A Clinical Study of the Therapeutic Effects of Electromyography-Free Injection of Botulinum Toxin A in the Treatment of Children with Spastic Cerebral Palsy

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Abstract

Objective: To evaluate the therapeutic effect of electromyography-free injections of botulinum toxin A in the treatment of children with spastic cerebral palsy.

Methods: Sixty-eight children with cerebral palsy that had lower limb spasticity, were injected with botulinum toxin A at several muscular sites without the use of electromyography. The injection sites were located by Reverse Stretching and Palpation. After injection, the children underwent stretching of the spastic muscle involved and started functional training the next day. They were supported by an AFO or a KAFO for one week and commenced enhanced functional training until 3 months after the injection. The following parameters were assessed: the parental report of the injections effect, the adductor angle, the degree of the hip flexor angle, the popliteal angle and the angle of ankle dorsi-flexion. In addition two instruments were used to assess effect: a Modified Ashworth Scale (MAS) and the Gross Movement Functional Measure (GMFM-66). All this data was recorded at the following time intervals after injection: 3 days, 1 week, 2 weeks, 1 month, 2 months and 3 months.

Results: (1) The parents reported that Botulinum toxin A came into effect at 6-72 hours after injection, peaked 1-2 weeks later and that the effect persisted for more than 3 months. For a few children, the effects only lasted 1-2 months post-injection. The main side effects such as loss of appetite and weakness, were observed in children with serious spasm that required injections with large doses of Botulinum Toxin A. These side effects were not present after 3 weeks to 1 month post-injection. (2) The adductor angle, the hip flexor angle, the popliteal angle and the angle of ankle dorsi-flexion significantly improved 3 days after injection ($P<0.05$) and peaked at 1 month ($P<0.001$). The effect decreased 2-3 months after injection, but the children were still significantly improved compared with the parameters measured pre-injection ($P<0.05$). (3) The changes seen on the Modified Ashworth Scale (MAS) of the spastic muscle were consistent with the improvement seen with the other measures of ROM. (4) The GMFM-66 increased significantly 1 month post-injection ($P<0.05$) and this change was observed to persist. (5) The dosage was significantly correlated with the onset of side effects.

Conclusion: Botulinum toxin A in conjunction with orthotics and rehabilitation training effectively improved the movement functions of children with spastic cerebral palsy. The electromyography-free location and injection technique saves money, is convenient and is effective. The side-effects onset is correlated with the use of higher dosages.
Key words: Cerebral Palsy; spasticity; Botulinum toxin A; treatment

In 1980s, Scott[1] firstly used Botulinum toxin type A, LANTOX in treatment of strabismus. It is now widely used in treatment of blepharospasm[2], hemifacial spasm[3], cervical dystonia[4], and limb dystonia diseases[5]. In 1992, Cosgrove[6] used Botulinum toxin type A in clinical treatment of children with spastic cerebral palsy. In 1993, Koman[7] reported the success in use of Botulinum toxin type A in the therapy of dynamic equinovarus and pes pronatus in cerebral palsy. Further researches proved that using Botulinum toxin type A in the treatment of children with spastic cerebral palsy was effective, safe and harmless[8]. In 1997, Professor Liang Huiying in the Department of Rehabilitation, the Second Affiliated Hospital, Hebei Medical College firstly used LANTOX in the treatment of children with spastic cerebral palsy. With the help of rehabilitation training, an effective result was shown[9]. Previously, the injection technique was undergone mostly with the aid of electromyography or electric stimulus[10,11]. In order to locate precisely, we started to treat children with spastic cerebral palsy in the method of electromyography-free injections of botulinum toxin A in conjunction with orthotics and rehabilitation training. The result was shown as follows.

Information and method

1.1 Clinical information

From 1999 to May 2005, sixty-eight children with cerebral palsy in our department that had lower limb spasticity were injected with botulinum toxin A at several muscular sites without the use of electromyography. 28 patients underwent repeated therapy at 2-5 times. The treatments were 134 times in total. Excluding the patients who had monoplegia or limb spasticity, could not be reached and persist the rehabilitation therapy, there were totally 68 times of treatments for children with cerebral palsy that had lower limb spasticity with completed information. Modified Ashworth Scale (MAS) of the spastic muscle $\geqq$ Level II. Spasticity affected the balance of sitting and standing, walking and daily movement. 43 patients were male and 25 patients were female. The mean age was 47.18 ± 21.60 (15-108 months). Here came the exclusion standards. 1) Allergy or history of asthma. 2) Severe liver and kidney functional disorder. 3) Infections at injection sites and other sites on the body.

