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Gross Motor Function Improvement in Children with Cerebral Palsy: A Case Series of Single-Event Multi-Level Chemoneurolysis Using Botulinum Toxin-A and/or Phenol Injections

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Abstract

Objectives: Single-Event Multi-Level Chemoneurolysis (SEMLC) using Botulinum toxin-A (BTX-A) and phenol allows more spastic muscles to be treated in one session. Our purpose was to describe efficacy of SEMLC in children with cerebral palsy (CP) and factors associated with a positive outcome.

Design: Authors retrospectively reviewed medical records of children with CP who underwent SEMLC(s) and analyzed factors that possibly associated with Gross Motor Function Classification System (GMFCS) improvement.

Results: 146 SEMLCs in 98 patients aged 7.64 [SD 4.26] years were reviewed. GMFCS at beginning varied: I - 24%; II - 12%; III - 18%; IV - 22%; V - 24%. After the procedure(s), GMFCS was improved 1-2 levels in 12 patients. Younger age at first injection ($p<0.001$), regularly receiving SEMLC ($p=0.030$) and more treatment sessions ($p=0.045$) were associated with improvement in GMFCS level. For every one-year increase in age at first injection, children were 23% less likely to improve their GMFCS level ($p=0.013$).

Conclusions: An improvement in GMFCS level was associated with children with CP who started SEMLC at a younger age and who had regular SEMLCs. Early intervention and continuum of care for children with CP relates to functional improvement.

Keywords

Single-event multi-level chemoneurolysis, Cerebral palsy, Botulinum toxin injection, Phenol injection, Gross motor function

Abbreviations

BTX-A: Botulinum toxin-A, CP: Cerebral Palsy, GMFCS: Gross Motor Function Classification System, SEMLC: Single-event Multi-Level Chemoneurolysis, SEMLS: Single-Event Multilevel Surgery

Introduction

Toxin injection has been a common option to manage spasticity in children with cerebral palsy (CP). Multi-level injections are recommended based on the fact that most patients have diffuse spasticity rather than focal spasticity. In order to achieve optimal limb alignment, a number of muscle groups are targeted [1]. Bakheit et al. reported that multi-level Botulinum toxin-A (BTX-A) injections resulted in a better overall response than single level treatments [2]. Other researchers have reported that the benefit of Single-Event Multi-Level Chemoneurolysis (SEMLC) is not only the body structure but also other aspects of function, activity, and participation [3-5]. Noticeably, previous studies that reported the efficacy of SEMLC used only one chemoneurolytic agent at a time, BTX-A [3-5]. In order to inject multi-level muscles, a larger dose of BTX-A is needed, which unfortunately can increase the potential for adverse effects [1]. Because the total maximal dose per person per session is strictly limited [6,7], either the patient receives a smaller dose per muscle or fewer spastic muscles can be treated in a single session. In order to allow more muscles to be treated, a combination of chemoneurolytic agents such as BTX-A and phenol or alcohol has been used in one session without exceeding the maximum recommended dose for either agent [8,9]. Kolaski et al. [10] and Gooch and Patton [11] reported the safety profile of combining agents (BTX and phenol) in a single session to manage spasticity in children. However, there is scarce evidence for the efficacy of the combined-agent treatment.

Many authors have described patient characteristics and procedural factors, which associated with favorable outcomes after chemoneurolysis with BTX-A. Yap et al. revealed that younger age of patients receiving BTX-A treatment was associated

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with greater change in motor function (GMFM-66) [12]. Fazzi et al. reported a greater improvement in the gait pattern and selective motor control in children who had less limb involvement (hemiplegia>diplegia>quadriplegia) and a lower level of impairment [13] Moreover, Bakheit et al. found that multi-level injections were associated with better outcomes compared to single-level injections [2].

The aims of the present study were (i) to evaluate the efficacy of SEMLC on improving spasticity, joint range of motion, and functional outcome and (ii) to examine whether factors such as age, number of treatment events, number of injections per session and type of CP are associated with Gross Motor Function Classification System (GMFCS) improvement.

