Cortical somatosensory evoked potentials and spasticity assessment after Botulinum Toxin Type A injection in children with cerebral palsy

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Abstract

Purpose: The mechanism of Botulinum Toxin Type A (BTX-A) action at the neuromuscular junction is well known. But from the introduction of BTX-A, some authors have suggested a central action of BTX-A and possible side effects far from the site of injection. Some studies demonstrate an improvement of cortical SEPs associated with reduction of spasticity after BTX-A injection. The aim of the present study was to determine the effect of BTX-A treatment on cortical somatosensory potentials (SEP).

Material and methods: A group of twenty nine children ranging from 2 to 17 years old with cerebral palsy were studied. Each patients spasticity level was evaluated before, 2 weeks and 6 weeks after BTX-A injection by the Modified Ashworth Scale and modified Gait Physician's Rating Scale. The SEPs from lower and upper extremities were performed before and between 2 and 6 weeks (19.34±8.82 days) after BTX-A administration.

Results: The mean spasitity level was significantly lower 2 and 6 weeks after BTX-A injection. The gait analysis by modified Physician's Rating Scale (PRS) showed significant improvement two weeks and six weeks after BTX-A injection. SEPs results were abnormal before BTX-A injection in 25 children with cerebral palsy. However we didn't find any significant changes of SEPs latencies after BTX-A injection.

Conclusions: The results of SEP after BTX-A administration in children with cerebral palsy do not confirm the central action of BTX-A on somatosensory pathways. We did not find any significant changes of SEP latencies associated with clinical reduction of spasticity. It seems that SEP results could support the opinion, that BTX-A does not have any direct central effect on sensory pathways. Remote side effects may be explained by an indirect mechanism due to modification of the central loops of reflexes or to hematogenous spread of BTX-A.

Key words: Botulinum Toxin Type A, cerebral palsy, somatosensory evoked potentials, spasticity.

Introduction

Cerebral palsy (CP) is a chronic disorder of movement and posture caused by nonprogressive damage to the developing brain [1]. CP was classified into spastic diplegia, spastic hemiplegia, spastic tetraplegia, extrapyramidal and mixed types [2]. Spastic diplegia is the most common form of CP. The use of Botulinum Toxin Type A (BTX-A) for treating spasticity and in particular the motor problems of children with CP, has attracted much attention in the last years. BTX-A treatment has a sound scientific basis and enough data regarding successful clinical experience [3]. Therefore, it is commonly accepted as a safe and effective treatment of spasticity [4]. Side effects are uncommon, and usually mild and transient. They are restricted to pain at the injection site, local functional weakening of the injected muscle or adjacent muscles [5]. A transient flu-like syndrome lasting a few days has been reported in a number of patients, but the cause for this is not known. There have also been few reports of aspiration pneumonia due to pharyngeal dysfunction, temporary urinary incontinence [6], positive effect on constipation [5] and dysphagia [7]. Two patients with limb spasticity developed features of generalised botulism [8]. The mechanism of BTX-A action at the neuromuscular junction by inhibiting the release of the acetylocholine (Ach) is well known. However, since the introduction of BTX-A, some authors have suggested a central action of BTX-A, probably by reversible transport [9,10]. This action could help to explain some side effects far from the site

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Table 1. **Muscle spasticity assessment by Modified Ashworth Scale after Botulinum Toxin Type A (BTX-A) injection**

	Left lower limb		Right lower limb	
	Mean ±SD	P	Mean ±SD	P
Before BTX-A injection	2.15±0.87		2.36±0.76	
Two weeks after BTX-A	1.80±0.61	<0.001	1.94±0.64	<0.001
Six weeks after BTX-A	1.84±0.46	<0.001	1.95±0.63	<0.001

Table 2. **Gait analysis by Physician's Rating Scale (PRS) after Botulinum Toxin Type A (BTX-A) injection**

	Left lower limb		Right lower limb	
	Mean ±SD	P	Mean ±SD	P
Before BTX-A injection	1.45±0.92		1.25±0.06	
Two weeks after BTX –A	1.71±0.71	<0.001	1.67±0.86	<0.001
Six weeks after BTX-A	1.72±0.75	<0.001	1.61±0.97	<0.001

of injection. These conclusions are mostly based on experimental data. Somatosensory evoked potentials (SEP) are used as a very sensitive diagnostic test to identify dysfunction in sensory pathways. The aim of the present study was to determine the effect of BTX-A treatment on cortical SEP with median and tibial nerve stimulation.

