Relação entre Níveis GMFCS e Seleção de Músculos/Doses de Toxina Botulínica em Doentes Pediátricos Paralisia Cerebral: Coorte Retrospetiva de 17 Anos

Botulinum toxin and Gross Motor Function Classification System: a 17-year Retrospective Study on Target Muscles and Doses

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Resumo

Introdução: A toxina botulínica tipo A (BoNT-A) é amplamente utilizada no tratamento da espasticidade focal em idade pediátrica, particularmente em crianças com paralisia cerebral (PC), principal causa de espasticidade nesta população. As injeções de BoNT-A têm como objetivo melhorar funcionalidade, padrões de marcha, posicionamento, higiene, deformidades e controlo da dor.

Objetivos: O objetivo deste estudo, retrospetivo e monocêntrico, foi analisar a aplicação de onabotulinumtoxinA e abobotulinumtoxinA em crianças com PC, utilizando cada sessão de injeção como unidade de análise. Examinou-se a relação entre níveis do Gross Motor Function Classification System (GMFCS) e os músculos-alvo e, secundariamente, descrevemos características demográficas, doses e reações adversas.

Métodos: Analisaram-se todas as sessões de injeção realizadas entre 2007 e 2023 em doentes com menos de 19 anos. Consideraram-se como deambulantes as crianças que caminhavam de forma independente ou com auxiliares de marcha (GMFCS ≤ III), enquanto que as não deambulantes necessitavam de cadeira de rodas (GMFCS > III). Comparações entre os 2 grupos foram efetuadas com teste Mann–Whitney (IBM SPSS v.28). A significância estatística definiu-se como $p < 0,05$, e os efeitos foram reportados com intervalos de confiança a 95%.

Resultados: Analisaram-se 883 sessões de injeção em 163 crianças (idade mediana 8,2 IQR 5,1-1,23). Foi administrada OnabotulinumtoxinA (627 sessões) e AbobotulinumtoxinA (256 sessões) com doses médias de 187 UI (IC 95%: 179–194) e 564 UI (IC 95%: 544–586), respetivamente. As doses foram significativamente superiores nas crianças não deambulantes, tanto em valores totais como ajustados ao peso ($p < 0,001$). Os músculos mais frequentemente injetados nas não deambulantes foram adutores e isquiotibiais, enquanto nas deambulantes predominaram os gastrocnémios, solear e tibial posterior. Não foram reportadas reações adversas graves nem alergias.

Conclusões: A BoNT-A é um tratamento eficaz e seguro da espasticidade em crianças, independentemente do GMFCS. A seleção individualizada dos músculos e a definição da dose em função da funcionalidade e objetivos

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***Recebido/Received:** 09/2025. **Aceite/Accepted:** 11/2025. **Publicado online/Published online:** 07/2026. **Publicado/Published:** 05/2026.*

terapêuticos são essenciais para otimizar resultados. Clinicamente, estes resultados sustentam a utilização de protocolos individualizados de BoNT-A, integrados em programas de reabilitação de longo prazo. A principal limitação é o seu desenho retrospetivo e monocêntrico, que poderá condicionar a generalização dos resultados.

Palavras-chave: Reabilitação Pediátrica, Toxina Botulínica, Neurotoxina, Espasticidade, Paralisia Cerebral, Gross Motor Function Classification System

Abstract

***Background**: Botulinum toxin type A (BoNT-A) is widely used to manage focal spasticity in children with cerebral palsy (CP), the leading cause of spasticity in childhood. Injections aim to improve function, gait, positioning, hygiene, appearance, and pain control.*

***Objectives**: This single-center retrospective study analyzed the use of onabotulinumtoxinA and abobotulinumtoxinA in children with CP, using each injection session as the unit of analysis. We examined the relationship between Gross Motor Function Classification System (GMFCS) levels and the muscles targeted, and secondarily described demographics, doses, and adverse reactions.*

***Methods**: All injection sessions performed between 2007 and 2023 in patients under 19 years old were reviewed. Ambulatory children were defined as those walking independently or with walking aids (GMFCS ≤ III), while non-ambulatory children required a wheelchair for mobility (GMFCS > III). Duplicate records were removed prior to analysis. Between-group comparisons were performed using the Mann–Whitney U test(IBM SPSS v.28). Statistical significance was set at $p < 0.05$, with effects reported using 95% confidence intervals.*

***Results**: A total of 883 BoNT-A injection sessions were analyzed in 163 children (median age 8.2 IQR 5.1-12.3). OnabotulinumtoxinA (627 sessions) and abobotulinumtoxinA (256 sessions) were administered at mean doses of 187 IU (95% CI 179–194) and 564 IU (95% CI 544–586). Doses were significantly higher in non-ambulatory children for both total and weight-adjusted values ($p < 0.001$). The most frequently injected muscles in non-ambulatory children were the adductors and hamstrings, while ambulatory children more often received injections in the gastrocnemius, soleus, and tibialis posterior. No severe adverse events were reported.*

***Conclusions**: BoNT-A is a safe and effective treatment for pediatric spasticity across all GMFCS levels. Adapting muscle selection and dosing according to functional level optimizes therapeutic outcomes and helps prevent deformities. Clinically, this supports individualized toxin protocols integrated into long-term rehabilitation programs. The main limitation is the retrospective, single-center design, which may restrict generalizability.*

***Keywords:** Pediatric Rehabilitation; Botulinum Toxin; Spasticity; Cerebral Palsy; Gross Motor Function Classification System.*

