



Original Article

Focal treatment of spasticity using botulinum toxin A in cerebral palsy cases of GMFCS level V: evaluation of adverse effects^{☆,☆☆}

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ABSTRACT

Objective: To report on the experience of injections of botulinum toxin A (BTA) in a series of patients with cerebral palsy of Gross Motor Function Classification System (GMFCS) level V. **Methods:** This was a retrospective case series study on 33 patients with cerebral palsy of GMFCS level V who received 89 sessions of BTA application (of which 84 were Botox[®] and five were other presentations), in which the basic aim was to look for adverse effects.

Results: The mean number of application sessions per patient was three, and the mean age at the time of each injection was 4 + 6 years (range: 1.6–13 years). The muscles that most frequently received injections were the gastrocnemius, hamstrings, hip adductors, biceps brachii and finger flexors. The mean total dose was 193 U and the mean dose per weight was 12.5 U/kg. Only one patient received anesthesia for the injections and no sedation was used in any case. No local or systemic adverse effects were observed within the minimum follow-up of one month.

Conclusion: The absence of adverse effects in our series was probably related to the use of low doses and absence of sedation or anesthesia. According to our data, BTA can be safely used for patients with cerebral palsy of GMFCS level V, using low doses and preferably without sedation or anesthesia.

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Tratamento focal da espasticidade com toxina botulínica A na paralisia cerebral GMFCS nível V – Avaliação de efeitos adversos

RESUMO

Objetivo: relatar a experiência da aplicação de toxina botulínica A (TBA) em uma série de pacientes com paralisia cerebral (PC) GMFCS nível V.

Métodos: estudo retrospectivo de série de casos, 33 pacientes com PC GMFCS nível V que receberam 89 sessões para aplicação de TBA (84 Botox[®] e cinco outras apresentações), em busca basicamente de efeitos adversos.

Palavras-chave:

Paralisia cerebral

Espasticidade muscular

Toxinas botulínicas

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Resultados: o número médio de sessões para aplicação por paciente foi três e a idade média em cada injeção foi 4+6 anos (1,6-13 anos). Os músculos mais frequentemente injetados foram gastrocnêmios, isquiotibiais, adutores do quadril, bíceps braquial e flexores dos dedos. A dose média total foi 193 U e a dose média por peso foi 12,5 U/kg. Somente um paciente recebeu anestesia para as injeções e sedação não foi usada em qualquer caso. Não foram observados efeitos adversos locais ou sistêmicos dentro de seguimento mínimo de um mês. **Conclusão:** a ausência de efeitos adversos em nossa série está provavelmente relacionada ao uso de doses baixas e ao não emprego de sedação ou anestesia. De acordo com nossos dados, a TBA pode ser usada de forma segura em pacientes com PC GMFCS nível V, em doses baixas e preferencialmente sem sedação ou anestesia.

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Introduction

Botulinum toxin type A (BTA) has been used for more than two decades for treating spasticity in cerebral palsy cases, especially in the age group from two to eight years and in cases of focal dynamic deformities, with the main aim of postponing surgical procedures through controlling the deformity. Many studies have shown that if the total dose, dose per unit weight and application technique are respected, BTA is safe to use and adverse effects are practically absent.¹

However, some rare cases of serious adverse effects have been reported over the last few years, relating to patients with Gross Motor Function Classification System (GMFCS) level V. These are patients with severe impairment who cannot walk, present little or no control over their head position and often have respiratory dysfunctions of various degrees. The reports have concluded that there is a relationship with the preexisting respiratory dysfunctions, such as pseudobulbar palsy, which suggests that other types of therapy should be used for treating these patients.²⁻⁶ Despite the generalized pattern of spasticity, BTA may be indicated for patients with GMFCS level V in an attempt to improve posture and positioning, alleviate discomfort and facilitate care and orthosis use.⁶

In our experience, BTA has been shown to be completely safe, independent of the GMFCS level. The aim of this study was to report on our experience of applying BTA to a series of patients with cerebral palsy of GMFCS level V.

Materials and methods

Between 2000 and 2010, 188 patients with cerebral palsy underwent 412 sessions of BTA application, performed by the first author. Of these, 33 patients were at GMFCS level V. They received BTA in 89 sessions and were the target of the analysis in this study. A free and informed consent statement was obtained from all the patients, for application of the medication and for use of the data relating to the treatment, while maintaining confidentiality of identity. The study was approved by the Circle Research Ethics Committee (Serra Gaúcha Foundation).