Material and methods

A group of twenty nine children (15 girls and 14 boys) with CP was studied. Patients ranging from 2 to 17 years old (6.26±3.74 years) were assessed. They included 18 patients (62.5%) with spastic diplegia, 8 patients (27.5%) with spastic tetraplegia and 3 (10%) with spastic hemiplegia. Informed consent was obtained following a full explanation of the procedures undertaken. Our general indication for botulinum toxin injection in spasticity treatment was the presence of a dynamic contracture interfering with function, but in the absence of a fixed myostatic contracture [11]. The patient's selection criteria, target muscles, injection sites, dosage and dilution of toxin were based on commonly accepted recomendations [3,11]. The subjects were not previously treated with BTX-A. We injected the lower limb muscles, including the hip flexors and adductors, the hamstring group and the calf muscles (gastrocnemius and soleus). We used DYSPORT (Beaufort Ipsen) in 27 children and BOTOX (Allergan Inc.) in 2 children. The total dose of BTX-A was 20 IU/kg body weight (range 300-1 600 IU per patient) for DYSPORT, and 6 IU/kg body weight (100 IU per patient) for BOTOX. Each patient's spasticity level was evaluated before, 2 weeks and 6 weeks after treatment by the Modified Ashworth Scale [12]. Gait analysis was tested by the modified Physician's Rating scale [5]. The Somatosensory Evoked Potentials (SEP) from lower and upper extremities were performed before BTX-A injection and between 2 and 6 weeks (19.34±8.82 days) after BTX-A administration. All the children were tested in full conciousness without sedation, both for ethical reasons and in light of the known effects of sedatives on cortical SEP components. We used MEDELEC Sapphire Premiere to record SEP. Tests were performed according to standards accepted by most clinical laboratories [13,14]. However, due to apparent difficulties in obtaining reliable SEPs components, we used a modified method. Only cortical responses were recorded. The band-pass 20-100Hz was used. Recordings in response to unilateral median nerve stimulation were obtained from the contralateral cortex (C3' or C4') referred to Fpz [15]. The surface electrode for tibial nerve stimulation was placed on Cz referred to Fpz [16]. It was difficult to achieve stable wave forms in children with CP without sedation. We decided to identify wave components N1, P1, N2, P2. Only the latencies of SEP components were measured. Due to developmental changes of SEP waveforms, this wide age ranged group was divided in three subgroups: A) 1-3 years old, B) 4-8 years old and C) 9-17 years old. Data were compared with STATISTICA 6.0 PL. Wilcoxon signed-rank test was used.

Results

Spasticity level changes evaluated by a Modified Ashford scale are presented in *Tab. 1*. Mean spasticity level was significantly lower two and six weeks after BTX-A injection. The gait analysis by modified Physician's Rating Scale (PRS) showed significant improvement two weeks and six weeks after BTX-A injection. PRS results are presented in *Tab. 2*. The SEPs responses were flat in 2 patients, with no identifiable responses in one children. Therefore, we calculated SEP data for 26 patients. The abnormal latencies were defined as changes above the mean plus 2 standard deviations. In 25 children SEPs results were abnormal before BTX-A administration. The results of cortical SEPs before and after BTX-A injection are presented in *Tab. 3* and *Tab. 4*. We didn't find any significant changes of MedianSEPs and TibialSEPs latencies after BTX-A injections.