Introduction

Botulinum toxin type A (BoNT-A), a neurotoxin derived from Clostridium botulinum, is a cornerstone in the management of spasticity in children with cerebral palsy (CP). By inhibiting acetylcholine release at the neuromuscular junction, it produces temporary, localized muscle relaxation that facilitates functional gains, pain reduction, and the prevention of musculoskeletal deformities when integrated within multidisciplinary rehabilitation programs.[1,2,3]

Spastic CP, the most prevalent subtype, is characterized by increased muscle tone, exaggerated reflexes, and restricted motor function. Spastic CP affects approximately 2–3 per 1000 live births worldwide and represents a major cause of childhood physical disability.[2,4,5] The degree of motor impairment is commonly classified using the Gross Motor Function Classification System (GMFCS), a validated five-level scale ranging from independent ambulation (Level I) to complete dependence for mobility (Level V)[6,7]. This functional stratification guides treatment objectives, from enhancing gait and participation in ambulant children to improving comfort, hygiene, and pain control in non-ambulant individuals.

The application of botulinum toxin in pediatric spasticity is well-supported by evidence. Its primary indications include reducing focal spasticity to improve functional abilities, alleviating pain associated with muscle overactivity, and delaying the progression of musculoskeletal deformities. Injections in adductor or iliopsoas muscles, when combined with physiotherapy and orthotic management can help prevent hip displacement in children with severe spasticity, a frequent complication in non-ambulatory patients[8,9,10]. Additionally, the treatment can optimize the use of orthotic devices and facilitate therapeutic interventions such as stretching and strength training.[11] For these reasons, botulinum toxin injections are often integrated into individualized treatment plans tailored to each child's developmental stage and clinical needs.[12,13]

The goals of treatment with botulinum toxin vary depending on the GMFCS level and include a spectrum of functional and preventive objectives. For children in GMFCS Levels I and II, the primary aim is to enhance gross motor abilities, such as walking efficiency, balance, and participation in physical activities. In GMFCS Levels III and IV, objectives focus on improving comfort and functionality, such as optimizing the use of assistive devices and minimizing secondary complications like contractures. For children in GMFCS Level V, the emphasis lies on improving quality of

life by reducing pain, facilitating hygiene care, and maintaining passive range of motion.[12,14]

Yet, despite broad adoption, real-world data describing how injection patterns, muscle selection, and dosing vary across GMFCS levels over long-time spans remain scarce. Few studies have systematically linked functional severity (GMFCS) with specific injection targets, dose intensity, and repetition of sessions, controlling for factors such as age and weight.[15,16]

Dosing guidelines for botulinum toxin in pediatric spasticity are essential to ensure both effectiveness and safety.[12,14,17] For abobotulinumtoxinA (Dysport), the recommended dosing typically ranges from 15 to 30 units per kilogram per session, with a maximum total dose of 1000 units, whichever is lower.[18] Specific dosing recommendations for the upper and lower limbs are as follows: for the upper limbs, the dose is generally between 8 and 16 units per kilogram per limb, with the total dose not exceeding 16 units per kilogram or 640 units, whichever is lower. For the lower limbs, the recommended doses range from 10 to 15 units per kilogram per limb, with the total dose not exceeding 30 units per kilogram or 1000 units, whichever is lower, for the entire treatment session, regardless of the number of muscles treated.[18] This flexible dosing regimen is designed to tailor the treatment to the individual child's needs, taking into account the severity of spasticity and their prior response to botulinum toxin therapy.

In contrast, for onabotulinumtoxinA (Botox), when treating both the upper and lower limbs in pediatric patients, the total dose should not exceed the lower of 10 units per kilogram or 340 units within a 3-month period, whichever is lower.[19] The dosing is adjusted based on the muscle groups being treated. For the upper limbs, the typical dosage is 6 units per kilogram, with a maximum of 200 units, whichever is lower. For the lower limbs, the recommended dose is slightly higher, at 8 units per kilogram, with a maximum of 300 units, whichever is lower.[19] Overall, the total dose should not exceed 10 units per kilogram, with an absolute maximum of 340 units per session. These guidelines are carefully designed to balance therapeutic efficacy with the safety of botulinum toxin treatment in pediatric spasticity.[19]

Moreover, while multiple BoNT-A formulations are available, onabotulinumtoxinA and abobotulinumtoxinA are not bioequivalent. Their "units" reflect distinct biological assays and cannot be directly compared without appropriate normalization. Therefore, understanding dosing behavior across formulations requires standardized, label-based metrics that preserve pharmacological validity.[20,21]

This study aimed to characterize the long-term use of onabotulinumtoxinA and abobotulinumtoxinA in a tertiary pediatric rehabilitation center, describing patterns of muscle selection, dose distributions, and functional targets according to GMFCS levels. A secondary objective was to explore demographic data, adverse events and temporal trends over 17 years of clinical practice. By integrating absolute and label-relative dosing metrics, this work provides a pragmatic view of BoNT-A use in pediatric spasticity under real-world conditions as well as its integration into multidisciplinary treatment plans over the years.

Methods

Study design and setting

This was a retrospective observational study conducted at a tertiary pediatric rehabilitation center, encompassing all botulinum toxin type A (BoNT-A) injection sessions performed between 2007 and 2023. The unit of analysis was the injection session, rather than the patient, to account for multiple procedures per child. Clinical and procedural data were extracted from structured medical records.

