ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY
Research Article

Economic Analysis of Comprehensive Rehabilitation of Children with Spastic Forms of Cerebral Palsy with and without Botulinum Neurotoxin Type A Injections

Zmanovskaia VA[1]*, Popkov DA[2], Uzdina AI[1], Ushakova SA[3] and Levitina EV[3]

[1]*Children Psychoneurological Treatment and Rehabilitation Center "Nadezhda", Tyumen, Russia*

[2]*Russian Research Center for Reconstructive Traumatology and Orthopaedics Named After G.A. Ilizarov, Kurgan, Russia*

[3]*Tyumen State Medical University of the Ministry of Health of the Russian Federation, Tyumen, Russia*

***Corresponding Author:** Zmanovskaia VA, Children Psychoneurological Treatment and Rehabilitation Center "Nadezhda", Tyumen, Russia.

Received: December 11, 2019; **Published:** January 10, 2020

Abstract

Objective: Conduct a comparative economic analysis of comprehensive rehabilitation for children with CP aged from 2 to 14 years with and without botulinum neurotoxin type A (BoNT-A) injections.

Materials and Methods: We followed 149 children with spastic forms of CP (GMFCS II-IV) - 78 boys and 71 girls aged from 2 to 14 years. The study group included 108 children getting abobotulinumtoxinA injections (BoNT-A injections) in the comprehensive rehabilitation program and the control group included 41 children with similar comprehensive treatment without BoNT-A injections, which is the current standard of complex therapy. While conducting an economic analysis (budget impact analysis, BIA and cost-effectiveness analysis, CEA), only direct costs were taken into account: the cost of BoNT-A therapy, rehabilitation and surgeries.

Results: Children with CP in the study group required their first surgical correction by the age 10.5 ± 2.8 years. 5 children (4.6%) required repeated operations. The children in the control group receiving standard therapy (without BoNT-A injections) were first operated on at the age of 6.7 ± 2.1 years. 39 children (95%) required repeated operations in the control group during their 10 to 12 year period of active growth and development. The economic analysis confirmed that including abobotulinumtoxinA as part of the CP treatment regime would provide savings of 24.744 690.2 roubles per 100 children compared to standard therapy without BoNT-A injections over a 12-year follow-up period. Achieving 1% effectiveness in children with CP using BoNT-A would cost 1,854,426 roubles, however achieving similar outcomes in children with CP without BoNT-A would cost 40,702,271.6 roubles. If BoNT-A therapy was included as part of the comprehensive rehabilitation program, the savings could provide medical treatment for an additional 14% children opposed to a more expensive treatment regime without BoNT-A.

Conclusion: The use of abobotulinumtoxinA as part of comprehensive rehabilitation for children with CP is economically justified. Long-term therapy of children with CP using BoNT-A can provide savings of 24 744 690 roubles per 100 patients compared to the standard therapy over a 12-year follow-up period. Using the statistical data issued on January 01, 2018 of the registry of children with CP in the Tyumen region, the budget savings could be 5,938,726 roubles per year.

Keywords: *Cerebral Palsy; Spasticity; GMFCS; Botulinum Toxin Type A; AbobotulinumtoxinA (BoNT-A); Multi-Level Injections; Botulinum Therapy; SEMLS-Single-Event Multilevel Surgery*

Introduction

The medical expenses for children with cerebral palsy (CP) are more than 10 times the expenses of children without CP. If we include the expenses incurred by intellectual incapacity, which occurs in 50% of CP cases, the expenses are 26 times more than normally developed children [8,17].

Numerous Russian and international trials have shown that two thirds of children with spastic forms of CP regularly get injections of botulinum neurotoxin type A (BoNT-A) for spasticity - the most common type of abnormal muscular tone in children with CP. The key mechanisms in pathogenesis of joint contractures, limb deformities, complete and incomplete joint dislocations and other secondary orthopaedic complications are insufficient and disproportional growth of the musculotendinous units in relation to the length of the bone segments; as well as muscle retraction developed in long-term spasticity [1,5,9,20].

Secondary orthopaedic complications require orthopaedic surgical interventions to provide correction, restore normal anatomical proportions and relations between different parts of the locomotion system and maintain the maximum possible functionality in any neurological damage [6,10,13].

The contemporary concept of surgical interventions for orthopaedic complications in CP implies performing a single-event multi-level surgery (SEMLS) aimed at simultaneous correction (at a single-event operation) of all existing orthopaedic complications accompanied by a single rehabilitation period for both lower limbs [4,15].