Methods

A retrospective chart review was conducted with approval from the Columbia University Institutional Review Board. The authors reviewed medical records of children with CP from January 2011 to November 2012. The authors included patients with a diagnosis of CP who were aged 6 months to 17 years at the time of the first SEMLC and who underwent at least one eligible SEMLC. The eligible SEMLC was defined as a procedure that injected two or more levels of a limb(s) using BTX-A and/or 5% phenol in a single event by a pediatric physiatrist (H.K.). We excluded patients who underwent only one round of SEMLC that (i) had a dose increase of oral antispastic medications and/or intrathecal baclofen pump after the procedure (ii) underwent orthopedic surgery and/or selective dorsal rhizotomy less than a year prior to the injections and (iii) had no follow-up after SEMLC. Demographic data including sex, age, type of CP, functional status, in addition to procedural details such as number of muscles injected, injection episodes and follow-up period were collected. Regular SEMLC was considered to be more than one round of SEMLC within a 12-month period.

The expanded and revised Gross Motor Function Classification System (GMFCS) [14,15] was used to define the functional level of children with CP. The GMFCS level prior to the first SEMLC was defined as a baseline functional level, and the GMFCS level at a follow-up visit of the last SEMLC was the final GMFCS level. Pre- and post-SEMLC findings, including passive joint range of motions, spasticity and GMFCS level were documented in medical records at every clinic visit by the same doctor (H.K.). The Thomas test [16] and popliteal angle [17] were used to assess the degree of hip flexor and hamstring tightness, respectively: the greater the degree, the less the flexibility. The degrees of ankle dorsiflexion with knee extended and knee flexed were used to assess gastrocnemius and soleus muscle flexibility, respectively; a positive reading (degree measured >0) means that the ankle can be passively dorsiflexed beyond the neutral position, whereas a negative reading (degree measured <0) means that the ankle cannot be moved to the neutral position due to the tightness. The Modified Ashworth Scale (MAS) was used to quantify the degree of spasticity [18]. A follow-up visit was usually between 2 to 6 weeks after the procedure. These methods and measurements are standard practice and follow-up procedures at CUMC.

Statistical analysis

Data were analyzed using SPSS (version 21.0, Armonk, NY). Continuous variables are summarized as mean [standard deviation] and categorical variables as frequency (percentage). For categorical variables, Chi-squared or Fisher's exact tests, where appropriate, were used. Continuous variables were analyzed with a Student's t, equal variances were not assumed. Pre-and post-procedure range of motion and MAS were compared by paired t-test. Logistic regression was used to determine factors that were associated with a change in GMFCS. Statistical significance was set at an=0.05 and 95% confidence intervals (CI 95) were determined.

Procedures

Most of the SEMLC procedures were performed under general anesthesia to prevent pain and anxiety especially in children who could not cooperate and when extensive multi-level injections with combined BTX-A and 5% phenol were planned. Patients who could cooperate well and tolerate the pain received injections under local anesthetic agents (4% Lidocaine cream and/or Ethyl Chloride spray). The goals of treatment were the main consideration for clinicians to choose muscles to be injected [6]. OnabotulinumtoxinA (BOTOX, Allergan, Irvine, CA) was used from 12 – 20 units/kg and no more than 400 units per session [1,7]. It was usually diluted in preservative free normal saline to a concentration of 100 units (U)/ml. A double dilution (50 U/ml) was applied in patients who had low body weight that allowed for only a small total dose of BTX-A, but required injections in many muscles. Less than 50 U of OnabotulinumtoxinA per site was injected to decrease the risk of diffusion to blood circulation; multiple site injections to one muscle were applied if a large dose was needed [1]. The procedures were performed under electrical stimulation and/or ultrasound guidance to maximize the effect and minimize complications from misplaced injections [9].

