INTRODUCTION

The botulinum toxins are a family of proteins, produced by Clostridium botulinum, which inhibit the release of acetylcholine in the neuromuscular junction. In 1980, Alan Scott (1) successfully experimented a chemically purified form of one serotype, “Botulinum Toxin A” (BTA), on humans for the recovery of strabismus. Some years later, other researchers reported positive experiences with the use of BTA injections in the treatment of blepharospasm (2,3) and cervical dystonia (4). Nowadays, BTA is well known in clinics as an agent used to weaken spastic muscles in patients with conditions such as stroke, cerebral palsy (CP) and traumatic brain injury (TBI).

Botulinum toxin A (BTA) therapy plays several roles, particularly in the management of paediatric cerebral palsy (CP). However, few studies contain objective documentation of gait changes. The main aim of this study was to provide objective information on the outcome of the treatment. Gait analysis data from 20 normal subjects and 23 CP children were collected before and after BTA injections into the gastrocnemius-soleus complex. The follow up was performed 1 month after the first injection. The kinematic and kinetic data revealed significant improvements in dynamic ankle dorsiflexion, both in stance and in the swing phase, an improvement of equinus foot upon initial contact and better support in stance. The results of this study are promising, but studies of other joints involved in gait, such as the knee, are also needed.

KEY WORDS: Botulinum Toxin A, cerebral palsy, equinus, gait analysis, gastrocnemius.

SHORT-TERM EFFECTS OF “BOTULINUM TOXIN A” AS TREATMENT FOR CHILDREN WITH CEREBRAL PALSY: KINEMATIC AND KINETIC ASPECTS AT THE ANKLE JOINT

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INTRODUCTION

The botulinum toxins are a family of proteins, produced by Clostridium botulinum, which inhibit the release of acetylcholine in the neuromuscular junction. In 1980, Alan Scott (1) successfully experimented a chemically purified form of one serotype, “Botulinum Toxin A” (BTA), on humans for the recovery of strabismus. Some years later, other researchers reported positive experiences with the use of BTA injections in the treatment of blepharospasm (2,3) and cervical dystonia (4). Nowadays, BTA is well known in clinics as an agent used to weaken spastic muscles in patients with conditions such as stroke, cerebral palsy (CP) and traumatic brain injury (TBI).

Botulinum toxin A (BTA) therapy plays several roles, particularly in the management of paediatric cerebral palsy (CP). Primarily, BTA therapy is effective as a diagnostic agent, used to determine whether weakening a spastic muscle will be beneficial. Moreover, it is also a good analgesic agent, for example in cases associated with adductor release surgery, which creates severe post-operative pain and spasms. Finally, BTA therapy plays an essential role in the management of dystonia, in situations where muscle

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lengthening is required but any surgical intervention would be unpredictable or excessive, and in the conservative management of both dynamic equinus secondary to calf spasticity and crouch gait caused by hamstring spasticity.

The satisfactory results obtained by the use of BTA in the lower limb muscles of patients with CP have supported the concept that an improvement in muscle balance can be produced by BTA injections into dominant spastic muscles (5-7). Objective documentation of paediatric gait changes after BTA injection (5,8,9) is, however, too scarce and incomplete to clarify in detail the effects induced by BTA therapy and to prove its real efficacy. A biomechanical approach to analysis of the movement changes provoked by BTA injections may constitute the necessary objective means of quantifying the role of BTA therapy in relation to other conservative measures. We set out to provide objective and quantitative information on the outcomes of BTA treatment by analysing the results of clinical examination as well as ankle joint kinematics and kinetics measured, during level walking, before and after BTA injections into the gastrocnemius/soleus muscle complex.

MATERIALS AND METHODS

Subjects, procedure and equipment

We studied a group of children with dynamic calf contracture, selected for BTA treatment and able to walk independently. The group comprised children with diplegia (6 females and 4 males, mean age 6 years and 3 months, age range from 4 to 9 years), or hemiplegia (7 females and 6 males, mean age 9 years and 6 months, age range from 4 to 15 years). Four criteria were followed for subject selection: diagnosis of CP, problems with “equinus foot” due to increased spasticity in the calf muscles, absence of retraction and no previous orthopaedic surgery at lower limb level. Twenty normal children (10 females and 10 males, mean age 10 years and 6 months, age range from 6 to 14 years) served as the control group.

All the subjects were volunteers and their parents gave their informed consent to the children’s participation in the study. This study was approved by the ethics committee of the IRCCS C. Mondino Institute of Neurology, Pavia, Italy.