The contemporary approach is that orthopaedic surgical interventions to correct orthopaedic complications and improve the gait should be performed only when secondary orthopaedic problems have developed. Depending on the individual characteristics, the first orthopaedic operation in patients with GMFCS I-III ranges from 7 to 14 years [16,18,25].

It is generally considered that orthopaedic surgical intervention aimed at gait improvement should be postponed until active growth and development of the locomotion system are completed as operations performed at an earlier age are associated with an increased risk of failures, relapses and less predictable treatment outcomes [23].

Consequently, at the first stage therapeutic interventions in children with CP should include measures for abnormal spastic muscle tone correction with BoNT-A injections to prevent joint contractures development as this method has proven its effectiveness and is included as part of basic therapy of local CP spasticity in world practice for over 20 years [7,11,12,25].

BoNT-A has the biggest impact on healthcare economics in the early age group of children with CP. That, in turns, brings up the question of how cost effective is long-term therapy with BoNT-A preparations providing improved clinical outcomes [24].

Objective of the Study

The objective was to carry out a comparative cost effectiveness analysis of comprehensive rehabilitation of children with CP aged 2 to 14 years with and without BoNT-A injections.

Materials and Methods

First, we searched randomized clinical trials in the bibliographic databases: Medline, Medscape, PubMed, Cochrane Library, as well as in the international database of open clinical trials clinicaltrials.gov [14,19,21,22].

Second, there is a Russian pharmacoeconomic study “Pharmacoeconomics of the use of botulinum toxin preparations in comprehensive treatment of cerebral palsy” [2] was devoted to the pharmacoeconomics of CP in Russia, particularly pharmacoeconomics of spastic forms of CP [3].

To set up the tasks of the analysis, we followed up 149 children with spastic forms of CP (GMFCS II-IV) - 78 boys and 71 girls aged from 2 to 14 years from 2001 to 2017. The study group included 108 children with spastic forms of CP getting abobotulinumtoxinA injections included in their comprehensive rehabilitation program. The control group contained 41 children with similar comprehensive treatment without BoNT-A injections. The two groups did not have any significant differences by gender, age or clinical forms of the disease. The comprehensive rehabilitation program included individualized massage therapy, exercise therapy, dynamic proprioceptive correction (costumes “Adele”, “Graviton”), corrective positioning, orthotics, electrostimulation of weakened muscles, reflex therapy, hydrotherapy (underwater massage treatment, arm and leg whirlpool bath), serial casting.

In our analysis, botulinum neurotoxin type A - Dysport® was used for intramuscular injections. The injection dosage, points and frequency were determined on an individual basis. The toxin was delivered as a cooled power containing 500U of Clostridium Botulinum Haemagglutinin Complex, 125 mg human albumin and 2.5 mg lactose. 500U abobotulinumtoxinA was reconstituted with 2.5 ml 0.9% normal saline, so as 1 ml solution contained 200U of preparation. The solution was injected IM into one or two injection points. The injections were done quickly without any anesthesia to avoid stress reaction in children. The total medication dosage ranged from 225 to 750U, with 14 to 30 U/kg (mean 28 ± 4 U/kg). The total permissible dose was calculated according to body weight and was distributed depending on the muscles to be injected. The muscles for abobotulinumtoxinA injection were selected depending on the prevailing motor dysfunction syndrome in children with CP. Time-to-retreatment with abobotulinumtoxinA injections was 180 - 200 days in 70% of the children treated.

While conducting this economic analysis only direct costs were taken into account: costs of BoNT-A injections, costs of rehabilitation in accordance with approved orders by the Ministry of Health of the Russian Federation issued on June 15, 2015 №340n and June 16, 2015 №349n on the standards of medical care in a policlinic, a day care center; a 24-hour inpatient hospital and the costs of orthopaedic operations.

The cost of pharmacotherapy with botulinum neurotoxin type A was calculated based on the maximum sale prices on abobotulinumtoxinA set by pharmaceutical manufacturers for medicines on the list of vital and essential drugs. On January 01, 2018 the producer price of one 500 U vial of abobotulinumtoxinA was 14,389 roubles. Taking into account the dose range accepted in the cost effectiveness analysis and the calculated cost of botulinum therapy, we determined that during a 6-month course of treatment the patient would receive one 500U vial of abobotulinumtoxinA along with standard therapy.

The cost of standard therapy for children with CP was calculated in accordance with the territorial programme of compulsory health insurance in the Tyumen region in 2018 and constituted 35,492.39 roubles in a day care center and 67,947.45 roubles in a 24-hour inpatient hospital.