Participants and functional classification

Pediatric patients with spastic cerebral palsy who received BoNT-A injections were included regardless of subtype of CP or ambulatory status. Both male and female participants were included, ranging in age from 17 months to 19 years. Functional severity was classified according to the Gross Motor Function Classification System (GMFCS), grouped as ambulatory (levels I–III) and non-ambulatory (levels IV–V). This study employed convenience sampling, with patients included based on the availability of clinical records. There was no randomization. A complete case analysis was performed, excluding records with missing data.

Patients were included in the study based on the application of specific eligibility criteria. The inclusion criteria required participants to be under the age of 19, have a diagnosis of cerebral palsy, receive follow-up care in the Pediatric Physical and Rehabilitation Medicine Department, and undergo treatment for spasticity with botulinum toxin type A (BoNT-A). Our pediatric patients regularly attended rehabilitation appointments and were treated with BoNT-A as part of a structured program involving frequent and sequential toxin injections. These children also received regular physical therapy and were enrolled in a hip dislocation surveillance program.

The exclusion criteria ruled out patients who refused to participate in the study, had clinical records with significant missing data, or had undergone prior invasive treatments specifically for spasticity, such as baclofen pump implantation or selective dorsal rhizotomy. Additionally, patients with concurrent diagnoses that could interfere with the outcomes of botulinum toxin treatment and spasticity, such as acquired central nervous system pathologies (e.g., neoplasms), were excluded from the study.

The Hospital Garcia de Orta Ethical Committee approved this study (approval number and date: 32/2020, 18 June 2020). All parents or legal guardians were asked to carefully read and sign an informed consent. Researchers ensured the confidentiality of study participants and the data collected from them. The study was conducted according to the criteria set by the Declaration of Helsinki, with pertinent National and International regulatory requirements.

Intervention

The intervention aimed to manage focal spasticity in both upper and lower limbs by targeting specific muscles based on the patient's functional needs and Gross Motor Function Classification System (GMFCS) level. The injections were tailored to achieve therapeutic goals such as improving gait patterns, positioning, functionality, and hygiene care, as well as preventing deformities, managing pain, and addressing hip dislocation risks. The intervention involved selecting target muscles (e.g., adductors, hamstrings, gastrocnemius) and adjusting doses according to individual patient requirements, ensuring a patient-specific approach in both ambulatory and non-ambulatory children.

Data were collected from medical records, including demographic information, GMFCS level, injected muscles, total dose of BoNT-A, dose per kilogram (dose/kg), and any reported adverse reactions.

The intervention was not modified for the purposes of this study. Decisions regarding the doses and muscles to be injected were made by physicians with over 5 years of experience in the technique. The team of physicians responsible for the pediatric botulinum toxin clinic did not undergo significant changes over the 17 years covered by this study, with the team consisting of a maximum of three members throughout. The analysis is retrospective, and the conduct of this study did not interfere in any way with the intervention, which followed the standard practices and guidelines of the department where it was carried out. The physicians who treated the patients were not involved in the collection or analysis of data. The research was conducted by independent investigators.

Injection technique

All injections were performed by experienced rehabilitation physicians using anatomical landmarks for guidance. The needle used was 27G, 4 cm, attached to 1 mL insulin-type syringes. OnabotulinumtoxinA was typically reconstituted with 1 mL of 0.9% normal saline; in selected cases, 2 mL were used to facilitate accurate handling of small doses. AbobotulinumtoxinA was reconstituted with 2.5 mL of 0.9% normal saline. Most muscles were treated with a single injection site, with the number of sites tailored to muscle volume and the predefined clinical objective. Target muscles were chosen on the basis of clinical examination, pain- or spasticity-related functional limitations, radiographic hip changes, and therapeutic goals agreed with caregivers and the child. Sedation and analgesia protocols evolved over time: inhaled nitrous oxide at 50% was used routinely from 2014 to 2023, whereas prior to that period midazolam and chloral hydrate were employed. A minimum interval of 6 months was observed between injection sessions. No antibiotic or other systemic prophylaxis was administered.

Dosing approach and normalization

BoNT-A doses were determined individually according to patient weight, distribution of spasticity, and treatment goals. Given that onabotulinumtoxinA and abobotulinumtoxinA are not bioequivalent, data for each formulation were analyzed separately. To enable exploratory cross-formulation comparisons without assuming dose equivalence, session doses were normalized to the pediatric product-label maximum recommended cumulative dose (RCM) and expressed as a percentage. The RCM was 10 U/kg or 340 U (whichever was lower) for onabotulinumtoxinA, and 30 U/kg or 1,000 U (whichever was lower) for abobotulinumtoxinA.

For each session, relative measures were calculated as:

- Relative dose/kg = observed IU/kg ÷ label maximum/kg
- Relative total dose = observed IU ÷ label maximum absolute dose

Expressing doses as percentages of the maximum recommended per RCM provides a normalized, pharmacologically meaningful metric that avoids assuming bioequivalence between onabotulinumtoxinA and abobotulinumtoxinA. This allows visual comparison of treatment intensity across Gross Motor Function Classification System (GMFCS) levels without unit conversion biases.

However, real (absolute) doses remain clinically relevant and easily interpretable by practitioners. For that reason, we present specific muscle dose in raw dose values (IU and IU/kg). This dual approach preserves external validity and clinical applicability, while enabling cross-formulation consistency in exploratory comparisons.

Outcome measures

The primary outcome measures included the total dose and dose per kilogram (dose/kg) of BoNT-A (OnaBoNT-A and AboBoNT-A), the distribution of injections across various muscles, and a comparison of the muscles targeted in patients classified under different GMFCS levels (≤3 vs. >3). Additionally, the study analyzed the selection of muscles for injection based on functional levels (walking vs. non-walking) and explored trends in muscle targeting influenced by therapeutic goals such as functional improvement or positioning. We also compared relative doses of Ona- and Abobotulinumtoxin A across all GMFCS levels.

