who suffered from painful spasms; and (2) children who did not respond to maximal dose of oral antispasticity agents such as diazepam or baclofen and/or those who experienced intolerable side effects from the medications. The exclusion criteria included: (1) Known hypersensitivity to baclofen; (2) cardiovascular or pulmonary insufficiencies; (3) severely impaired liver or renal function; and (4) abnormal CSF flow such as hydrocephalus with shunt in-situ.

Protocol

Informed consent was obtained from the parents or guardians. Oral anti-spasticity agents were tailed off before the trial. Spinal needle was inserted by one of the investigators, a consultant anaesthetist, using aseptic technique at L3-L4 level. Intrathecal catheter was threaded with catheter tip at around T12 level.

The intrathecal baclofen used in the present study was "Lioresal Intrathecal", which was supplied in single-use ampules with a concentration of 500 μg/ml. The trial dose was given in an open-label manner. Bolus injection of intrathecal baclofen , starting at a dose of 25 μg (given in two ml saline slowly over at least one minute) and increased by 25 μg increments at least 24 hours apart, until an optimum dose was reached for tone reduction. The maximal bolus of baclofen was 100 μg, above which there might be risk of respiratory complication. Children who did not respond adequately to 100 μg baclofen would need very high daily dose for CIBI, which would be very expensive.[11]

Two designated physiotherapists assessed the children independently three times a day (at 2-hour, 4-hour and 6-hour after the bolus injection) during the study period. Both were blinded to the dose of baclofen given. Muscle tone of upper and lower extremities was measured by Ashworth score. Reduction of one point or more was regarded as a positive response.

All the children were transferred to a high dependency area for close monitoring during the trial period. The potential side effects from the drug (e.g. hypertension, drowsiness, confusion) were monitored. The total duration of indwelling catheter would not exceed seven days to minimize the risk of infection. All intrathecal injections were given under aseptic conditions with bacterial filter in-situ.

Statistical Analysis

Overall changes in the muscle tone over time within the group were analyzed by Friedman's test, which is the non-parametric equivalent of a repeated measures analysis of variance (ANOVA) with a single group. The study protocol was approved by the Ethics Subcommittee of the Joint Hospital Management Committee of Caritas Medical Centre.

Results

Instead of presenting the Ashworth scores of individual muscle groups separately, we have calculated the mean scores of the upper and lower extremities for each patient. The average Ashworth scores for the upper and lower extremities after different doses of intrathecal baclofen were listed in Tables 2 and 3. The average Ashworth scores at different time intervals after injection were listed in Tables 4 and 5.

Lower Extremities

The baseline average Ashworth scores in the lower extremities ranged from 2.0 to 2.4, with a mean of 2.1. The average Ashworth score decreased from a baseline of 2.1 to 1.5 four hours after injection. Figure 1 shows the average lower extremity score from 2-hour to 6-hour post-injection. The muscle tone was reduced within two hours after the bolus injection of baclofen, and the effect persisted throughout the 6-hour observation period (Friedman's test $p<0.05$). Figure 2 shows the average Ashworth score after

Table 3 Average upper extremity Ashworth score at different doses of intrathecal baclofen

Patient	Baseline	25 μg	50 μg	75 μg	100 μg
1	3.6	3.1	3.7	3.7	ND
2	2.0	2.9	3.0	3.0	2.0
3	2.0	1.8	1.2	1.2	ND
4	2.1	2.3	2.0	2.0	ND

Table 4 Average lower extremity Ashworth score at different time intervals after injection of baclofen

Patient	Baseline	2 hours	4 hours	6 hours
1	2.4	1.6	1.6	1.5
2	2.0	1.5	1.7	1.8
3	1.6	1.2	1.0	1.3
4	2.0	1.8	1.8	1.7

Table 5 Average upper extremity Ashworth score at different time intervals after injection of baclofen

Patient	Baseline	2 hours	4 hours	6 hours
1	3.6	2.8	4.0	3.6
2	2.0	1.9	2.3	2.8
3	2.0	1.5	1.3	1.4
4	2.1	1.9	1.8	2.6