To calculate the costs of surgical correction, the basic standard costs on high-tech medical care were used. The expenditure list included the costs of the operation; anesthesia care; hospitalization; direct and indirect labour costs; costs of preparations and disposable materials, food, hospital linen, medical equipment, reagents and chemicals; laboratory tests and instrumental diagnostics made in other medical settings; telecommunication; transportation, community facilities, maintaining equipment, rent for property use, software, etc., as well as social benefit costs for medical staffing established by the legislation of the Russian Federation.

The calculation of standard orthopaedic operations was carried out according to the section "Elimination of defects and deformities by the method of cutaneous and musculotendinous plasty" of the government medical benefits scheme. For single-event multi-level operations, costs for such types of interventions included correcting osteotomy of the lower limb bones, reconstructive and plastic surgery on the foot bones with auto- and allografts, implants, osteosubstitution materials, metal constructions and elimination of defects and deformities by cutaneous and musculotendinous plasty, bone auto- and alloplasty with external and internal fixators. The total cost of a single-event multilevel operation was 353,230 roubles.

Results and Discussion

Follow-up of 108 children with CP in the study group receiving abobotulinumtoxinA injections in a comprehensive rehabilitation program showed that children required their first surgical correction for gait improvement at the age of 10.5 ± 2.8 years (min - 8 years 4 months; max - 13 years). 5 children (4.6%) required a repeated operation by the age of 14 years.

The 41 children from the control group who did not get abobotulinumtoxinA injections in the comprehensive rehabilitation program underwent their first operation on average at 6.7 ± 2.1 years (min - 5 years 8 months, max - 9 years). 39 children (95%) experienced gait

pattern worsening in the control group during their 10 to 12 year period of active growth and development, which required repeated orthopaedic surgical interventions.

All children with CP aged from 2 to 12 years old received on average 23 standard courses of rehabilitation in a day care center. During their postoperative period, children with CP received 4 courses of rehabilitation for 2 years in a 24-hour inpatient hospital.

The data in table 1 and 2 show that the costs for a 1 year period of comprehensive treatment with abobotulinumtoxinA (BoNT-A) per patient in the study group was 20,620.6 roubles less than the costs of standard treatment per CP child without BoNT-A in the control group. For 12 years it is a saving of 247,446.9 rubles per patient.

Parameter	Cost of standard therapy + abobotulinumtoxinA with single-event operation, n = 103	Cost of standard therapy + abobotulinumtoxinA with repeated operations, n = 5
Cost of preparation - botulinum neurotoxin type A	31,312,206	1,097,785
Cost of medical care in a day care center	84,081,471.9	4,081,624.9
Costs of medical care in a 24-hour inpatient hospital	27,994,349.4	2,717,898
Cost of orthopaedic operation	36,382,690	3,532,300
Total cost	179,770,717.3	11,429,607.9
Cost per one child	1,745,346.8	2,285,921.6
Cost per 100 children	96.4%	4.6%
	168,251,428.6	10,515,239.2
	178,766,667.85	
Cost per one child in the study group for a 12-year follow-up period	1,787,666.7	
Cost per one child in the study group for a 1-year follow-up period	148,972.2	

Table 1: *Expenditure list comparing standard CP treatment with abobotulinumtoxinA for 1 year and a 12-year follow-up period.*

Parameter	Cost on standard therapy without BTA, with single-event operation, n = 2	Cost of standard therapy without BTA with repeated operations, n = 39
Cost on preparation - Botulinum toxin type A	0	0
Costs of a medical care in a day care center	1,632,649.9	31,836,673.83
Costs of a medical care in a 24-hour inpatient hospital	543,579.6	21,199,604.4
Cost of orthopaedic operation	706,460	27,551,940
Total cost	2,882,689.5	80,588,218.23
Cost per one child	1,441,344.8	2,066,364.57
Cost per 100 children	5%	95%
	7,206,723.9	196,304,634.2
	203,511,358	
Cost per one child in the control group for a 12-year follow-up period	2,035,113.6	
Cost per one child in the control group for a 1-year period	169,592.8	

Table 2: *Expenditure list comparing standard CP treatment without abobotulinumtoxinA for 1 year and a 12-year follow-up period.*

A Budget Impact Analysis was also used to calculate all costs related to the introduction of a new treatment regime compared to those of an already existing treatment regime. The calculation of costs was carried out using the formula:

BIA = Cost 1- Cost 2

where:

Cost 1 - total cost of the first treatment method, roubles;

Cost 2 - total cost of the second treatment method, roubles;

BIA - Budget Impact Analysis, roubles.

