Botulinum toxin as adjuvant therapy for hypertonic dysfunction in a neuro-rehabilitation cohort

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Research Article

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Abstract

**Purpose:** Botulinum toxin (BTX) is a neurotoxin produced by the bacterium Clostridium botulinum, in recent decades, BTX has become an important adjunct treatment to neurological or rehabilitative strategies. We aimed to describe the clinical aspects of patients admitted to a rehabilitation hospital who were treated with BTX for spasticity and dystonia.

**Methods:** This was a historical cohort; data was collected from the electronic charts of all outpatients treated with BTX between 2014 and 2016 in the spasticity and movement disorders service of a quaternary, open access, rehabilitation hospital. The inclusion criteria were limb spasticity due to traumatic brain injury (TBI), and stroke; limb tremor; cervical dystonia; and generalized limb dystonia from any cause in addition to pain that limits rehabilitation. We used relatively lower doses than those generally published in the literature. Therapeutic response was determined by the Goal attainment scale (GAS), pain (graded by visual analogue scale), independence for daily living activities, target joint range of motion (pre- and post-application), and gait analysis (only for walkers patients).

**Results:** A total of 63 patients were enrolled in this study with a mean follow-up of 2 years. There was significant improvement in joint restriction with 66.7% of patients reporting improvement in the GAS scale; best improvement occurred with orthoses and limb adjustments.

**Conclusions:** Most patients have improved functionality on the GAS scale after treatment with BTX, which is used as an adjunct therapy in subjects already in rehabilitation programs. The main rehabilitation objectives with the GAS scale were achieved in most patients.

**Introduction**

Botulinum toxin (BTX) is a neurotoxin produced by the bacterium Clostridium botulinum, which is an anaerobic bacterium that grows in soil, untreated water, and contaminated or poorly preserved food. C. bacterium produces different toxin serotypes; in 1820, Justinus Kerner (1786-1862), a physician and romantic poet, published his first monograph on "sausage poisoning," summarizing 76 case reports and providing a complete clinical description of what is now known as botulism [1,2]. Studies have identified different strains and serologically diverse toxins classified as types A, B, C, D, E, F, and G. However, among these, only types A and B are commercially available. Types C and F have been used in humans only experimentally [3,4,5,6,7,8,9].
In 1977, the Food and Drug Administration (FDA) authorized the testing of BTX in humans for the treatment of strabismus [2]. In the early 1980s, its use was expanded to treat blepharospasm, hemifacial spasm, cervical dystonia, and adductor spasm of the lower limbs, among other underlying indications such as spasmodic dysphonia, oromandibular dystonia, hand dystonia, and more recently, spasticity of the limbs [10]. In recent decades, BTX has become an important adjunct treatment to neurological or rehabilitative strategies. In a rehabilitation hospital setting, the use of BTX is based on individualized, multidisciplinary programs that aim to achieve patient goals [11,12].

**Objective:**

We aimed to describe the clinical aspects of patients admitted to a rehabilitation hospital who were treated with BTX for diseases such as spasticity and dystonia related to several medical conditions.

**Methods**

This was a historical cohort; data was collected from the electronic charts of all outpatients treated with BTX between 2014 and 2016 in the spasticity and movement disorders service of a quaternary, open access, rehabilitation hospital.

The following ranges of BTX dosage were applied to several muscles:

- Cervical muscles: 15-100 u
- Upper Limbs: 5-100 u
- Low Limbs: 25-200 u

**Eligibility criteria:**

The inclusion criteria were limb spasticity due to traumatic brain injury (TBI), and stroke; limb tremor; cervical dystonia; and generalized limb dystonia from any cause in addition to pain that limits rehabilitation.

**Exclusion criteria:** Spinal cord injury, hemifacial spasm, blepharospasm, and laryngeal dystonia were not analyzed due to an insufficient number of patients and difficulty in retrieving their data.
The variables collected included age, sex, topographic region/nature of the neurological lesion, site at injection, outcomes measured using the Goal Attainment Scale (GAS), and improvements in pain, hygiene, functionality, deformity, dressing, range of movement, and use of orthosis. Adverse effects were considered if definite causal relationships could be inferred, with concomitant functional impairment in daily life activities.

Walker patients were categorized according to Perry’s classification criteria and subjected to three-dimensional gait analysis (Gait Analysis Laboratory) before and after BTX treatment.

