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Case Report OMICS International

Baclofen Treatment for Pain in Non-functional Children with Cerebral Palsy –A Brief Report

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Abstract

Baclofen, a GABA-B agonist, reduces hypertonia by increasing spinal inhibition and improves motor function in functional children with cerebral palsy. We hypothesized that oral baclofen reduces pain and improves daily care in nonfunctional children with spastic cerebral palsy. To test this children residing in nursery homes with hypertonia causing pain or interfering with daily care were enrolled in this randomized, double blind, placebo controlled, crossover pilot study. Participants were examined before, during and after 13 weeks of baclofen (2 mg/kg/day) and placebo for pain (Brief Pain Inventory and Dalhousie Pain Survey), ease of care (care and comfort questionnaire) and overall treatment assessment (specific questionnaire, designed for this study). Two participants completed this pilot (ages 7 and 8 years). Pain was reported to interfere less on peak dose of baclofen treatment compared to placebo in one child (p=0.0001) and care tended to be easier in the other (p=0.05). Blinded caregivers recommended continuing baclofen. No significant side effects were reported. Baclofen, an inexpensive safe medication, may alleviate pain in nonfunctional spastic children.

Keywords: Brief Pain Inventory and Dalhousie Pain Survey; Care and comfort questionnaire; Hypertonia; Range of motion; Nursery home

Introduction

Recurrent and chronic pain of moderate intensity has been documented in most children suffering from cerebral palsy (CP,) the common cause of disability in children (2:1000 live births). The spastic, hypertonic element of this congenital motor disorder may be one an important source of pain. 70% of children with CP experience recurrent chronic pain of moderate intensity on a daily or weekly basis [1,2]. Physiotherapy required on a daily basis involves painful exercises and may be limited by pain. Pain evaluation in children is generally based on childrens' report or parents' impression. However, in severely disabled children with limited communication, pain assessment is challenging. Difficulty in pain evaluation may lead to underestimation of pain resulting in under or over treatment. However, in these children with hypertonia and limited communication one may estimate pain indirectly by ease of daily care and child's comfort. Baclofen, a GABA-B receptor agonist, is one of few medications reducing hypertonia in CP [3]. Oral baclofen was found effective in improving daily function in children with CP in a randomized double blind study [4] and Intrathecal baclofen has been shown to alleviate pain in 50% of patients thus improving daily care and communication in severely affected children [5]. Nevertheless need for baclofen treatment, its efficacy and impact on daily life in nonfunctional children with CP has not been studied. Oral baclofen treatment is safer and cheaper than intrathecal administration; however, its impact on hypertonia related pain has not been formally evaluated in nonfunctional children with CP. The goal of this study was to assess effectiveness of oral baclofen in reducing pain and improving daily care in nonfunctional hypertonic children with CP. To test this we started a prospective double blind randomized crossover pilot.

Case report

Participants: Children from nursery homes who were nonfunctional (Gross-Motor-Function-Classification-System level 5) and suffered from hypertonia that caused pain or difficulty in daily care were enrolled (n=3) and completed (n=2) the study:

Child #1, a 7-year-old girl was born after 34 weeks of gestation with low apgar scores (6 at 5 minutes). Her MRI demonstrated diffuse extensive encephelomalacia. Parents were second degree cousins; infectious, genetic and metabolic workup was negative. She was blind with no voluntary movements but occasionally reacted to her name. Seizures were treated with lamotrigene. On examination she smiled occasionally and initiated random vocalization. She had some dystonia in her upper limbs. Spasticity was most prominent in lower limbs with a positive Babinsky sign and clonus. Treatment with levodopa was ineffective.

Child #2, an 8-year-old boy, was born after 32 weeks of gestation, to non-consanguineous parents. He had non-progressive spastic quadriplegia due to an unknown cause. He did not have any voluntary movements or any apparent communication. During examination he tended to fixate his gaze to the right with intermittent nystagmus. Dystonic hand posture increased when excited. He had generalized spasticity hyperactive deep tendon reflexes and Babinski sign was negative.

Child #3, a 7.5-year-old boy, was resuscitated following a domestic accident at infancy. Seizures were treated with Phenobarbital. His only

voluntary movement was epistotonic posturing as a response to touch and suction. On examination he did not fixate gaze had arm dystonia, knee hyperextention, leg spasticity and clonus.