The dose of 5% phenol for each muscle was calculated, based on the severity of spasticity, size of the muscle and patient's body weight as well as the calculation for BTX-A. Unpublished data showed 0.1 ml of 5% phenol had comparable effect as of 10 units of OnabotulinumtoxinA. The injection of 5% phenol was limited to less than 0.5 ml per site to decrease the risk of fibrosis [9]. Intramuscular injections to motor points were applied under nerve stimulation guidance with a 100-ms pulse width square wave ranging in intensity from 1 to 3mA. Isolated target muscle contraction was confirmed before infusing the phenol.

BTX-A was used primarily, and 5% phenol was additionally applied in cases where the maximum recommended dose of BTX-A was not enough to cover all of the target muscles [19]. The two agents were never injected to the same muscle or same compartment due to the concern that the phenol might denature BTX-A.

Results

Ninety-eight patients with 182 SEMLCs were screened, and 146 SEMLCs were eligible for comparing clinical findings pre- and post-procedures. The mean age of the patients at the time of first SEMLC was 7.64 [SD 4.26] years. Baseline characteristics of the subjects are shown in table 1. SEMLC was performed 1 - 4 rounds per each subject with a mean of 1.86 [SD 1.02]. A mean time interval between sessions was 5.74 [SD 2.10] months. The patients had been followed in the clinic from 0.5 to 19.83 months, with the mean of 6.91 [SD 5.54] months. Most of the procedures (72%) used combined BTX-A and 5% phenol in a session, 28% used a single chemoneurolytic agent. The mean OnabotulinumtoxinA dose was 285.08 [SD 92.14] units (U) or 12.32 [SD 3.25] U/kg. The mean 5% phenol injection was 2.26 [SD 1.14] ml or 0.11 [SD 0.07] ml/kg. The mean total number of muscles injected per session was 13.67 [SD 5.35], 7.88 [SD 2.76] muscles were injected by BTX-A and 5.79 [SD 5.04] were injected by 5% phenol. The most frequently injected muscles are shown in table 2. The hamstring and iliopsoas muscles were injected primarily by BTX-A, as opposed to hip adductors, which were mainly injected

Table 1: Baseline characteristics

Characteristics	N=98 (%)
Male sex	57 (58%)
Topographical type	
- Hemiplegia	14 (14%)
- Diplegia	22 (22%)
- Tripletgia	8 (8%)
- Quadriplegia	54 (55%)
GMFCS level	
- I	23 (24%)
- II	12 (12%)
- III	18 (18%)
- IV	22 (22%)
- V	23 (24%)

Table 2: Most frequently muscles injected by BTX-A and phenol (N)

	Overall	BTX-A	Phenol
Upper extremity	Brachialis (103)	Pronator teres (68)	Brachialis (61)
	Pronator teres (72)	Adductor pollicis (56)	Triceps (7)
	Adductor pollicis (56)	Brachiallis (42)	Infraspinatus (4)
	Pronator quadratus (36)	Pronator quadratus (36)	Pronator teres (4)
	Flexor carpi ulnaris (32)	Flexor carpi ulnaris (30)	Brachioradialis (3)
Lower extremity	Hamstrings (263)	Hamstrings (227)	Gastrocs (153)
	Gastrocs (223)	Iliopsoas (193)	Hip adductors (139)
	Hip adductors (217)	Hip adductors (78)	Peroneus longus (100)
	Iliopsoas (193)	Gastrocs (70)	Tensor fasciae latae (56)
	Peroneus longus (131)	Tibialis anterior (35)	Quadriceps (51)

Table 3: The mean comparisons of passive range of motions and spasticity between pre and post-SEMLC #

Tests	Pre-SEMLC	Post-SEMLC	Difference	P-value
Thomas test	31.10 [25.52]	15.95 [16.20]	15.15 [23.52]	< 0.001*
Popliteal angle (degrees)	101.10 [31.42]	61.05 [28.40]	40.05 [26.77]	< 0.001*
ADF (KE) (degrees)	-10.23 [20.82]	2.91 [11.70]	13.14 [16.76]	< 0.001*
ADF (KF) (degrees)	8.14 [15.13]	15.14 [10.85]	7.00 [14.42]	< 0.001*
MAS at ankles	2.22 [0.61]	1.52 [0.77]	0.70 [0.74]	< 0.001*
MAS at elbows	2.30 [1.20]	1.89 [1.14]	0.41 [0.54]	< 0.001*

mean [SD], * P-value<0.05,

ADF (KE): Ankle Dorsiflexion with Knee Extended, ADF (KF): Ankle Dorsiflexion with Knee Flexed, MAS: Modified Ashworth Scale