4) Use of medicine which enhanced the obstruction of transmission of nerve signal within one week, such as quinine, aminoglycoside antibiotic and morphine. 5) Injecting patients with severe muscle contraction. 6) Patients who took anti-spasm medicine or was injected phenol and alcohol within 3 months. 7) Failure in coordinating the therapy.

1.2 Method

1.2.1 **Signing an agreement** In depth inquiry of patients' allergy history before injection. Illustration of injection purpose and side effects. Obtaining patients' and relatives' approval and an agreement was signed.

1.2.2 **Confirmation of dosage** It was confirmed by the size of muscles and the extent of spasm. The mean dosage was 17.73 ± 6.08 U/kg. The maximum dosage was 30 U/kg. The time interval was 2 days (consecutively). The mean overall dosage was 239.56 ± 94.27 (80-520U).

1.2.3 **Method of dilution** LANTOX manufactured by the Lanzhou Institute of Biological Products was used. The dosage was 100-110U per ampere. The concentration was 50-55u/ml. It was dissolved and diluted with 2ml of 0.9% normal saline water. Each point was 10u/0.2ml.

1.2.4 **Location and injection** In the aid of electromyography-free injection, the injection sites were located by Reverse Stretching and Palpation. Suitable postures were taken to facilitate the reverse stretching of the target muscle. The target muscle was reversely stretched along the axial direction to trigger clonus, spasm or hypermyotonia. The spastic muscles were palpated by the therapist. The injection sites were located on the muscle with severe spasm at the site-site distance interval at 1-3cm^2. Multi-location injections were done by Reverse Stretching and Palpation. Cleaning and massage was avoided within 6 hours after injection.

1.2.5 **Rehabilitation training and use of orthotics** The rehabilitation training was strengthened from the 2nd day onwards. Training was focused on the stretching of adductor, hamstring muscle and triceps muscle of calf and the strength of antagonistic muscle. Functional trainings like balance, standing and walking should not be neglected. Training of walking was assisted with an AFO or a KAFO after one week. The rehabilitation training and use of orthotics should be persisted till 3 months after injection.

1.3. Therapeutic index

1.3.1 Therapeutic effectiveness and side effects were reported by parents before injection and at 3 days, 1 week, 2 weeks, 1 month, 2 months and 3 months after injection. The adductor angle, the hip flexor angle, the popliteal angle, the angle of

ankle dorsi-flexion, a Modified Ashworth Scale (MAS) and the Gross Movement Functional Functional Measure (GMFM-66) were assessed.

1.4 Statistical analysis Software SPSS14.0 was used for analysis of variance (ANOVA).

Results

2.1 **Parents' reports** Botulinum toxin A came into effect at 6-72 hours after injection and peaked 1-2 weeks later and the effect persisted for 4-10 months. For a few children, the effects only lasted 1-2 months post-injection. The recession of the effect was more significant among younger children. 90% of patients persisted the use of orthotics every day. 10% of children used orthotics discontinuously due to different reasons.

2.2 **Variation in joint motion** The adductor angle, the hip flexor angle the popliteal angle and the angle of ankle dorsi-flexion significantly improved 3 days after injection ($P<0.05$) and peaked at 1 month ($P<0.001$). The effect decreased 2-3 months after injection but the children still improved significantly compared with the parameters measured pre-injection ($P<0.05$). See Table 1.

2.3 **Modified Ashworth Scale (MAS)**

The MAS of the adductor, hamstring muscle and triceps muscle of calf decreased significantly 3 days after injection ($P<0.05$) and peaked at 1 month. The effect lasted till 2-3 months and then increased while still below the level measured pre-injection. It still showed a significant difference between 3 months before injection and after injection ($P<0.05$). See Table 1.

2.4 **Variation of GMFM-66**

The GMFM-66 increased significantly 1 month post-injection ($P<0.05$) and this change was observed to persist. See Table 1.

2.5 **Side effects and undesirable effects** The dosage was significantly correlated with the onset of side effects. Among the 10 patients with higher dosages, drowsiness, loss of appetite and weakness were found 24 hours after injection. All side effects disappeared after 1-2 weeks to 1 month. No significant undesirable effects were shown.