The study was approved by Shaare Zedek Medical Center Helsinki committee and parents signed informed consent form (https://clinicaltrial.gov #NCT00752934).

Intervention: Two trial periods (placebo and Baclofen) each lasting 13 weeks each with a 2-week non-treatment (washout) period in between were randomly allocated by a non-blinded research assistant. Child #1 and #2 were assigned to baclofen followed by placebo. Child # 3 completed the placebo trial but dropped-out before baclofen treatment due to a severe H1N1 infection. Baclofen protocol included a weekly increase in dosage (from 2.5 once a day to 7.5 mg three times a day, week 1-7) until reaching peak dose of (~2 mg/kg/day) for five weeks (8-12 weeks) eventually tapering off (week 13). Placebo capsules were arranged in an identical manner. While a non-blinded pediatric neurologist (AA) was assigned to manage medical issues, all evaluators were blinded.

Outcome measures

Main

1) Pain: Two caregivers per child filled the Brief Pain Inventory and Dalhousie Pain Survey weekly [6].

2) Ease of care: caregivers filled the care-and-comfort questionnaire at baseline and peak treatment [7].

3) Overall treatment assessment: At the end of each period caregivers answered 4 questions: Was the treatment helpful? Harmful? Adverse effects noted? Continue treatment?

Secondary

4) Adverse Effects: Caregivers assessed a list of symptoms weekly (e.g. 'how bothersome were symptoms on a scale of 0 to 10 this week?'; Table 1).

5) Goal attainment: Physiotherapists set 3 goals using the goal-attainment- scale (GAS) [8] that were re-assessed at peak dose.

6) Range of motion: physiotherapists measured (goniometer) dynamic measures (R1) and passive measures (R2) at the ankle, hip, elbow and wrist at baseline and peak dose [9].

Statistical analysis

Statistical analysis was performed using Excel (Microsoft, Windows 8.0). Paired two-tailed-t-tests were used to compare the treatment periods within subjects; level of significance was set at 0.05.

	Child #1 7-year-old girl					Child #2 8- year-old boy				
	Baclofen		Placebo		T-test	Baclofen		Placebo		T-test
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
Tiredness	0.64	1.28	3.7	3.62	<0.05	0.67	1.61	0.43	1.13	0.37
Irritability	2.64	3.67	6.3	3.62	<0.05	1	2.66	2.13	2.7	0.18
Hypotonia	0.43	1.16	0.33	0.71	0.21	0.67	1.61	0	0	0.19
Difficulty dressing	1.07	2.89	5.4	2.88	0.07	2	4.47	4	3.46	0.19
Urinary retention	0.71	2.67	0.5	1.27	0.13	0	0	0	0	None
Constipation	0.33	1	4.3	3.53	0.1	0	0	2	2.45	<0.05
Swallowing difficulties	1.57	3.03	5.7	3.06	0.08	0.58	1.38	1.2	2.17	0.24
Sleep problems	0.9	2.23	2.67	2.06	0.25	0	0	1.2	1.79	0.09
Vomiting	0	0	0	0	None	2.33	3.58	0	0	0.11
Apathy	0.64	1.08	0.2	0.63	0.09	0	0	0	0	None
Communication problems	0	0	1	1.5	0.19	0	0	0	0	None
Rash	0	0	0	0	None	0	0	0	0	None
Muscle cramps	1.5	3.53	8.2	1.69	<0.05	0.33	1.15	2.83	2.99	<0.05
Feeding difficulties	2.57	2.95	8	1.76	<0.05	0.5	1.73	2	2.45	0.08
Seizures	0	0	0	0	None	0	0	0	0	None

Table 1: Adverse effects.

Results

Data acquisition: Pain and adverse effects were reported by at least one caregiver throughout most of the study period (45/55 weeks; 82%). Ease of care report was fully obtained however some of the items were found irrelevant by the caregiver (13/28; 46%). Range of motion was fully measured (RD and GBS performed 3/10 and 7/10 respectively).

Pain: Pain interfering with activity was reported by Brief–Pain-Inventory to be lower at the peak (weeks 8-11) of baclofen treatment (0.31, SD 0.79) compared to placebo for the equivalent period (5.41, SD 2.17, 2- tailed-paired-t-test, $p<0.0001$) for child #2, but not for child #1 ($p=0.11$). Pain was reported to decrease over the treatment period in 1 of two baclofen and in 1 of the 3 placebo treatments (Figure 1). Pain intensity in child #1 tended to be lower (4.5, SD 0.7 on baclofen to 6.7, SD 1.5 on placebo, $p=0.12$), but not in child #2 ($p=0.38$).