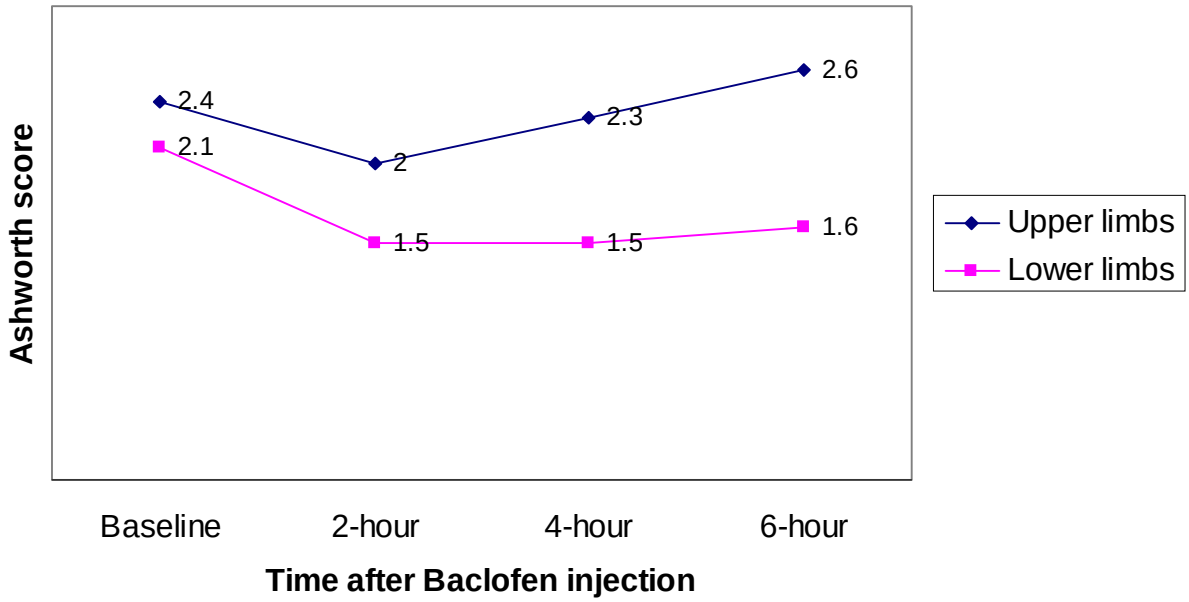

Figure 1 Average Ashworth score at different time intervals after baclofen injection

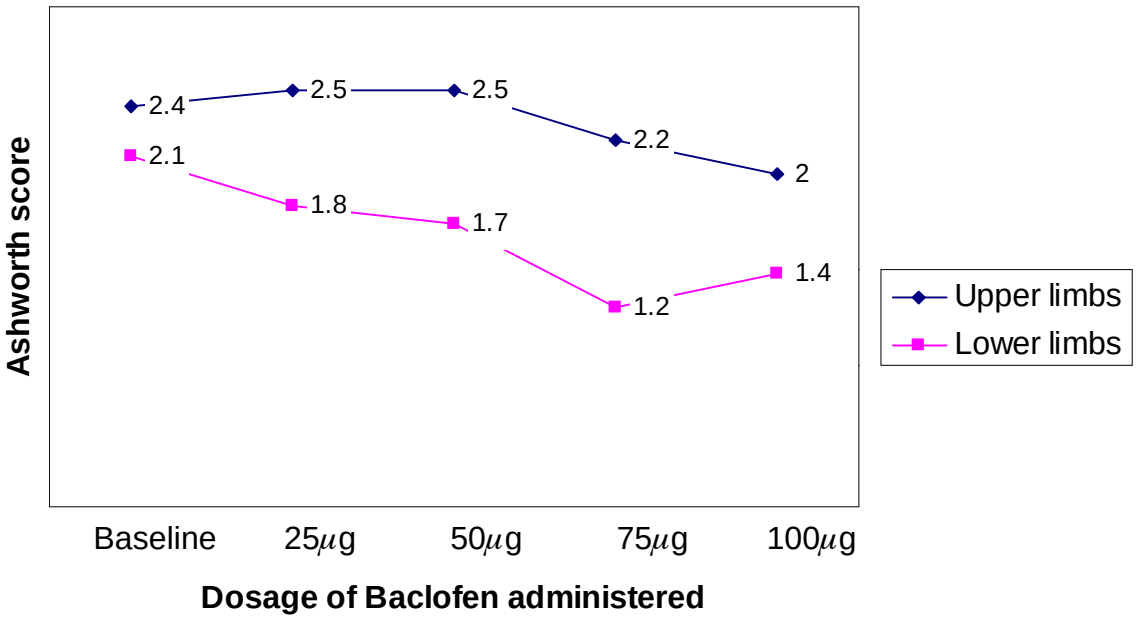

Figure 2 Average Ashworth score after different doses of baclofen injection

different doses of baclofen. The average muscle tone was reduced after bolus injections of 75 μg and 100 μg of baclofen. Three patients had their muscle tone reduced to nearly normal, with average Ashworth scores from 1.0 to 1.3 (Table 2).