Results

Among the patients, 25 were male and eight were female. Their mean age at the time of the applications was four years and six months (minimum age of one year and six months and maximum of 13 years). Around 50% of the patients presented a clinical report of difficulties in swallowing and three were using gastrostomy as the sole means of feeding. Several patients had histories of pulmonary complications and 12 had already needed hospital treatment. At the time of the injections, all the patients were in a good state of health, without using antibiotics. The application sessions took place without sedation or anesthesia, except in one case in which anesthesia was administered by means of a mask.

The patients came for the sessions after orthopedic assessment, in which planning for which muscles the BTA would be applied to was conducted, along with calculation of the total dosage and the dosage per application point. The total dose and dose per unit weight, the muscles injected and the dose per application point were recorded. The results and any occurrences of adverse effects were noted during the follow-up.

Botox[®] was the presentation of BTA used in 84 injections, and other presentations were used in five cases: two applications of Dysport[®] and three of Prosigne[®]. The mean total dose of Botox[®] was 193 U, ranging from 100 to 300 U. The total dose of Dysport[®] was 500 U in the two applications, with a mean dose of 45 U/kg in one application and 50 U/kg in the other. The total dose of Prosigne[®] was 200 U in the three applications and the doses per unit weight were 14, 12.5 and 16 U/kg. In 62 injections, the mean dose was 12.5 U/kg for the Botox[®] presentation, with a range from 6 to 22 U/kg; in 27 injections, the dose per unit weight was not identified in reviewing the medical file.

The mean number of sessions per patient was 2.7; 13 (40%) had only one session and eight (24%) had two. Two patients (6%) had nine sessions. The minimum interval between the applications was six months.

The muscles most frequently injected were the gastrocnemius (61 injections), hamstrings (54), hip adductors (30), biceps brachii (28) and long flexors of the fingers (26). The other muscles injected were the wrist flexors, thumb adductor and pronator teres. The mean number of muscle groups injected per session was three. Three muscle groups were injected in 31 sessions, two muscle groups in 23 and one

muscle group in 11. In almost all the sessions, the application was bilateral.

Discussion

BTA makes an unquestionable contribution toward management of spasticity. The great majority of studies in the literature have demonstrated low rates of complications and adverse effects. A review in 2009 on studies conducted between 1990 and 2008 (20 studies in the meta-analysis, with 882 participants) showed that there were only 35 adverse events, which were all mild, including respiratory infections, bronchitis, pharyngitis, asthma, muscle weakness, urinary incontinence, falls, convulsions and nonspecific pain. It concluded that BTA was safe to use in cerebral palsy cases.¹ Côté et al.⁷ reviewed the report system of the Food and Drug Administration (FDA), in the United States, covering the years 1989–2003, searching for adverse effects from BTA (Botox[®]) for esthetic or cosmetic use. They identified 1437 reports of adverse effects: 1031 from cosmetic use and 406 from therapeutic use. In both types of indication, the majority of the patients who had adverse effects were women with a mean age of 50 years. Among the 406 cases of adverse events from therapeutic use, 217 were classified as serious, including 28 deaths (due to respiratory arrest, myocardial infarction, stroke, pulmonary embolism and pneumonia, including aspiration pneumonia), and 26 of them had underlying diseases. The mean age among the patients who died was 44 years. It is important to emphasize that this study did not cite the diagnoses of the patients treated with BTA and did not make any age distinction for patients under the age of 20 years. Therefore, no parallel with our data can be traced out.⁷

Patients with GMFCS level V present spasticity with deformities at multiple levels that often require a broader approach, with use of oral or intrathecal medications. However, there are indications for focal management of spasticity, with a view to improvement of the positioning and facilitation of the use of orthoses and daily care.