Secondary outcome measures encompassed demographic characteristics, including the age and sex distribution of the study population and trends observed in these parameters over the 17-year study period. Safety was assessed by recording any adverse reactions associated with BoNT-A injections. This comprehensive approach provided insight into the tailored use of BoNT-A to address specific needs in this patient population.

Statistical analysis.

All analyses were conducted in IBM SPSS Statistics v28 (Armonk, NY, USA); generalized estimating equations (GEE) were fitted in Python using statsmodels. The distribution of continuous variables was assessed for normality, and results are presented as mean ± standard deviation or median [interquartile range, IQR], as appropriate. Categorical variables are expressed as counts and percentages. Normality was assessed with the Shapiro–Wilk test. Because each child could contribute multiple injection sessions, the unit of analysis was the injection session. For continuous outcomes, we fitted GEE with a Gaussian family and an exchangeable working correlation structure, clustering by patient ID, to compare GMFCS levels (I–V; reference level: I), reporting adjusted mean differences ( ) with 95% confidence intervals. To compare the injected muscles between the two functional groups (ambulatory and non-ambulatory), the Mann–Whitney U test was used. Categorical variables were compared using chi-square tests or logistic regression, with odds ratios (OR) and 95% confidence intervals. To account for repeated treatment sessions per child, comparisons of botulinum toxin doses across GMFCS levels were performed using Generalized Estimating Equations (GEE) with a normal distribution and identity link. Separate models were fitted for total dose (IU) and weight-adjusted dose (IU/kg), with GMFCS level as a categorical predictor. Results are reported as coefficients (mean difference vs GMFCS I) with 95% confidence intervals (CI) and p-values. Statistical significance was set at $p < 0.05$.

Results

Descriptive Analysis of the Sample

A total of 163 pediatric patients with cerebral palsy participated in this study, encompassing 89 males (54.6%) and 74 females (45.4%), with a median age of 8.2 years (IQR 5.1-12.3), ranging from 17 months to 19 years. The cohort underwent 883 sessions of BoNT-A injections, 627 of which (71%) were injected with OnaBoNT-A, and 256 (29%) with AboBoNT-A. The disparity in the number of sessions likely reflects differences in clinical indications, dosing regimens, and product availability over the study period. Table 1 summarizes the baseline characteristics of the population.

Comparison Between Formulations

As expected, the median total dose per session and dose adjusted by body weight differed significantly between the two formulations. For OnaBoNT-A, the median total dose was 200 [IQR 100–225], with a median dose per kilogram (dose/kg) of 10.0 [IQR 7.1–13.3]. In contrast, AboBoNT-A exhibited higher dosing values, with a median total dose of 500 [500–500] and a median dose/kg of 18.6 [12.5–23.5] (Table 1).

These results underscore differences in the pharmacological properties and clinical application strategies of OnaBoNT-A and AboBoNT-A, as well as the importance of dose individualization based on patient-specific factors such as age, weight, and clinical presentation.

Comparison Between GMFCS levels

After accounting for repeated sessions per child, higher functional severity was associated with higher weight-adjusted doses. For onabotulinumtoxinA, dose/kg was higher in GMFCS IV (β=+2.79 IU/kg, 95% CI 0.73–4.85; p=0.008) and V (β=+2.55 IU/kg, 95% CI 0.55–4.55; p=0.013) vs GMFCS I; total dose was modestly higher in GMFCS IV (β=+34.5 IU, 95% CI 0.7–68.3; p=0.045). For

Table 1 - Baseline characteristics of study population.

	Total (n=163)	OnaBoNT-A group	AboBoNT-A group
Age (years)	8.2 [5.1–12.3]	7.0 [4.1–9.7]	11.4 [7.3–14.5]
Sex (male/female)	89(54.6%)/74(45.4%)	—	—
Injections	883 (100%)	627 (71%)	256 (29%)
Total Dose (IU)	—	200 [100–225]	500 [500–500]
Dose/Kg (IU/Kg)	—	10.0 [7.1–13.3]	18.6 [12.5–23.5]

Continuous variables are expressed as medians and IQR; categorical variables are expressed as counts (percentages). The unit of analysis is the injection session.

abobotulinumtoxinA, dose/kg was higher in GMFCS III (β=+5.97, 95% CI 3.74–8.19; p<0.001), IV (β=+8.98, 95% CI 4.26–13.69; p<0.001), and V (β=+11.08, 95% CI 4.66–17.50; p=0.0007), whereas differences in total dose were not statistically significant.

Re-analysis with cluster-robust GEE confirmed that dosing is primarily driven by functional severity (GMFCS), especially for weight-adjusted dosing, supporting individualized protocols by functional level.

Median relative total doses indicate that both formulations were typically administered at ~50–60 % of their label-recommended maximum, with higher relative doses in more severely affected (non-ambulatory) children. This pattern reflects individualized titration according to functional status and therapeutic goals rather than uniform dosing practices.

Table 2 shows the relative doses of Ona- and Abobotulinumtoxin A, as percentages of the maximum recommended per product label (RCM), and Table 3 shows the total number of sessions, total doses and doses/Kg for each formulation, both considering the level of severity of GMFCS.

Table 2 - Doses expressed as percentages of the maximum recommended per product label (RCM).