Discussion

In pediatric neurology, the use of SEPs to assess somatosensory pathways is of particular relevance, as the clinical examination of the sensory system is often difficult in young

***Table 3*. Tibial Somatosensory Evoked Potentials (SEP) Latency Before and After Botulinum Toxin Type A (BTX-A) injection**

Group of patients	Tibial SEP Latency (ms)	Preinjection	Postinjection	P value
Group A: Age 2-3 years N=16	N1	18.40± 5.58	17.51±4.83	0.63 NS
	P1	22.85±5.44	20.75±4.66	0.17 NS
	N2	27.20±6.33	24.85±4.90	0.39 NS
	P2	32.91±6.06	32.41±4.39	0.97 NS
Group B: Age 4-8 years N=24	N1	19.24±4.96	20.48±6.71	0.16 NS
	P1	24.39±5.79	24.67±6.75	0.65 NS
	N2	28.07±5.69	28.04±6.91	0.69 NS
	P2	34.02±6.72	34.25±7.10	0.81 NS
Group C: Age 9-17 years N=12	N1	22.35±4.61	21.95±5.53	0.58 NS
	P1	27.09±5.02	25.85±6.33	0.28 NS
	N2	32.16±7.52	30.58±8.84	0.44 NS
	P2	37.36±7.97	34.29±8.87	0.11 NS
TOTAL Age 2-17 years N=52	N1	19.77±5.20	19.98±6.05	0.71 NS
	P1	24.62±5.62	23.82±6.31	0.31 NS
	N2	28.84±6.54	27.74±7.13	0.33 NS
	P2	34.53±6.94	33.71±6.81	0.59 NS

P value from Wilcoxon signed-rank test vs preinjection. NS – not significant

***Table 4*. Median Somatosensory Evoked Potentials (SEP) Latency Before and After Botulinum Toxin Type A (BTX-A) injection**

Group of patients	Median SEP Latency (ms)	Preinjection	Postinjection	P value
Group A: Age 2-3 years N=16	N1	13.53±3.37	12.09±4.12	0.75 NS
	P1	18.18±5.08	16.37±5.51	0.07 NS
	N2	25.18±8.12	22.83±6.07	0.60 NS
	P2	30.93±9.22	29.39±7.93	0.86 NS
Group B: Age 4-8 years N=24	N1	15.23±2.47	15.81±2.59	0.08 NS
	P1	19.43±3.56	20.43±3.61	0.25 NS
	N2	27.31±5.03	27.83±5.95	0.96 NS
	P2	33.32±7.05	34.44±7.47	0.42 NS
Group C: Age 9-17 years N=12	N1	15.30±2.79	16.62±0.63	0.39 NS
	P1	19.64±3.22	20.88±1.09	0.57 NS
	N2	27.74±5.35	29.95±1.93	0.27 NS
	P2	33.23±6.58	37.79±2.50	0.18 NS
TOTAL Age 2-17 years N= 52	N1	14.71±2.90	14.96±3.34	0.18 NS
	P1	19.09±3.99	19.40±4.25	0.93 NS
	N2	26.74±6.19	26.94±5.89	0.79 NS
	P2	32.50±7.65	33.83±7.34	0.12 NS

P value from Wilcoxon signed-rank test vs preinjection. NS – not significan

patients. The alterations in wave form occur with growth and development [15,17]. The latencies of each component depend on the maturation of myelination, the length of an axon, the synaptic delay and the distribution of an electric field. Of these factors, the first two may have the greatest influence on the developmental changes of the peak latencies [17]. The sensory pathways were not thought to be involved in children with cerebral palsy. However, some studies in children with the spastic diplegic form of CP have revealed that their somatosensory transmission from the lower extremity was significantly abnormal. A significant difference of N13-N20 conduction time of SEPs was found between the subjects with CP and the control group [18]. SEPs were positively correlated with mental retardation in CP children [19]. Furthermore, prolonged N20 and P25 latencies of SEPs in children with Developmental Coordination Disorder were found [20]. SEP waveforms after selective posterior rhizotomy showed a noteworthy improvement [21,22]. SEP waveforms improved also after taking diazepam as the spasticity decreased [23]. These results have suggested that the lesions of patiensts with CP might be not limited strictly to the motor system. Abnormal cortical SEPs stimulated from involved limbs have also been recorded in other patients with pure motor descending-pathway dysfunction like lateral sclerosis [24,25] and hereditary spastic paraparesis [26,27]. Our observations that abnormal SEPs responses are common in children with spastic forms CP are consistent with previous reports [21,22]. The reasons for these abnormal SEPs are unclear. The results of studies concerning the central action of BTX-A as assessed by evoked potentials are controversial. In the Park et al. study [28], SEPs were recorded before and 7 days after the Botulinum Toxin Type A injection in children with CP. They found that the normal response of cortical SEP increased after