A clinical team made up of a paediatric orthopaedic surgeon, a paediatric neurologist and a physical therapist examined each child. All the subjects underwent an initial interdisciplinary clinical-functional assessment; the patients were also re-examined one month after the BTA injections. The interdisciplinary clinical-functional assessment included:

– neurological examination;
– static range of motion (ROM) at the hip, knee and ankle joint;
– dynamic muscle length (10);
– spasticity assessment (Ashworth’s modified scale);
– selective motor control test (10);
– gross motor function measure (GMFM);
– observational gait analysis (video recording);
– 3-dimensional gait analysis (3DGA).

In fact, the effects induced by the BTA therapy were systematically monitored up to the sixth month after the injections. However, although our long-term assessment of these subjects is still in progress, it does not fall within the scope of this initial paper on BTA therapy, which instead focuses on the short-term effects.

The experimental data collected using a motion measurement system (ELITE System, BTS S.p.A., Milan, Italy) and a force plate (AMTI, MA) were submitted to 3DGA. The motion analyser, allowing the reconstruction of the 3D trajectories of passive markers suitably placed on the subject, was equipped with six cameras working at a sampling rate of 50 Hz. The cameras were located along the two sides of a 10 metre-long straight walkway where walking variables are measured. The markers were placed over the right and left shoulders, the spinous process of C7, the right and left anterior superior iliac spines, and the
sacrum (midway between the posterior superior iliac spines); furthermore, for each lower limb a marker was placed over the lateral aspect of the great trochanter, on a rod positioned midway along the lateral aspect of the thigh, over the lateral femoral epicondyle, over the lateral aspect of the head of the fibula, on a rod positioned midway along the lateral aspect of the shank, over the lateral malleolus and over the fifth metatarsal head. The force platform, incorporating strain gauges to transduce the ground reaction force arising during the stance-phase of a stride, was placed around five metres along the walkway.

The subjects were asked to walk barefoot at natural speed along the walkway, starting from a point that allowed them to place one foot on the force plate without any modification of cadence or stride length. After a training period intended to make the subject feel comfortable with the procedure, seven trials for each foot were recorded from each subject. Kinematic and kinetic data reduction was based on Euler angles and Euler’s equations of motion, respectively (11).

Following the basal motion acquisitions, BTA injections into the gastrocnemius/soleus complex of the patients were performed. Two sites of injection (medial and lateral gastrocnemius muscle) were used with an initial dose of 2-6 U/kg body weight per muscle (10) (BOTOX®, Allergan Inc.).

As indicated above, the effects of the BTA injections were then monitored, from both the clinical and the biomechanical point of view and using the same protocols, for several months. However, this paper, whose aim is to detail the initial reaction of the patient to BTA (a factor governing the possible acceptance of the child as a candidate for BTA therapy) deals only with the short-term aspects of the analysis, i.e., it is restricted to the follow up one month after injections.

Statistical analysis

The 3DGA measures of the young patients were compared with those of the age-related normal subjects; the follow-up data were also compared with the basal values. Student’s t-test (p≤0.05 and p≤0.0001 for paired data) and the Wilcoxon test (p≤0.001 for paired data) were used for comparison.

Kinematics. The ankle angle upon initial contact (AAIC), the dorsiflexion peak during the stance phase (DFSt) and the plantarflexion peak during the swing phase (PFSw) (see the example in Fig. 1) were evaluated before and after the BTA treatment.

![Fig. 1 - Plot of the ankle joint angle vs gait cycle (%) for a normal subject. Arrows show kinematic parameters the ankle joint that were evaluated for each subject.](image)

Kinetics. The kinetics of the ankle joint was assessed by means of the parameters described below.

In CP children, the ankle joint moment was always characterised by a “double bump” pattern; this feature may be attributed to triceps surae spasticity/clonus (12) that gives rise to two peaks, solely of plantarflexion (P1 and P2 in Fig. 2). The ankle joint moment of a normal child (Fig. 2, see over) is also characterised by two peaks, but the well known dorsiflexion peak (P1) occurs in the first half of the stance-phase.