Toxin	GMFCS level	n sessions	Relative total dose	Relative dose/kg
OnaBoNT-A	1	117	50% [29–59]	76% [44–105]
OnaBoNT-A	2	99	47% [29–59]	93% [61–120]
OnaBoNT-A	3	55	59% [29–88]	91% [75–111]
OnaBoNT-A	4	155	59% [44–88]	115% [86–150]
OnaBoNT-A	5	96	59% [29–59]	108% [85–128]
AboBoNT-A	1	113	50% [50–50]	42% [35–62]
AboBoNT-A	2	65	50% [50–50]	54% [45–70]
AboBoNT-A	3	28	50% [50–50]	68% [45–76]
AboBoNT-A	4	71	50% [50–60]	72% [56–83]
AboBoNT-A	5	79	50% [50–75]	78% [67–95]

Continuous variables are expressed as medians and IQR; categorical variables are expressed as counts (percentages). The unit of analysis is the injection session.

Table 3 - Total doses per session and doses/Kg by GMFCS level (unit = injection session).

Onabotulinumtoxin A			
GMFCS	**n**	**Total dose (IU)**	**Dose/kg (IU/kg)**
1	117	170 [100–200, range 20–300]	7.6 [4.4–10.5, range 1.1–15.8]
2	99	160 [100–200, range 50–400]	9.3 [6.1–12.0, range 3.2–16.7]
3	55	200 [100–300, range 50–400]	9.1 [7.5–11.1, range 2.5–15.4]
4	155	200 [150–300, range 60–400]	11.5 [8.6–15.0, range 1.9–22.2]
5	96	200 [100–200, range 50–350]	10.8 [8.5–12.8, range 4.5–20.6]
Abobotulinumtoxin A			
GMFCS	**n**	**Total dose (IU)**	**Dose/kg (IU/kg)**
1	113	500 [500–500, range 125–1000]	12.5 [10.6–18.8, range 2.5–31.2]

2	65	500 [500–500, range 100–1000]	16.3 [13.4–20.9, range 1.9–33.3]
3	28	500 [500–500, range 250–1000]	20.4 [13.5–22.7, range 9.4–35.7]
4	71	500 [500–600, range 200–1250]	21.7 [16.7–25.0, range 5.6–50.0]
5	79	500 [500–750, range 200–1000]	23.3 [20.0–28.6, range 8.3–55.6]

Values are median [interquartile range, range]. Unit of analysis: injection session.

Table 4 - Doses/Kg per muscle and GMFCS level.

Onabotulinumtoxin A			
	GMFCS ≤ 3	**GMFCS > 3**	**P value**
Adductor Pollicis	0,01	0,12	<0,001
Pronator Teres	0,42	0,01	<0,001
Biceps Brachii	0,399	0,553	0,963
Flexor Carpi Radialis	0,268	0,117	<0,001
Flexor Carpi Ulnaris	0,289	0,046	<0,001
Rectus Femoris	0,06	0,65	<0.001
Gastrocnemius	4,03	3,4	0,233
Tibialis Posterior	0,17	0,36	0,26
Adductors	1,008	3,25	<0,001
Medial Hamstrings	0,99	2,17	<0,001
Abobotulinumtoxin A			
	GMFCS ≤ 3	**GMFCS > 3**	**P value**
Adductor Pollicis	0,0197	0,0785	0,756
Pronator Teres	0,3063	0,1735	0,414
Biceps Brachii	0,5637	1,56	<0,001
Flexor Carpi Radialis	0,2343	0,5773	0,003
Flexor Carpi Ulnaris	0,0818	0,4155	<0,001
Rectus Femoris	0,0448	0,3344	0,009
Gastrocnemius	8,2618	4,5378	<0,001
Tibialis Posterior	1,1058	0	<0,001
Adductors	0,7698	7,5701	<0,001
Medial Hamstrings	2,3067	6,6163	<0,001

Continuous variables are expressed as means

After statistically confirming that significant differences existed in toxin doses across the different GMFCS severity levels, we proceeded to compare treatment patterns and injected muscles between ambulatory and non-ambulatory patients. The choice of target muscles and dosing strategies for BoNT-A injections demonstrated significant variation across GMFCS levels, reflecting distinct therapeutic goals for ambulatory and non-ambulatory children and highlighting the need for precise dose adjustment based on functional status and therapeutic objectives (Table 4). Additionally, Graphs 1 and 2 illustrate the distribution of injected muscles for OnaBoNT-A and AboBoNT-A across GMFCS levels, highlighting a clear alignment of muscle selection with functional priorities. Finally, Table 5 shows the probability of injecting any upper or lower limb muscle regarding the ambulatory or non-ambulatory status of the patient.

Across both toxins, muscle injection patterns differed visibly by ambulatory status: non-ambulatory children (GMFCS IV–V) had markedly higher odds of receiving proximal lower limb injections — especially hip adductors and hamstrings — while ambulatory children (GMFCS I–III) more frequently received injections targeting distal lower limb or upper limb muscles (Table 5).

These contrasts were consistent across both onabotulinumtoxinA and abobotulinumtoxinA, with several odds ratios exceeding 10, highlighting the strong association between functional severity and muscle selection in routine clinical practice (Table 5).