Recently, reports of cases in which severe complications, including death, occurring through administration of BTA in cerebral palsy cases were published, with linkage to greater severity of functional impairment (GMFCS level V). The adverse effects most frequently reported have been respiratory difficulties and urinary incontinence, which can almost always be explained by local and/or hematogenic dissemination of the drug and autonomic denervation through retrograde migration. Adverse effects of generalized weakness from BTA in treatments for spasticity and dystonia have also been described and likewise explained in terms of systemic dissemination with pre-synaptic inhibition. One study in which a muscle biopsy was performed in a muscle distant from the application site demonstrated denervation. Retrograde axonal transport therefore cannot be ruled out.^{2,3,8-10} Clinical conditions of botulism have been described after administration of BTA, almost always related to excessively high doses, such as 40 U/kg. Other authors reported a similar case, in a patient with GMFCS level, from the description, who was using gastrostomy. No use of anesthesia or sedation was cited. The patient's condition of severe respiratory difficulty,

ptosis, fecal impaction, urinary retention and fever was interpreted as iatrogenic botulism.^{11,12}

In the literature, there seems to be a relationship between high total doses and occurrences of adverse effects, not necessarily in cases with GMFCS level V. In 2001, Bakheit et al.¹³ examined the data from 758 patients (94% with spastic cerebral palsy and 29% quadriplegic) who had received 1594 treatments with BTA (Dysport[®]). Sedation or anesthesia was used in 31% of the cases. The patients were not classified using the GMFCS, and it was only stated that 13% of them could only walk at home, while the others were able to walk in the community. The mean dose used was 22.9 U/kg and the maximum total dose was 2360 U. Adverse effects were found in 7%, among which the most frequent were localized muscle weakness (which was explained as resulting from local dissemination of the drug) and urinary incontinence (explained as autonomic dysfunction). These were mainly correlated with high total doses (greater than 1000 U), but there was no correlation with the functional level or the dosage per unit weight. Weakness in distant muscles occurred in a small percentage of cases and, according to these authors, may have been due to chemical denervation. They concluded that BTA was safe for treating spasticity in children when used at doses of less than 1000 U (for Dysport[®]), and that lower doses could be used without impairing attainment of the desired results.¹³ It needs to be taken into consideration that there is no precise correlation between the doses of Botox[®] and Dysport[®].

The relationship between complications and GMFCS level V was demonstrated by Howell et al. in 2007.⁵ They published a case report on an adverse reaction to application of 400 U of BTA (Botox[®]), i.e. 20–25 U/kg, in a nine-year-old patient who presented quadriplegic spastic cerebral palsy of GMFCS level V and was treated under general anesthetic. This patient was using gastrostomy. He developed respiratory difficulty after the first injection, which was repeated after the second, third and fourth injections, and on the last three occasions had to be admitted to hospital. The authors explained the respiratory complications on the basis of the presence of pseudobulbar palsy, which alters laryngeal and pharyngeal function. These are under neural control, mediated by cholinergic terminals, and are therefore subject to blockage through the action of BTA. The authors stated that BTA might spread beyond the muscle motor points in certain circumstances and speculated that it would not be possible to rule out allergic reactions as a cause of the adverse effects that occurred. They concluded that patients with GMFCS level V, who often present risk factors such as pseudobulbar palsy, respiratory difficulties and swallowing problems, should receive much lower doses of BTA, i.e. between 4 and 6 U/kg.⁵

In 2010, Naidu et al.¹⁴ published the results from 1980 BTA in lower limbs, under anesthesia applied through a mask, among 250 patients of GMFCS level V.¹⁴ There was a low complication rate in the general sample (1% with incontinence and 1.3% with respiratory abnormalities), and these complications were correlated with use of high doses of BTA. The mean dose used was 252 U in total (13.4 U/kg) and the mean number of muscle groups was three. Among these, the gastrocnemius and hamstrings were the muscles most frequently injected. There was one death, which was related to respiratory complications resulting from epilepsy. The risk of

respiratory complications was correlated with GMFCS level V and to the presence of pseudobulbar palsy, histories of respiratory diseases and use of inhaled anesthesia. Among the 71 patients in the general sample who showed adverse effects, 24 received a second dose of BTA and two developed new adverse effects. The authors recommended that patients with GMFCS level V should not be treated with BTA, while those with level IV should receive a maximum dose of 18 U/kg. In our study, reapplications were made, without any appearance of adverse effects, even in the patients who presented some degree of respiratory dysfunction or swallowing difficulty and gastrostomy. It should be noted that in our sample, no anesthesia or sedation was used and the doses used were smaller.