To summarise the relation between the peaks of the ankle joint moment, the “double bump” ankle moment pattern was characterised...
by the straight line (mp₁) to peak plantarflexion in the first half of the stance and the straight line (mp₂) to peak plantarflexion in the second half of stance as shown in Fig. 2. The angle between mp₁ and x axis (α₁) and the angle between mp₂ and x axis (α₂) were used to define an index (M) representing the morphology of the ankle joint moment [1].

\[
M = \frac{Tg(\alpha_1)}{Tg(\alpha_2)} \tag{1}
\]

When M<0, the pattern of the ankle moment is normal (in fact α₁<0). When M>0, the pattern of ankle joint moment is abnormal or pathological (“double bump pattern”). Another index representing the area beneath the ankle joint moment (M_{area}) was computed from the integral of the moment curve. In particular, high M_{area} values may be related to a “double bump pattern”.

The instantaneous dorsi/plantarflexion power at ankle joint (P_{ank}) was computed as:

\[
P_{ank} = M_{ank} \omega_{ank} \tag{2}
\]

in which \(M_{ank}\) is the ankle dorsi/plantarflexion moment normalised to body weight (Nm/kg) and \(\omega_{ank}\) is the ankle joint angular velocity (rad/sec).

Figure 3 shows power absorption and generation at the ankle joint in a healthy subject during the taking of a step and reveals absorption (negative power in the central part of the stance phase) and generation (positive power) in the phase immediately preceding the leg swing (pre-swing).

The filled-in areas inside these curves represent, respectively, the work absorbed (W_{abs}, grey area in Fig. 3) during the stance phase, and the work generated (W_{gen}, black area in Fig. 3) in the pre-swing phase - i.e., the subject’s push-off capacity (for moving the leg forward in the swing phase). The W_{abs} and W_{gen} values were calculated according to the formulae given below [3] and these variables were used to describe the various subjects investigated.

\[
W_{abs} = \int_{T_0}^{T_1} P_{ank} dt \quad W_{gen} = \int_{T_1}^{T_2} P_{ank} dt \tag{3}
\]

RESULTS

The patients, their relatives and the physiotherapists involved in this study all expressed satisfaction with the treatment, which was found to be well tolerated by the patients.

As regards the clinical results, only the ROM of the ankle joint and the assessment of spasticity at ankle joint level using the Ashworth scale are presented in this paper.

Table 1 gives the results of the ROM of the ankle joint evaluated with knee extended and knee flexed, pre and post treatment.

Table 2 summarises the results of assessment of spasticity at the ankle joint using the Ashworth scale (score 0-4). The results of the clinical examination showed important improvements following the BTA treatment, while those of the gait analysis showed significant improvements in ankle joint kinematics following botulinum toxin treatment. It is possible to observe (Fig. 4) that before BTA injec-
tion the ankle joint pattern is mainly plantar and the foot position upon the contact with the floor is in “equinus”.

After BTA injection, the behaviour of ankle joint is more normal. These observations are reinforced by analysis of the kinematic and kinetic parameters previously defined.

Table 3 summarises the results relating to the ankle plantar-dorsiflexion indices.

The increase in the AAIC (first column) points to an improvement in equinus foot upon initial contact with the ground (p<0.05).

In addition to this, the post BTA treatment

| Table 1 - Ankle ROM of the treated limbs (one in hemiplegic, both in diplegic subjects). |
|-----------------------------------------------|---------------|----------------|
| Ankle ROM                                      | Ankle ROM     |
| knee extended                                 | knee flexed   |
| (degrees)                                     | (degrees)     |
| mean ± s.d.                                   | mean ± s.d.   |
| Pre injection                                 | 102.66 ± 12.65| 87.50 ± 7.00   |
| Post injection                                | 86.33 ± 5.49  | 81.01 ± 5.94   |
| Mean difference                               | 16.33 ± 10.08 | 6.42 ± 3.63    |
| T-test for paired data                        | p<0.0001      |

| Table 2 - Assessment of spasticity at ankle joint level (one in hemiplegic, both in diplegic subjects) using the Ashworth Scale (scores 0 to 4). |
|-----------------------------------------------|---------------|---------------|
| No. of subjects                              | Pre injection | Post injection|
| 10                                            | 2             | 1             |
| 13                                            | 3             | 2             |
| Wilcoxon test for paired data                 | p<0.001       |

| Table 3 - Ankle plantar-dorsiflexion indices of the treated limbs (one in hemiplegic, both in diplegic subjects). |
|-----------------------------------------------|---------------|---------------|
| AAIC [degrees]                                | DF Peak in    | PF Peak in    |
| mean ± s.d.                                   | stance [degrees] | swing [degrees] |
| Normal subjects                               | -1.3 ± 2.1    | -9.6 ± 3.9    |
| Pre Injection                                 | -14.2 ± 6.9   | -14.2 ± 9.7   |
| Post Injection                                | -6.6 ± 4.4*   | -12.9 ± 7.9   |
| Abbreviations: AAIC = ankle angle upon initial contact; DF = dorsiflexion; PF = plantarflexion. |
| * p<0.05                                      |               |               |
dorsiflexion peak values demonstrate a significant dorsiflexion (p<0.05) not present prior to injection. The plantarflexion peak in swing demonstrated non significant (p>0.05) increases.