Graph 1. Most frequent injected muscles in children with cerebral palsy, according to GMFCS level, in the Onabotulinumtoxin A Group

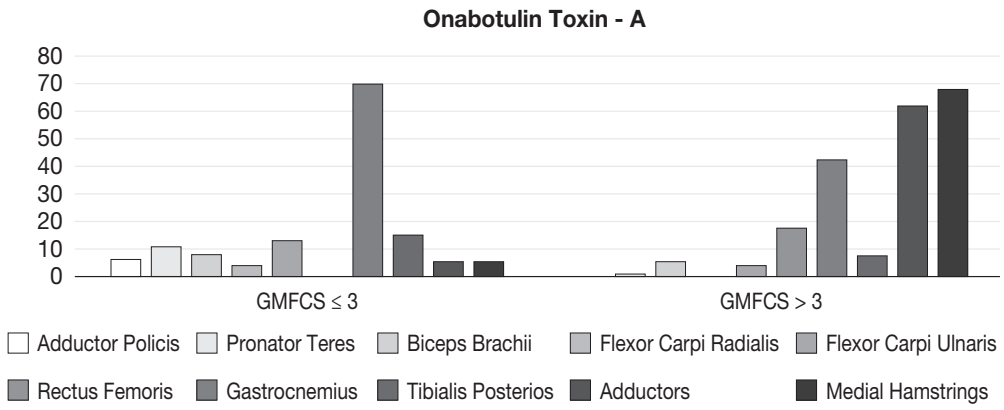
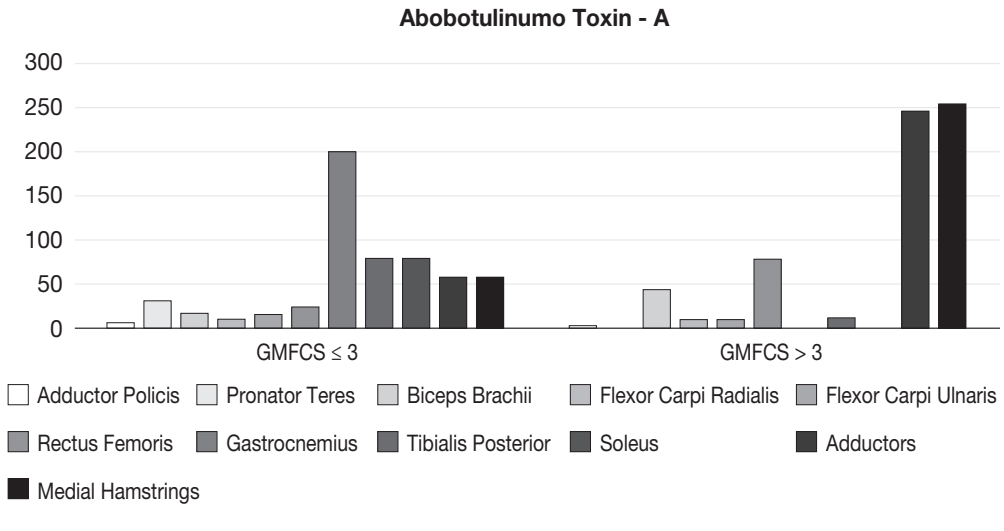


Figure 1 - Músculos-Alvo sob TBA nos membros inferiores.

Graph 2. Most frequent injected muscles in children with cerebral palsy, according to GMFCS level, in the AbobotulinumtoxinA Group



Bars represent mean total dose per muscle

Figure 2 - Músculos-Alvo sob TBA nos membros inferiores.

Table 5 - Odds of muscle injection by functional status.

Muscle	Ambulatory n/N (%)	Non-ambulatory n/N (%)	OR (non-amb vs amb)	95% CI	p-value
Onabotulinumtoxin A					
Upper limb muscles					
Biceps brachii	47/271 (17.3%)	45/256 (17.6%)	0.98	0.63–1.54	0.943
Pronator teres	56/271 (20.7%)	3/256 (1.2%)	21.97	6.78–71.17	0.000
Flexor carpi radialis	37/271 (13.7%)	14/256 (5.5%)	2.73	1.44–5.19	0.002
Flexor carpi ulnaris	42/271 (15.5%)	6/256 (2.3%)	7.64	3.19–18.31	0.000
Adductor pollicis	28/271 (10.3%)	3/256 (1.2%)	9.72	2.92–32.38	0.000
Lower limb muscles					
Adductors (hip)	37/271 (13.7%)	107/256 (41.8%)	0.22	0.14–0.34	0.000
Rectus femoris	4/271 (1.5%)	30/256 (11.7%)	0.11	0.04–0.33	0.000
Hamstrings	41/271 (15.1%)	79/256 (30.9%)	0.40	0.26–0.61	0.000
Gastrocnemius	107/271 (39.5%)	97/256 (37.9%)	1.07	0.75–1.52	0.708
Soleus	14/271 (5.2%)	1/256 (0.4%)	13.89	1.81–106.42	0.011
Tibialis posterior	13/271 (4.8%)	18/256 (7.0%)	0.67	0.32–1.39	0.279
Abobotulinumtoxin A					
Upper limb muscles					
Biceps brachii	23/206 (11.2%)	37/150 (24.7%)	0.38	0.22–0.68	0.001
Pronator teres	16/206 (7.8%)	9/150 (6.0%)	1.32	0.57–3.07	0.521
Flexor carpi radialis	8/206 (3.9%)	19/150 (12.7%)	0.28	0.12–0.66	0.003
Flexor carpi ulnaris	4/206 (1.9%)	16/150 (10.7%)	0.17	0.05–0.51	0.002
Adductor pollicis	2/206 (1.0%)	1/150 (0.7%)	1.46	0.13–16.26	0.758
Lower limb muscles					
Adductors (hip)	14/206 (6.8%)	59/150 (39.3%)	0.11	0.06–0.21	0.000
Rectus femoris	1/206 (0.5%)	7/150 (4.7%)	0.10	0.01–0.82	0.032
Hamstrings	36/206 (17.5%)	52/150 (34.7%)	0.40	0.24–0.65	0.000
Gastrocnemius	93/206 (45.1%)	25/150 (16.7%)	4.12	2.47–6.85	0.000
Soleus	31/206 (15.0%)	3/150 (2.0%)	8.68	2.60–28.97	0.000
Tibialis posterior	30/206 (14.6%)	0/150 (0.0%)	52.01	3.15–857.87	0.006

Odds ratios estimate the odds of injection in non-ambulatory versus ambulatory children (GMFCS >III vs ≤III). Outcome per muscle coded as injected=1 if dose/kg>0 in that session. Logistic regression used, with Haldane–Anscombe correction if separation occurred. Unit of analysis: injection session.