A consensus published in 2010 advised that the total dose and the dose per unit weight should be calculated more carefully in patients with GMFCS level V and in those presenting respiratory dysfunctions and/or dysphagia, and that an interval of not less than six months should be given between applications.⁶

On the other hand, even with higher doses, in 2010 Unlu et al.¹⁰ published the results from administration of BTA under sedation (midazolam) among 71 patients, of whom 33% presented GMFCS level V. There was no mention of any complications or adverse effects, with doses of 15–20 U/kg of Botox® or 30 U/kg of Dysport®, and the maximum doses were respectively 300 U and 500 U. The absence of complications may have been related to nonuse of anesthesia.

However, this relationship with nonuse of anesthesia could not be proven in another study, in which adverse effects were observed in 76 patients with GMFCS level V who had received BTA under sedation or anesthesia through a mask. Among these patients, 72% presented histories of dysphagia and almost half were using gastrostomy. The authors monitored the appearance of sentinel events, i.e. worsening of dysphagia, generalized weakness and infectious events of the lower airways. Adverse events occurred in more than 20% of the total number of cases. Among level V patients, three presented worsening of dysphagia and four had an infectious event of the lower airways; all of them had histories of dysphagia. There were no deaths. None of the patients who showed sentinel events had received BTA under general anesthesia.⁹

Most reports that have described adverse events from BTA have indicated that dissemination to locations far from the application sites, such as the swallowing and/or respiratory muscles, as possible causes of complications. However, it is unclear in the literature whether serious complications such as respiratory dysfunction and death might be related to underlying conditions that were now in a threshold state, given that these patients generally presented adverse effects that were directly related to BTA. This population of patients is frequently dependent on gastrostomy for feeding, since they present aspiration of foods to the airways, which has often been documented. Thus, these are situations in which deep sedation or anesthesia could be incriminated as the cause of significant lack of protection of the airways, thereby favoring aspiration and retention of secretions. Such conditions in these patients could be lethal.¹⁴ Olney et al.¹⁵ used electroneuromyographic to investigate distant neuromuscular effects (in the biceps brachii) after application of 280 U of BTA in the neck muscles. They did not find any electrophysiological signals of

pre-synaptic blockage and concluded that higher dose could be used if necessary. Thus, it could be presumed that only incontinence could be attributed solely to use of BTA, given that respiratory complications are very common in these patients, even without any intervention, and it could also be asked whether the sedation and/or anesthesia procedure alone might be incriminated. They suggested that options other than anesthesia using a mask and adaptation of doses would be desirable among patients with GMFCS levels IV and V. Occurrences of urinary and/or fecal incontinence are often difficult to register among patients with GMFCS level V, who generally do not have sphincter control.

In our study, we did not have any adverse effects, possibly because the doses used were low: a mean of 193 U (12.5 U/kg). In only 15 applications did the patients receive more than 15 U/kg, and in only two cases, more than 20 U/kg; and no sedation or anesthesia was used. This mean dose was lower than the mean doses used in studies in which complications were shown.^{5,13,14} It seems that it was impossible to make any correlation with preexisting respiratory pathological conditions in our sample, given that we did not have any complications. This occurred even though around 50% of the patients had clinical reports of difficulties with swallowing and aspiration (three patients were using gastrostomy as the sole route for feeding), several patients had histories of pulmonary complications and 12 required hospital treatment.

The literature shows that adverse effects from using BTA for treating spasticity in cerebral palsy cases are rare. Such effects include generalized muscle weakness, urinary incontinence, botulism and respiratory complications, and they correlate mainly with the respiratory complications at GMFCS level V. It is important to emphasize that the respiratory adverse effects occurred in patients who received high doses, already had underlying respiratory dysfunctions and underwent sedation or anesthesia for the applications. The adverse effects might be related to systemic dissemination or autonomic dysfunction due to retrograde pre-synaptic inhibition. Studies have recommended that these patients, who often present risk factors such as underlying respiratory and swallowing difficulties and have not received BTA, should be treated with low doses without sedation or anesthesia, since there is a likely correlation between these factors and the complications. In our study, in which the patients were treated with intermediate doses, without sedation or anesthesia, there were no complications.

Conclusion

From our findings, BTA can be used for focal treatment of spasticity in patients with cerebral palsy of GMFCS level V, provided that low doses are used, without using sedation or anesthesia.

Conflicts of interest

The authors declare no conflicts of interest.

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