Table 1 Comparison of variation in measurements between pre-injection and post-injection $\underline{x} \pm s$

Data	Frequency	Before	After treatment

		injection	3 days	1 weeks	1 month	2 months	3 months
Adductor angle	68	56.98 ± 15.33	64.33 ± 14.80*	75.66 ± 14.86*	82.79 ± 13.25**	79.70 ± 13.18*	73.23 ± 14.34*
Hip flexor angle	68	60.07 ± 17.60	68.01 ± 16.41*	78.16 ± 13.40*	88.53 ± 8.81**	85.74 ± 8.20*	80.37 ± 8.11*
Popliteal angle	68	98.43 ± 12.76	104.85± 11.93*	113.68± 13*	122.35± 10.27**	118.46 ± 10.62*	112.43 ± 10.12*
Angle of ankle dorsi-flexion	68	-20 ± 12.98	-12.06 ± 9.55*	-2.57 ± 8.91*	5.81 ± 7.56**	3.68 ± 8.08*	-1.47 ± 8.59*
MAS	68	4.38 ± 0.59	3.59 ± 0.57*	2.62 ± 0.59*	1.79 ± 0.58**	2.24 ± 0.67*	2.81 ± 0.69*
GMFM-66	68	49.79 ± 7.42			56.47 ± 7.57*	62.92 ± 7.05*	69.21 ± 7.00*

Test level a=0.05, *P<0.05, **P<0.001

Discussion

Spasticity is the main reason of motion disorder of spastic cerebral palsy. The common methods for treatment of spastic cerebral palsy include 1) oral medicine, 2) injection of phenol or absolute alcohol at the site of muscle or nerve stem, 3) intrathecal injection of chlorobenzene butanoic acid, 4) physiotherapy and 5) extension of tendon and selective incision of posterior spinal cord. Oral medicine is effective in muscle relaxation. However, it causes side effects such as drowsiness, muscle weakness. Physiotherapy is less effective but the effect can last longer. Both method 3) and 5) are destructive therapies and are mostly used in older children. Bontulinum toxin is a higher poisonous exotoxin produced during the cultivation of Clostridium botulinum. It is usually in a complex form of neurotoxin and hemagglutinin. Botulinum toxin is a potent muscle relaxant which blocks release of acetylcholine at neuromuscular junction. It is widely used in treatment of dystonia diseases[13]. A lot of studies showed the safety and efficiency of the use of botulinum toxin type A in the treatment of children with spastic cerebral palsy [8, 9, 12].

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The key to the treatment is the precise location of target muscle. Previous studies focused mainly on electromyography and electrical stimulation injections[10, 11]. These injections were thought to be more long-lasting than free hand injection. Some studies found that there was no significant effect difference between the localization injection of Botulinum toxin type A in the aid of electromyography and non-localization injection[8]. Some authors suggested that different treatments should be used on different sites of muscles. Free-hand injection could be applied on triceps muscle of

calf. The above two methods could be used in the other groups of muscles[10]. Since the above two injection methods require specific equipment and injection syringes and recurring syringes increase patients' expenses, they are not commonly used in China market.

The multi-focal injection by Reverse Stretching and Palpation was imitated initiated by our department for the treatment of children with spastic cerebral palsy. It showed a significant effect. Both parents' report and the measurements showed that there was significant change 3 days to 1 week after injection. The measurements peaked after 1 month and increased after 2-3 months except GMFM-66. The values did not reach to the pre-injection level. It was important that the measurement of GMFM-66 which was functionally correlated improved gradually. The overall dosage in two days was less than or equal to 24U/kg. No side effects were shown when the daily dosage was less than 12U/kg. 10 children had side effects such as drowsiness, loss of appetite and weakness. All side effects disappeared after 1-2 weeks to 1 month. It was more likely to have side effects when the overall dosage in 2 days was close to 24U/kg. Mulit-focal injection helped to eliminate the side effects and diffusion to non-target muscles caused by high dose injection. No children showed significant undesirable responses. Electromyography-free injection eliminated the pain caused by EMG and uncoordinated localization errors. Due to satisfactory effects and mild side effects, dependence on the therapy of this group of patients was better. The dependence on the daily use of orthotics reached 90%. 28 patients persisted the therapy for 2-5 times. It should be noted that without the conjunction with orthotics and rehabilitation training, LANTOX could not enhance its therapeutic effectiveness. Since the therapy was reversible, repeated injection was required every 3-6 months. This increased patients' financial burden and decreased patients' dependence on the repeated therapy.

Conclusion

Botulinum toxin A in conjunction with orthotics and rehabilitation training effectively improved the movement functions of children with spastic cerebral palsy. The electromyography-free location and injection technique saves money, is convenient and effective. The side-effect onset is correlated with the use of higher dosages.

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