OnaBoNT-A Group:

Non-ambulatory children (GMFCS > 3) predominantly received injections in lower limb muscles related to positioning and deformity prevention, with the adductors, medial hamstrings, and rectus femoris being the most frequently targeted. These children also received significantly higher mean doses/kg compared to ambulatory children (GMFCS ≤ 3), such as 3.25 IU/kg vs. 1.008 IU/kg for the adductors ($p < 0.001$) and 2.17 IU/kg vs. 0.99 IU/kg for the medial hamstrings ($p < 0.001$). This pattern aligns with the therapeutic focus on hip stability, wheelchair positioning, and prevention of musculoskeletal complications in non-ambulatory patients. In contrast, ambulatory children received higher doses in upper limb muscles, such as the pronator teres (0.42 IU/kg vs. 0.01 IU/kg, $p < 0.001$) and flexor carpi ulnaris (0.289 IU/kg vs. 0.046 IU/kg, $p < 0.001$), aiming to improve upper limb function, which is crucial for activities of daily living and participation in physical, social, and sports tasks. These patterns in muscle selection and dosing strategies highlight the distinct therapeutic goals across GMFCS levels, with a dual focus on improving gross motor function in ambulatory children and preventing secondary complications in non-ambulatory children.

AboBoNT-A Group:

A similar pattern was observed for AboBoNT-A, with non-ambulatory children receiving higher doses/kg in lower limb muscles such as the adductors (7.57 IU/kg vs. 0.77 IU/kg, $p < 0.001$) and medial hamstrings (6.62 IU/kg vs. 2.31 IU/kg, $p < 0.001$). Interestingly, the gastrocnemius was an exception, with ambulatory children receiving higher doses/kg (8.26 IU/kg vs. 4.54 IU/kg, $p < 0.001$), reflecting the focus on managing spastic gait patterns such as toe-walking in this group. However, ambulatory children again exhibited higher doses in the gastrocnemius (8.26 IU/kg vs. 4.54 IU/kg, $p < 0.001$), reflecting a focus on improving dynamic movement patterns.

Safety

No severe adverse events occurred among the 883 injection sessions. Six minor adverse reactions (0.68%, equivalent to 0.7 events per 100 injection sessions) were recorded, all of which resolved completely without sequelae. Three events were related to transient vomiting or desaturation during nitrous oxide sedation, and three involved transient dysphagia following upper-limb injections. Table 6 shows the adverse events associated with BoNT-A injection sessions.

Discussion

This study provides a comprehensive characterization of botulinum toxin type A (BoNT-A) usage in pediatric spasticity management over a 17-year period in a specialized reference center. By analyzing 883 injection sessions in 163 children with cerebral palsy (CP), we identified key patterns in dosing and muscle selection tailored to Gross Motor Function Classification System (GMFCS) levels, emphasizing the individualized approach to spasticity treatment.

Table 6 - Adverse events associated with BoNT- A injection sessions.

Year	Description	Toxin	Site	Onset	Resolution	Severity	Relationship
2010	Transient dysphagia without aspiration	Abo	Upper limbs	2 weeks post-injection	Resolved after 2 months	Mild	Possibly related to toxin diffusion
2015	Vomiting immediately after injection	Ona	Lower limbs and Upper limbs	2 weeks post-injection	Resolved immediately	Mild	Related to nitrous oxide
2016	Oxygen desaturation to 88% during nitrous oxide sedation, reversed with oxygen therapy	Abo	Lower limbs and Upper limbs	During procedure	Resolved within 15 min	Mild	Related to sedation
2020	Vomiting	Abo	Lower limbs	4 min post-procedure	Resolved immediately	Mild	Related to nitrous oxide
2021	Worsening of pre-existing dysphagia (PEG in place)	Ona	Upper limbs	1 week post-injection	Resolved after 2 months	Mild	Possibly related to toxin diffusion
2022	Vomiting (ate before sedation)	Ona	Lower limbs	During procedure	Resolved immediately	Mild	Related to sedation

Summary of minor adverse events observed during 883 botulinum toxin type A injection sessions in 163 pediatric patients with cerebral palsy. All events resolved completely without sequelae. Events are listed in chronological order. Abo - AbobotulinumtoxinA; Ona – onabotulinumtoxinA.