Upper Extremities

The baseline average Ashworth scores in the upper extremities ranged from 2.0 to 3.6, with a mean of 2.4 (Table 3). There was no significant change in the average muscle tone of the upper extremities during the observation period (Figure 1). No definite reduction in the average Ashworth score was observed after different doses of intrathecal baclofen (Figure 2).

Three children developed excessive drowsiness, two after 75 μg and one after 50 μg of baclofen injection. All of them recovered spontaneously without intervention. One patient developed mild skin infection at the site of intrathecal catheterization, which resolved after catheter removal and conservative treatment.

Discussion

Spasticity is characterized by velocity-dependent increase resistance to passive muscle movement. In CP associated spasticity, the imbalance between the descending inhibitory impulses and the afferent excitatory impulses from the extremities result in hypertonicity.[9] Baclofen is a GABA agonist which acts presynaptically at the spinal level to inhibit the release of excitatory neurotransmitters. Baclofen is approximately 30% protein bound after oral administration. It has low lipid solubility and penetrates the blood brain barrier poorly.[14] The response to oral baclofen is highly variable; large doses may lead to lethargy, ataxia, confusion, decreased concentration and respiratory depression. Whilst the CSF baclofen levels were less than 12 ng/ml after oral administration,[15] patients who were receiving a constant intrathecal baclofen infusion of 400 μg/day had CSF levels of 380 ng/ml. The concomitant serum level were less than 5 ng/ml.[16] The 4:1 ratio between lumbar and cervical concentrations of baclofen also contribute to the relative lack of central side effects.[7]

Penn[7] demonstrated that intrathecal baclofen effectively reduced spasticity and spasms of spinal origin in 97% of patients. Coffey et al[8] revealed that CIBI was effective for the long-term treatment of intractable spasticity in patients with spinal cord injury and multiple sclerosis. The use of intrathecal baclofen in spasticity of cerebral origin is less well established. Albright et al[9] demonstrated that bolus intrathecal baclofen reduced the lower extremity muscle tone in 17 patients with congenital spastic CP. Tone in the upper extremities was not significantly affected. Meythaler et al[19] showed that bolus intrathecal baclofen significantly reduced the Ashworth score, spasm score and reflex score in the lower and upper extremities in 11 patients with acquired brain injury. Long-term follow-up study in 37 patients with cerebral spasticity treated by CIBI showed that muscle tone was significantly reduced in the upper and lower extremities. Upper extremity function and activities of daily living were also significantly improved.[10] Becker et al[11] reported 18 adult patients with supraspinal spasticity treated with CIBI for 13 to 54 months. Both the mean Ashworth score and the mean spasm frequency score were significantly reduced, with improved pain control, nursing care and mobilization. Armstrong et al[12] followed up 12 children with cerebral spasticity treated with CIBI for one to five years. All of them showed reduction in Ashworth scores, while most caretakers reported improvement in muscle tone, behaviour, sitting and general ease of care.

In the present study, there was a reduction in the average muscle tone of the lower extremities. Among the four patients with either spastic or mixed spastic and dyskinetic CP, the tone was reduced to nearly normal in three. Nonetheless, only one patient demonstrated a clinically significant reduction in the tone (i.e. a reduction of one point or more in the Ashworth score). The other two patients were only mildly hypertonic with baseline scores of 1.6 and 2, so it was difficult to demonstrate a clinically significant response. They appeared to be more hypertonic on examinations prior to the study, yet it is not uncommon for the tone in mixed spastic and dyskinetic children to vary from day to day. Concerning the patient who did not show a reduction in tone, she experienced excessive drowsiness at 50 μg of baclofen, so we did not increase the dose further. It was not sure whether she might respond to a higher dose.