injection. The SEPs exhibited more frequent improvement in the limbs with greater improvement of spasticity in grade and in younger patients. The latency was significantly shortened in the P1, N2 and P2 wave of the affected limbs tibial SEPs, and in the N1 and P1 wave of the affected limbs median SEPs in children with CP. However, latency and amplitude of SEPs from unaffected limbs did not differ significantly after BTX-A injection [28]. They suggested that the improvement of cortical SEPs with associated reduction of spasticity after BTX-A injection indicates that spasticity itself might partly contribute to the abnormal cortical SEP responses. These authors [28] found significant change in SEP latency after botulinum toxin injection. It was reported that the amplitude of cortical SEP was decreased during muscle contraction [29,30], but the change of SEPs latency during normal voluntary muscle contraction was not observed in other reports.

In our study, we didn't find any significant changes of SEPs latencies after BTX-A injections, although the level of spasticity was improved in Modified Ashford Scale and modified Physician's Rating Scale (PRS). We didn't assess the waveform amplitudes. The amplitude of the potential obtained from primary sensory area is very small and variable [17]. Additional problems arise with clinical recording in non co-operative young patients. Therefore, amplitude seems not to be a valuable parameter of SEPs, and normalised data in children were not established [15,17,32]. In adult patients with cervical dystonia, the amplitude of the pre-central P22/N30 component, recorded contralaterally to the direction of head deviation was significantly higher in patients before BTX-A treatment than after injection [33]. These changes of SEP after BTX-A presumably could be the result of higher excitability of the pre-central cortex contralateral to head rotation and its change after successful BTX-A treatment [33]. To find out whether BTX-A alters the excitability of cortical motor areas, Gilio et al. [34] studied intracortical inhibition with transcranial magnetic stimulation in patients with upper limb dystonia. One month following BTX-A injection patients had a test response inhibition similiar to that of normal subjects, whilst 3 months they showed less inhibition than normal subjects. These data suggest that BTX-A can transiently alter the excitability of cortical motor areas by reorganising intracortical circuits though peripheral mechanisms. In another study of the central effects of BTX-A which measured the SEP in 23 adult patients with idiopatic cervical dystonia, the authors did not find any statistically significant differences in latency and interlatency of N9, N13, N20 and P25 of SEP before and after BTX-A administration [35]. Also Brainstem Auditory Evoked Responses (BAER) did not significantly alter after BTX-A treatment in patients with cervical dystonia [35-37]. However, some authors reported a prolonged latency of wave III and shorter III-V interlatency of BAER after BTX-A treatment [38,39]. These controversial results of electrophysiological studies in BTX-A treatment seem to depend on a number of factors including different evoked potentials techniques, attachment of recording electrodes, different parameters assessed, varying periods following BTX-A injection. The studied groups of patients were small. Using transcranial magnetic stimulation over the motor cortex in patients with writer's cramp, reduced M response 2 to 4 weeks after BTX-A was recorded, and no other measures of motor system excitability showed significant changes [40]. The vibration induced facilitation of Motor Evoked Potentials in spasmodic torticollis decreased six weeks following BTX-A application, and demonstrated an increase in the value of amplitude after twelve weeks [41]. These observations suggest the denervation and reinnervation of the muscle spindles after BTX-A injection. BTX-A's effects on motor system excitability seems to be based mainly on its peripheral mechanisms of action [40]. Deafferentation of stimuli from muscle spindles after BTX-A injection could modify the central loops of reflexes and change the excitability of spinal neurons [42]. The haematogenous spread of small portions of BTX-A to distant muscles is also suggested [9,43].

The results of SEP after BTX-A administration in children with CP do not confirm the central action of BTX-A on somatosensory pathways. We did not find any significant changes of SEP latencies associated with clinical reduction of spasticity. It seems that SEP results could support the opinion that BTX-A does not have any direct central effect on sensory pathways. Remote side effects may be explained by an indirect mechanism due to modification the central loops of reflexes, or to haematogenous spread of BTX-A.

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