Our sample includes patients from 17 months to 19 years old because it is a convenience sampling from a tertiary hospital. At our clinical center, we have been administering botulinum toxin type A to children with spastic cerebral palsy younger than 24 months of age, recognizing that this is an off-label use. However, based on current evidence demonstrating its safety and efficacy in this age group, we consider it a valid therapeutic option.[22]

Our data suggest that BoNT-A administration is closely aligned with functional status. In non-ambulatory children (GMFCS IV–V), injections were mainly directed toward the adductors and hamstrings, reflecting a preventive approach focused on hip stability and the management of fixed deformities. In contrast, ambulatory children (GMFCS I–III) received more frequent injections in distal lower-limb and upper-limb muscles, particularly the gastrocnemius and tibialis posterior, to improve selective motor control and gait pattern. These patterns are consistent with prior evidence supporting a tailored use of BoNT-A according to functional level, balancing functional improvement with deformity prevention.[16]

The present analysis reinforces that dose requirements increase with GMFCS severity, even after accounting for repeated sessions per child. However, caution is warranted in interpreting dosing trends across toxins, as onabotulinumtoxinA and abobotulinumtoxinA are not bioequivalent, and their units cannot be directly compared. The two BoNT-A formulations differ in molecular structure, potency, and diffusion profile, and are not bioequivalent; therefore, dosing units are not interchangeable. Differences in formulation, potency, and diffusion profiles may contribute to distinct dosing behaviors observed in clinical practice. Future research should therefore consider toxin-specific analyses rather than pooled comparisons.

Over the 17-year observation period, several procedural and clinical aspects evolved. The same injector treated most patients, although other injectors collaborated from 2008 and 2022, respectively. Although the core clinical team remained largely consistent until 2021, gradual changes were implemented in pain management and sedation protocols. Initially, midazolam, chloral hydrate, and non-pharmacological distraction methods (such as music) were used; from 2014 onward, nitrous oxide became the standard approach. These changes likely improved procedural tolerance and safety, reflecting broader shifts in pediatric sedation practices. While our dataset did not formally capture procedural pain outcomes, this evolution underscores the importance of continuous adaptation in long-term clinical programs.

No severe adverse events were observed, supporting the favorable safety profile of BoNT-A, including in off-label use among children under 24 months[22,23]. The overall rate of adverse events was low (0.7 per 100 sessions), and all were mild and self-limited. Most were associated with sedation rather than the toxin itself, consistent with previous reports highlighting the safety of nitrous oxide-assisted BoNT-A procedures. The two transient cases of dysphagia followed upper-limb injections and resolved spontaneously, aligning with known diffusion-related effects. These findings reinforce the favorable safety profile of BoNT-A when appropriate monitoring and procedural protocols are followed.[24] Nonetheless, this conclusion should be interpreted cautiously given the retrospective nature of the study and the absence of systematic follow-up data on minor or transient adverse effects.

As a retrospective observational study, this research has its own limitations such as the possibility of biases related to data completeness. The reliance on medical records may have excluded patients with incomplete documentation or limited follow-up. Additionally, being conducted in a single specialized center, the results may not be fully generalizable to other settings or populations. Future prospective studies should incorporate standardized outcome measures, such as goal attainment scaling (GAS), Gross Motor Function Measure (GMFM), quality-of-life metrics and radiographic monitoring to better correlate injection patterns with meaningful functional and structural outcomes. Multicenter collaborations could further enhance external validity and allow for the development of standardized dosing algorithms across toxin formulations.

Our observations support the rationale for individualized dosing strategies guided by GMFCS level, reflecting real-world clinical results.

Conclusion

This study contributes to understanding how BoNT-A is applied in daily clinical practice, suggesting that treatment is adapted to functional status and clinical goals rather than fixed protocols. By documenting real-world patterns over nearly two decades, these findings provide a foundation for prospective, evidence-driven refinement of BoNT-A strategies in pediatric spasticity management, ensuring that treatment goals, whether functional or preventive, are met effectively.

Future research should aim to explore long-term outcomes associated with BoNT-A use, particularly its impact on quality of life, participation, and the prevention of orthopedic complications. Prospective studies with standardized outcome measures could further refine dosing strategies and muscle selection, enhancing the integration of BoNT-A into multidisciplinary management plans.

Acknowledgements

We would like to acknowledge the invaluable contribution of Dr. Cristina Duarte, who was one of the pioneers in

introducing botulinum toxin injections at the hospital where this study was conducted. For 15 of the 17 years covered by the study, Dr. Cristina Duarte was the physician responsible for administering the majority of treatments, and a significant portion of the data presented in this study is directly attributable to her dedicated work.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Considerations: This study was conducted in accordance with the principles of the Declaration of Helsinki and the recommendations of the International Committee of Medical Journal Editors (ICMJE). As this was an observational study that did not involve any modification to routine clinical practice, no additional risks were imposed on the participants.

Protection of Human Subjects: All procedures performed were part of routine clinical practice and did not interfere with participants' access to treatment. The safety and well-being of all participants were safeguarded throughout the study.

Data Confidentiality: The collected data were pseudonymized and processed in accordance with national and European data protection legislation, including the General Data Protection Regulation (GDPR). No identifiable personal information was included in the manuscript.

Previous Awards and Presentations: The authors declare that preliminary results of this study, included in the present manuscript, were presented at the 24th European Congress of the European Society of Physical and Rehabilitation Medicine (ESPRM), where they were well received by the participants.

Prémios e Apresentações prévias: Informamos que resultados preliminares do presente trabalho, submetido neste manuscrito foram apresentados no 24.º Congresso Europeu da Sociedade Europeia de Medicina Física e de Reabilitação, com boa receção dos participantes.

Conflitos de Interesse: Os autores declaram a inexistencia de conflitos de interesse. Apoio Financeiro: Este trabalho nao recebeu qualquer subsidio, bolsa ou financiamento. Proveniencia e Revisao por Pares: Nao solicitado; revisao externa por pares.

Conflicts of Interest: The authors have no conflicts of interest to declare. Financial Support: This work has not received any contribution grant or scholarship. Provenance and Peer Review: Not commissioned; externally peer-reviewed.

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