The tone in the upper extremities was not significantly reduced in the present study. Similar observations have been made in previous studies.[9,19] As the tone in the upper extremities was tested four hours after the bolus injection, there might not be enough time for the cephalic migration of baclofen into the cervical spinal cord.[9] Secondly, dystonia contributed significantly to the upper extremity hypertonicity in the two patients with mixed CP. The effect of bolus intrathecal baclofen is less predictable in dystonia,[10,20] and continuous infusion via an external micro-pump may occasionally be required to evaluate the responsiveness to intrathecal baclofen.[21]

Three patients experienced excessive drowsiness during the screening period. Two of them became drowsy at a dose of 75 μg. The sedation effect was mild and transient and did not preclude further increase in the dose. Both of them recovered spontaneously four to six hours after the injection. The third child developed drowsiness after 50 μg of baclofen. The dose was not increased further despite of inadequate clinical response. One patient developed fever and skin infection at the site of catheterization. CSF culture was sterile and she recovered after removal of the catheter and conservative treatment. Bolus intrathecal baclofen might result in sedation, bradycardia and hypotension.[12] In addition to these side effects, CIBI might also be complicated by respiratory depression, apnea, blurred vision, slurred speech, confusion, dysmetria, seizures and meningitis. Most would resolve after dose reduction.[7,12] Whilst respiratory depression from overdose could be reversed by physostigmine,[22] assisted ventilation might be required in severe cases.[23] No mortality related to CIBI have been reported.[7,8,10-12]

There were some biases in this pilot study. The sample size was small and the study was open-label. Nonetheless, the purpose of the screening trial was to ascertain the effective screening dose for tone reduction, which could be achieved by blinding the assessors to the dose of baclofen given. The Ashworth score is a relatively subjective scale for measuring spasticity, despite of the fact that it was widely used in previous studies.[7-9] A more

objective measurement of spasticity is required for future research. The presence of dystonic components in some of the subjects rendered it difficult to assess the baseline tone and subsequent tone reduction. Nonetheless, both patients with mixed CP were predominantly spastic. Moreover, as the response of dystonia to IT balcofen is less prominent and predictable as that in spasticity, the presence of dystonic components in the subjects would be expected to result in bias towards no effect. Any tone reduction following the screening trial would thus represent genuine response.

Over the past decade, CIBI has proven to be an effective treatment for severe spasticity of spinal and supraspinal origins. It helps to alleviate hypertonicity and painful spasms. Nursing care and mobilization became much easier, with improvement in activities of daily living.[7,8,10-12,24] CIBI resulted in a decrease in the average length of subsequent hospitalizations.[25] Gerszten et al.[26] reported that among 28 patients who were planned to undergo orthopaedic operations at the time of pump placement, 18 patients eventually did not require surgery for their lower extremity spasticity. Becker et al[27] found that CIBI also helped to alleviate autonomic dysfunctions such as hypertension, tachycardia, hyperhidrosis, hypersalivation and bronchial hypersecretion associated with supraspinal spasticity. The functional intelligibility of speech might also be improved.[28] Recently, Middel et al.[29] reported an one year follow-up study on 22 patients, showing that CIBI resulted in improved self-reported quality of life.

CIBI is an expensive form of therapy. A programmable implantable pump device (Medtronic) costs about HK $60,000. The estimated cost of drug is about HK$1200 to $1800 per month, based on a daily dose of 200 μg to 300 μg (10 μg vial of intrathecal baclofen costs about HK$2000). This is compared to a monthly cost of HK$100 to $200 for oral baclofen. However, it is not uncommon for children with severe spasticity to receive two to three anti-spasticity agents. Nance et al[30] reported the hospitalization costs related to spasticity for six patients amount to Canadian$306 in two years. As a result of decrease in hospitalization after pump implantation, there was a net saving of about Canadian$153 in the following two years. The costs on nursing care and physiotherapy should also be taken into account for an accurate cost-benefit analysis.

In conclusion, our preliminary data suggests that intrathecal baclofen is effective in lowering the lower extremity muscle tone in children with spastic CP. Children with severe spasticity who do not respond to conventional therapy should be recruited for a screening trial. Those who respond to bolus intrathecal baclofen may benefit from CIBI via programmable infusion pumps.

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