Table 4 summarises the results relating to the kinetic parameters.

The results of the M index, which is related to the shape of the ankle joint moment, show that the double bump moment is evident before the injection, in fact high M values underline the presence of the first peak (P1) in the ankle joint moment pattern.

After the treatment, M decreases significantly (p<0.05); in other words there is a decrease in the first peak (P1) and consequently an attenuation of the “double bump” morphology of the pattern.

The same observations are evident for the M_area index. After injection, the M_area decreases to near normal values.

No significant differences (p>0.05) are observed in the indices related to the subject’s capability of absorbing bodyweight during walking (W_abs) and push-off ability (W_gen).

DISCUSSION

In accordance with other reports (5), we found no side effects or complications, either local or generalised, following BTA injection. The dosage employed in our study was 2-6 U/kg body weight per muscle (10) (Botox®, Allergan Inc.).

Clinical evaluation demonstrated significant (p<0.0001) improvements in the ROM of the ankle joint, a finding that is again in accordance with other studies (7). The Ashworth scale results demonstrated a 1-point improvement (p<0.001), i.e., a significant reduction of spasticity.

Furthermore, BTA injections into the gastrocnemius muscle produced significant improvements in function as shown by objective gait outcome measures. The kinematic gait measurements found to be the most representative of the improvement in walking are sagittal plane AAIC and maximum dorsiflexion in the stance phase, while the observed increases in maximum plantarflexion in the swing phase are not significant.

These improvements are observed after the BTA treatment and may be related to the weakening of the spastic muscle as well as the muscle lengthening produced by BTA treatment.

With reference to the kinetic data, the parameters relating to the shape of the ankle joint moment showed that the kinetics of the ankle before treatment was characterised by a “double bump” ankle moment; this typical pattern is lost after the treatment.

Previous interpretations of the “double bump” ankle moment are related to the stretch reflex in stance or in the clonus that occurs in CP children (1). The change in the morphology of this pattern after the treatment may be related to better support following lengthening of the gastrocnemius.

No significant changes were observed as re-

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<tbody>
<tr>
<td>Normal subjects</td>
<td>-1.41 ± 0.9</td>
<td>38.4 ± 5.5</td>
<td>3.7 ± 0.5</td>
<td>24.5 ± 3.2</td>
</tr>
<tr>
<td>Pre Injection</td>
<td>2.42 ± 0.86</td>
<td>62.0 ± 15.19</td>
<td>5.5 ± 2.9</td>
<td>11.15 ± 4.5</td>
</tr>
<tr>
<td>Post Injection</td>
<td>0.36 ± 1.44*</td>
<td>49.2 ± 14.1*</td>
<td>4.9 ± 1.9</td>
<td>13.99 ± 3.9</td>
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Abbreviations: M = index representing the morphology of the ankle joint moment; M_area = index representing the area beneath the ankle joint moment; W_abs = work absorbed; W_gen = work generated. * <0.05
gards walking efficiency. In fact, neither the work expended in the absorption of bodyweight phase ($W_{ab}$) nor that expended in order to lift the foot from the floor and swing it forward ($W_{gen}$) showed significant improvements ($p>0.05$). It is possible that higher doses of BTA are needed to improve walking efficiency.

Our kinematic and kinetic indices are thus seen to be important in establishing an objective measure for evaluating the effects of botulinum toxin A treatment in the gastrocnemius muscle.

Future research is needed, focusing on i) follow up beyond the 1st month; ii) the time span required for successful treatment; iii) the optimal dose; iv) other joints affected by gastrocnemius spasticity, such as the knee joint.

In short, a whole rehabilitative programme needs to be planned that incorporates treatment with BTA.

On the basis of the preliminary results of this study, we can conclude that the injection of BTA may be considered useful in the treatment of children with CP, as it: increases the ROM of the joints, reduces spasticity, improves the muscular stretching response, improves the patient’s tolerance of castings, improves walking and delays the need for surgical intervention.

REFERENCES