Table 4: Twelve children improved their GMFCS from different rounds of SEMLC*

GMFCS level At before – after SEMLC	1st SEMLC	2nd SEMLC	3rd SEMLC
Level V to IV	2		
Level IV to III	5	2	
Level III to II	1		2
Level II to I		1	

*The total number in the table was 13 because there was a child who improved 2 levels from GMFCS level IV to II after the 2nd and 3rd rounds of SEMLCs.

by 5% phenol. For upper extremities, BTX-A was primarily used for the pronator teres, flexor carpi ulnaris and adductor pollicis, while 5% phenol was primarily used for brachialis.

Flexibility and spasticity were significantly improved after SEMLC as shown in table 3. The mean duration between the injections and follow-up visits was 40.99 [SD 32.02] days. Most of the patients (87.8%) maintained their functional level, while 12 patients showed level transition. Eleven patients improved one level of GMFCS, whereas one child improved two levels from GMFCS level IV to II (Table 4). No deterioration in GMFCS level in any subjects was observed in the present study. All children with GMFCS I did not change their level on GMFCS since level I is the highest functional level. Therefore, GMFCS improvement in subjects with GMFCS level II - V was appreciated in 16% (12/75).

We analyzed the characteristics of these best responders compared to others. Table 5 shows the factors that were associated with improvement of GMFCS level post SEMLC. These included: GMFCS at first visit, age at first SEMLC, number of procedures, and undergoing regular SEMLC. The patients who improved their GMFCS level were significantly younger at first SEMLC, compared to those who did not improve. For every one-year increase in age at first SEMLC, children were 23% less likely to improve their GMFCS level (Odds ratio 0.77, CI95: 0.62 – 0.95, p=0.013) (Table 6). The patients who had regular SEMLCs are 5 times more likely improve their GMFCS level compared to those who did not have regular SEMLCs (Odds ratio 5.00, CI95: 1.03 – 24.18, p=0.045). For every one round of SEMLC received, the patient was 91% more likely to improve their GMFCS level (Odds ratio 1.91, CI95: 1.08 – 3.35, p=0.025). Other factors including sex, type of CP and total number of muscles injected were not significantly associated with motor improvement. However, there was a trend that those patients who showed improvement in GMFCS had more muscles injected compared to those without improvement (21 versus 13 muscles respectively).

Discussion

The major finding of this study was that SEMLC was able to improve function as measured by GMFCS in proportion to the number of sessions of SEMLC and was more effective for younger patients. To enable the injection of more muscle groups yet remain within the safe total dose restrictions of BTX-A, phenol has been used in combination with BTX-A [19]. Most common unintended effect (UE) after SEMLC was temporary weakness.[20] UEs following SEMLC with BTX-A and phenol were summarized in our previous work [20]. Overall incidence of UEs of the group that received combined agent treatment was not different from the group that received BTX-A only [20]. The two chemoneurolytic agents were used together regularly for most of cases in the present study. However, there were some considerations for choosing an agent. Phenol was preferred for large muscles since it may cause fibrosis [9]. Hip adductor and neck muscles could be better treated with phenol since BTX-A may diffuse and cause bladder incontinence and dysphagia by relaxing the adjacent muscles [21]. This diffusion property of BTX-A is beneficial for severely distorted muscles and some muscles, such as iliopsoas and hamstrings, whose motor points can be difficult to identify for phenol injections [22]. BTX-A was chosen for painful areas since it has been shown to have an analgesic effect [21].