As a result of this Budget Impact Analysis, it was established that comprehensive treatment of children with CP with BoNT-A can provide savings of 24,744,690.2 roubles per 100 CP children over a 12-year period compared to using only standard therapy without BoNT-A injections. Per patient costs for the same period can be reduced by 247,446.9 roubles compared to using only standard therapy without BoNT-A injections.

The register of children with CP in the Tyumen region, patients with GMFCS II-IV and indications for botulinum therapy, made up 31% of the total child population with CP-a total of 288 children as of 01 January 2018.

The Budget Impact Analysis also revealed that using botulinum neurotoxin type A to treat this group of patients could provide a budget savings of 71,264,708 rubles over 12 years; a savings of 5,938,726 rubles per year.

Cost-effectiveness analysis: (CEA) is another basic economic analysis method that is used to compare the total costs of one or another treatment regime and the effectiveness of the treatment, expressed in the same unit measurement. In this trial, the criteria of effectiveness was the frequency of recurrent orthopaedic complications requiring a single-event operation as a percentage of total number of patients, where the key factor was performing an operation at a later age to result in a more favourable outcomes. A "cost-effectiveness" ratio was calculated for each treatment regime using the formula:

CER = $Cost_{CP}$/(F single-event operation, %),

where:

CER - cost-effectiveness ratio of the treatment regime;

$Cost_{CP}$ - direct medical costs per 100 children with CP on that treatment regimen;

F single-event operation - % of total number of patients who underwent a single operation.

Calculation of cost-effectiveness ratio for a group of children with abobotulinumtoxinA

CER = 178,766,667.85 roubles/96% = 1,854,426 roubles.

Calculation of cost-effectiveness ratio for a group of children without BoNT-A

CER = 203,511,358 roubles/5% = 40,702,271.6 roubles.

These calculations showed that achieving 1% effectiveness in children with CP with BoNT-A cost 1,854,426 roubles and achieving similar outcomes in children with CP without BoNT-A cost 40,702,271.6 roubles.

Cost effectiveness analysis allowed us to evaluate the ratio of direct medical costs of the treatment of children with CP to a comparative effectiveness of treatment in clinical trials and define the most beneficial type of therapy with the highest cost effectiveness ratio.

We also conducted a Missed Opportunity Analysis**.** This calculates the number of potential clients who could get medical care if a more cost-effective treatment regime is applied. The calculations were carried out using a formula:

$L = BIA_{CP}/Cost_{CP}$ (min)

where:

L- missed opportunities;

BIA_{CP} - total costs of a more expensive treatment of CP without BoNT-A per 100 children;

$Cost_{CP}$ (min) - costs of a less expensive treatment of CP per 1 child;

L=203,511,358 roubles/1,787,666.68 roubles = 114 children.

The Missed Opportunity Analysis revealed that including BoNT-A in the comprehensive rehabilitation program for children with CP was sufficient to provide medical treatment for additional 14% patients compared to a more expensive treatment regime without BoNT-A.

Conclusion

As a result of the compared economic analysis of a comprehensive rehabilitation program for children with CP with and without BoNT-A injections, the results showed that the use of abobotulinumtoxinA in the treatment regime for children with CP was economically justified.

The Missed Opportunity Analysis revealed that using BoNT-A in the comprehensive rehabilitation programme for children with CP was sufficient to provide medical treatment for an additional 14% children, compared to a more expensive treatment regime without BoNT-A.

The cost-effectiveness analysis enabled us to evaluate the most beneficial treatment with the most cost-effectiveness ratio - long-term treatment with BoNT-A resulting in prevention of secondary orthopaedic complications and a later need for more optimal surgical intervention, considering gait disturbance relapses and predictable treatment outcomes.

The long-term treatment of children with CP with botulinum neurotoxin type A compared to a standard treatment for a 12-year-follow-up period could provide savings of 5,938,726 roubles per year on CP treatment expenses in the Tyumen region.

Bibliography

1. Zmanovskaya VA., *et al*. "Long-term use of botulinum toxin type A: Dysport® in the comprehensive rehabilitation of children with spastic forms of cerebral palsy". *Journal of Neurology, Neurosurgery, and Psychiatry* 7 (2014): 33-36.

2. Kolbin AS., *et al*. "Pharmacoeconomics of the use of botulinum toxin preparations in comprehensive treatment of cerebral palsy".

3. Kulikov A., *et al*. "Pharmacoeconomic analysis of different types of treatment for spastic forms of cerebral palsy". *Pharmacoeconomics: Theory and Practice* 3.3 (2015).