Ease of care: Daily care tended to be easier on baclofen (3.8, SD 1.6) compared to placebo (4.5, SD 1.7; 2-tailed-paired-t-test, $p=0.051$) in child #1; no change was noted in child #2 ($p= 0.23$).

Overall treatment assessment: Baclofen was reported helpful for child #1 but not for child #2 baclofen or placebo treatments. None of the treatment regimens were reported harmful; constipation was reported on placebo (child #2). Recommendation to continue treatment was positive (child #1='yes', child #2='possibly') following baclofen but not for placebo ('no' for all 3 children).

Adverse Effects: There were no adverse effects reported. Actually, more somatic bothersome complaints occurred during placebo treatment than baclofen (0.71, SD 0.81 baclofen vs 2.07 SD 2.52 placebo; 2-tailed-non-paired-t-test, $p<0.05$). Baclofen significantly reduced muscle cramps in both children (Table 1).

Gas: Goal attainment following baclofen was more than expected for standing (child#1), as expected for sitting, feeding (child #1) and head control when seated on the floor (child #2) . Goal attainment was less than expected for dressing (child #1), head control on wheel chair (child #2) and much less for button press (child #2). Following placebo all goals were attained as expected except standing and dressing which were attained much more than expected (child #2).

Range of motion: No improvement was detected in hip adduction (2-tailed-paired-t-test, $p=0.94$ child #1 and 0.27 child #2), elbow flexion ($p=0.15$ and 0.13) palmar flexion ($p=0.054$ and $p=0.95$) and dorsal wrist flexion ($p=0.06$ and $p=0.14$). Ankle dorsiflexion was not included due to technical issues.

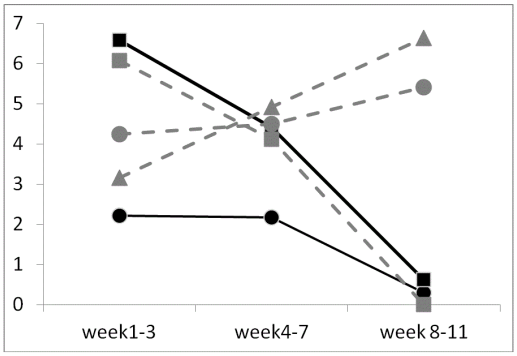

Figure 1: Pain on baclofen treatment and placebo.

Pain was reported lower using the Brief Pain Inventory. There was a significant change in average pain in child #1 (circle). While pain remained high on placebo treatment (grey dashed line, circles) average pain scores are lower on peak dose of baclofen treatment (black lines, circles). Child # 2 (square) had a decrease in pain both following both baclofen (black line) and placebo (grey dashed). The third child who dropped of the study was reported to have increasing pain (grey triangle) over time.

Discussion

This preliminary study suggest that baclofen at a dose of 2 mg/kg per day can ameliorate pain and assist in daily care in children with CP who are nonfunctional with limited communication. Questionnaires directed to caregivers assessing pain reduction are helpful if used systematically over time. We could not detect a change in ease of care maybe due to the fact that reports were only obtained at the beginning and end of the period. Inter-rater variability and fluctuating spasticity may necessitate several reports over time. Goal attainment improved more during placebo trial compared to baclofen treatment. This improvement may be attributed to gaining skills over time regardless to medical therapy. Alternatively baclofen may have induced weakness compromising some goals (i.e. head control). As expected range of motion seems less useful for assessment since measures between sessions are less reliable [9] and many of these children had already developed contractures. This study is limited in sample size and further studies regarding pain amelioration in nonfunctional children with CP is needed.

We did not encounter any significant adverse effects that discourage a trial of higher doses to achieve even greater clinical benefit. Interestingly baclofen treatment reduced somatic complaints. While it is known that baclofen has systemic effect (i.e., lowering gastroesophagael reflux), it is suggested that some somatic complaints may be affected by spasticity (i.e., constipation). In conclusion increasing awareness of hypertonia treatment in nonfunctional spastic children is imperative. Pain assessment is possible in non-communicative children with CP based on caregivers' report of pain and daily care. Ameliorating pain and discomfort with noninvasive medical treatment such as oral baclofen could not be over-emphasized in undertreated populations.

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