The beneficial effects of SEMLC for spasticity and flexibility presented in this study are not a surprise, since many publications have shown the similar results by using either BTX-A or phenol alone [9,21,23]. From those studies, we inferred that SEMLC using two chemoneurolytic agents would be beneficial in a single session. It is interesting to note that the GMFCS level was maintained or improved in the present study, whereas several articles revealed no change in GMFCS in children with CP despite positive outcomes after chemoneurolysis with BTX-A and/or phenol [4,24]. Unlu et al. reported improvements in spasticity and Gross Motor Function Measure (GMFM-88) scores after multi-level BTX-A injection in children with CP; however, the functional improvement was not big enough to show a difference in GMFCS level [4]. The stability of GMFCS was also observed after single-event multilevel surgery [24].

There are possible factors that may contribute to the discrepancy in functional outcomes after SEMLC in this study compared to others. The present study revealed that the improvement of GMFCS

Table 5: The association between patients' characteristics and the improvement of GMFCS

Factors	Improved GMFCS (n=12)	Non-improved GMFCS (n=86)	P-value
Male sex	8 (67%)	49 (57%)	0.524
Topographical type			
• Hemiplegia	0 (0%)	14 (16%)	0.131
• Diplegia	3 (25%)	19 (22%)	0.821
• Triplegia	2 (17%)	6 (7%)	0.251
• Quadriplegia	7 (58%)	47 (55%)	0.810
GMFCS at first visit			
• I	0 (0%)	23 (27%)	0.041*
• II	1 (8%)	11 (13%)	0.659
• III	2 (17%)	16 (19%)	0.871
• IV	7 (58%)	15 (17%)	0.001*
• V	2 (17%)	21 (24%)	0.553
Age at first SEMLC (years)	4.56 ± 2.18	8.08 ± 4.31	<0.001*
SEMLC times	2.50 ± 1.09	1.77 ± 0.98	0.045*
Regular SEMLC#	10 (83%)	43 (50%)	0.030*
The mean total number of muscle injected	21.01 ± 17.51	13.19 ± 5.17	0.152

*P-value < 0.05

Regular SEMLC was defined if the patient had >1 round of SEMLC within a 12-month period.

Table 6: Univariate Logistic Regression Analysis for improvement in GMFCS

Factors	OR (95%CI)	P-value
GMFCS at first visit		
I	0	0.988
II	0.955 (0.078 – 11.732)	0.971
III	1.313 (0.166 – 10.350)	0.796
IV	4.900 (0.890 – 26.969)	0.068
V	Reference	0.262
Age at first injection (years)	0.768 (0.623 – 0.945)	0.013*
Injection times	1.905 (1.084 – 3.348)	0.025*
Regular injection	5.000 (1.034 – 24.176)	0.045*

*P-value<0.05

level was seen in the group where the procedure started at a mean age of approximately four and a half years, before the age of 7 years when children with CP usually reach a plateau in their gross motor development [25]. Younger age at initial intervention is a crucial factor for better outcomes, which is consistent with many publications [2,12,13,26]. Treatment between 1 and 5 years of age, during the period of dynamic motor development, has the greatest chance of modifying the course of the disease [27]. On the contrary, surgical interventions to improve gait should be considered in children with CP after their gait maturation occurs, usually between the ages of 8 and 10 years [1]. This may explain the finding that though single-event multilevel surgery improves gait dysfunction [24], it does not usually change the GMFCS level since motor development has reached a plateau in older children [25]. The results of the present study emphasized the importance of early intervention; the older the age at first SEMLC, the less likely it is for GMFCS levels to be improved. Early treatment of spasticity can prevent secondary consequences, such as muscle shortening and joint contractures, and reduce the need for multi-level orthopedic surgery [28].