4. Popkov DA., *et al*. "The results of single-event multilevel orthopedic operations and early rehabilitation in combination with botulinum therapy in patients with spastic forms of cerebral palsy". *Journal of Neurology, Neurosurgery, and Psychiatry* 115.4 (2015): 41-48.

5. Abel M., *et al*. "Muscle-tendon surgery in diplegic cerebral palsy: functional and mechanical changes". *Journal of Pediatric Orthopaedics* 19 (1999): 366-375.

6. Aiona MD and Sussman MD. "Treatment of spastic diplegia in patients with cerebral palsy: part II". *Journal of Pediatric Orthopaedics* 13 (2004): S1-S38.

7. Brin MF and Blitzer A. "Botulinum toxin: dangerous terminology errors". *Journal of the Royal Society of Medicine* 86.8 (1993): 493-504.

8. CDC, Data and statistics for cerebral palsy (2016).

9. Damiano DL., *et al*. "New Clinical and Research Trends in Lower Extremity Management for Ambulatory Children with cerebral Palsy". *Physical Medicine and Rehabilitation Clinics of North America* 20.3 (2009): 469-491.

10. Dequeker G., *et al*. "Evolution of self-care and functional mobility after single-event multilevel surgery in children and adolescents with spastic diplegic cerebral palsy". *Developmental Medicine and Child Neurology* 60.5 (2018): 505-512.

11. FDA. Information for healthcare professionals: OnabotulinumtoxinA (marketed as Botox/Botox cosmetic), AbobotulinumtoxinA (marketed as Dysport) and RimabotulinumtoxinB (marketed as Myobloc). 2009.

12. Heinen F., *et al*. "European consensus table 2006 on botulinum toxin for children with cerebral palsy". *European Journal of Paediatric Neurology* 10 (2006): 215-225.

13. Lebarbier P and Penneçot G. "L'infirmité motrice d'origine cérébrale (IMOC)". *Revue de Chirurgie Orthopédique* 92 (2006): 393-395.

14. Mall V., *et al* . "Treatment of adductor spasticity with BTX-A in children with CP: a randomized, double-blind, placebocontrolled study". *Developmental Medicine and Child Neurology* 48.1 (2006): 10-13.

15. McGinley JL., *et al*. "Single-event multilevel surgery for children with cerebral palsy: a systematic review". *Developmental Medicine and Child Neurology* 54.2 (2012): 117-128.

16. Novacheck TF., *et al*. "Distal femoral extension osteotomy and patellar tendon advancement to treat persistent crouch gait in cerebral palsy. Surgical technique". *Journal of Bone and Joint Surgery* 91.2 (2009): 271-286.

17. Novak I., *et al*. "Clinical prognostic messages from a systematic review on cerebral palsy". *Pediatrics* 130.5 (2012): 1285-1283.

18. Rodda JM., *et al*. "Correction of severe crouch gait in patients with spastic diplegia with use of multilevel orthopaedic surgery". *Journal of Bone and Joint Surgery* 88.12 (2006): 2653-2664.

19. Russo RN., *et al*. "Upperlimb Botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial". *Pediatrics* 1195 (2007): e1149-1158.

20. Rutz E., *et al*. "Stability of the Gross Motor Function Classification System after single-event multilevel surgery in children with cerebral palsy". *Developmental Medicine and Child Neurology* 54.12 (2012): 1109-1113.

21. Scholtes VA., *et al*. "The combined effect of lower-limb multilevel Botulinum toxin type A and comprehensive rehabilitation on mobility in children with cerebral palsy: a randomized clinical trial". *Archives of Physical Medicine and Rehabilitation* 87.12 (2006): 1551-1518.

22. Sutherland DH., *et al*. "Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy". Gait and Posture 10.1 (1999): 35-38.

23. Svehlík M., *et al*. "The influence of age at single-event multilevel surgery on outcome in children with cerebral palsy who walk with flexed knee gait". *Developmental Medicine and Child Neurology* 53.8 (2011): 730-735.

24. Tedroff Kristina., *et al*. "To switch from Botox to Dysport in children with CP, a real world, dose conversion, cost-effectiveness study". *European Journal of Paediatric Neurology* XXX (2018): 1-7.

25. Wohlfarth K., *et al*. "Dose equivalence of two commercial preparations of botulinum neurotoxin type A: time for a reassessment?". *Current Medical Research and Opinion* 25.7 (2009): 1573-1584.

Volume 8 Issue 2 February 2020