However, the age at initial intervention is not the only factor for the different functional outcome in the present study. Unlu et al. reported no change in GMFCS after multi-level BTX-A injections in children with CP, although 56% of the subjects received the injections at age 1-4 years [4]. The use of two medications allowed for a greater number of muscles to be treated in a single session (13.67 [SD 5.35]), while in a previous study using BTX-A alone, approximately only 5 muscles were injected [29]. This suggests that treating a greater number of muscle groups or multi-level injections may produce a better outcome [2,29,30]. In this study, although there was no statistical significance of the mean total number of muscles injected between the improved and non-improved groups, the difference between these two groups seemed to be clinically significant: 21 versus 13 muscles. Decreasing the spasticity at multiple levels of a limb(s) may allow children with CP to learn how to use their muscles in a more normal pattern since they do not need to work against too spastic antagonistic muscles. Still, selection of muscles to be injected can be challenging, since spasticity may act as a splint for underlying weak muscles. Considering that muscle strength may be severely compromised in individuals with spastic CP [31], reducing spasticity excessively may cause problems rather than improve function. In support of this idea, it is notable that a diffuse decrease in spasticity has not shown impressive functional outcomes. For example, the effect of intrathecal baclofen (ITB) on diffuse multi-level spasticity has not shown great improvement in ambulatory function, since individuals often need their knee extensor spasticity to bear weight [32]. An advantage of SEMLC over ITB and oral antispastic drugs is that clinicians can treat the specific spastic muscles that cause functional problems.

Another factor associated with the functional improvement is consistent and regular treatments. The present study revealed that children who had more rounds of SEMLCs and who were regularly receiving injections were more likely to show improvement in their GMFCS level. Consistently scheduled SEMLCs may be beneficial for children with CP. This is not only because of the temporary effect of chemoneurolysis but also because of inherent growth of children. The growing bones in children with spastic CP may become distorted due to disparity of growth rate between the bones (faster rate) and the muscles (slower rate) [33]. As a result, secondary impairments such as muscle shortening and joint contractures can cause functional decline, especially during periods of accelerated growth [34]. Periodically repeated SEMLCs are needed to regain or maintain their function. The mean interval between procedures in the study was 5.74 months (SD 2.10) although BTX-A usually lasts only 3 to 4 months [9]. Combination of BTX-A and phenol may prolong the interval between repeated injections, since the effect of phenol lasts longer with an average of 6 months [21]. Still, the time interval between each SEMLC may be different for individuals due to many factors including growth rate and degree of spasticity. Children in the growth spurt period may need more frequent SEMLC in order to equalize the growth between bones and spastic muscles. Children who participate

more in strengthening exercises after chemoneurolysis may need less frequent SEMLC, since strength training has been shown to reduce the degree of spasticity [35]. Therefore, regular follow-up visits are recommended to assess and decide the proper timing of procedure.

Limitations

The limitations of this study are inherent in retrospective studies. Differences in GMFCS outcomes may be due to a methodology flaw by the assessment of outcomes by the treating clinician in a non-blinded fashion [24]. Additionally, GMFCS is the only functional parameter available in the medical records, even though it is not a sensitive tool for detecting small functional improvements after the procedure [36]. Other confounding factors such as frequency of therapy and brain development based on age were not controlled. It has been accepted that after SEMLC, physical and occupational therapies are essential components of the plan of care in order to facilitate elongation of spastic muscles, increase muscle strength, and promote the development of motor skills [1,37]. SEMLC is considered an adjunctive intervention in a comprehensive rehabilitation program for children with spastic CP to improve functional ability [3]. The gross motor function improvement seen in our patients may have been influenced by other unmeasured factors. As the results showed that children who had more rounds of SEMLCs and who were regularly receiving injections were more likely to show improvement in their GMFCS level, this could be a selection bias by excluding patients who received only one round SEMLC and never came back for follow up. A prospective study of SEMLC in children with CP using sensitive measurement tools such as GMFM, gait parameters and a tool used for assessing upper extremity function is encouraged.

Conclusion

SEMLC is a procedure that uses one or more chemoneurolytic agents (BTX-A and 5% phenol) to treat diffuse multi-level spastic muscles. The results highlight the role of SEMLC as a tool in promoting functional improvement in children with CP. This intervention should be considered in children with CP earlier rather than later and regularly scheduled with consideration for development and changing clinical status in order to maximize their potential for functional improvement.

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