We evaluated patients, including those who had adductor pelvic spasticity who were unable to clean their intimate areas and had difficulty changing diapers or washing their hands or axillas.

**Assessment tools:**

Therapeutic response was determined by GAS, pain (graded by visual analogue scale (VAS)), independence for daily living activities, target joint range of motion (pre- and post-application), and gait analysis (only for walkers patients). GAS was applied before and after the treatment, and the patient was assessed for the aims of the procedure (e.g., reducing pain during exercise, facilitating dressing up or hygiene, improving orthoses adaptation, etc.). If the patient achieved the expected level, the score was 0. It was divided into better or worse outcomes based on the GAS scale. If they achieved a better than expected outcome, this was scored as +1 (somewhat better) or +2 (much better). If they achieved a worse than expected outcome, this was scored as -1 (somewhat worse) or -2 (much worse). The same team evaluated the patients before and after treatment and at the follow-up at 2 years.

**Statistical analysis:**

A simple statistical evaluation was carried out using the variables mentioned earlier. For the statistical analysis, we used a descriptive analysis, with continuous variables expressed as mean and standard deviation for normally distributed variables, and as median and interquartile range for non-normally distributed variables. The results are shown as bars and graphics for better understanding. Categorical variables were expressed as frequencies and percentages. Due to the low statistical power and limited number of subjects enrolled, we were not able to perform correlations and eventual causality associations.
Results

A total of 63 patients were enrolled in this study with a mean follow-up of 2 years; the etiologic diagnosis of the cohort is shown in Figure 1, and the predominant neurological expression on clinical examination is shown in Figure 2. Most patients had a stroke (41.3%), as shown in Figure 1.

Table 1 depicts the baseline characteristics of the cohort of 42 patients who underwent gait assessment. The majority of patients who were assessed for gait were female (55%) and were predominantly right-handed (93%), as shown in Table 1.

We evaluated patients, including those who had adductor pelvic spasticity who were unable to clean intimate areas and had difficulty changing diapers or washing their hands or axila. In addition, we used orthoses to improve the rest position and functional activities. Pain relief was also a criterion for patient selection.

Perry's classification was used for dividing the patients (total, 42 patients who underwent gait assessment) before administering BTX, according to Table 2.

For limb spasticity, we found a total of 56% of patients using orthoses and 44% without. There was significant improvement in joint restriction (deformity) with 66.7% of patients reporting improvement in the GAS scale (defined by GAS of 0) with BTX injection for the upper and lower limbs, as shown in Table 3. The best improvement occurred with orthoses and limb adjustments, with 100% of patients reporting improvement, better adaptability using orthoses and more tolerability to extended use of the orthoses (GAS, 0) as shown in Table 4. The ability to handle objects (limb function) also improved in most patients (66.7%). Improvement in pain related to limb spasticity was reported in 90.9% of patients (Table 4). A total of 87.5% of patients reported hygiene improvement and 100% gained the ability to put on their clothes. All patients reported improvements in flexibility exercises (GAS score > 0). There was a 66.7% improvement in lower and upper limb spasticity during exercise, as reported by the patients.

It was observed that the prevalence of dystonia was 42.9 % and that of spasticity was 63.5%. Most patients with inferior limb spasticity were using orthoses, and the beneficial aspects related to handling limb orthoses were also analyzed using the GAS scale. A significant benefit was better tolerance and easier use of orthoses. In addition, the use of walking assistance was verified, and 66.7% of the patients with lower limb spasticity reported benefits in amplitude range after the use of BTX, observed in 3D gait analysis (3DGA). There was a 61.5% improvement in pain in the lower limbs (≥0) as shown in Table 4, 30.8% reported no difference (GAS, 1), and 7.7% reported worsening (GAS, 2),
The main adverse effect was mild temporary target muscle paresis for up to 5–10 days in 6 cases (9.52%) and pain at the injection site in 5 cases (9.93%). In most cases, muscle paresis did not translate into functional disability. There was only one case (1.58%) of cutaneous allergy, but there was no clear causal relationship to BTX. Two other (3.17%) patients reported muscle soreness for more than a few hours after the intramuscular injections, but we did not classify it as an important adverse effect.

We used the method associated with 3DGA to accurately describe how people walk, run, or jump in three dimensions. This was combined with force platform technology to provide a complete description of an individual's biomechanics. The whole process is based on cutting-edge science in the field of biomechanics. We found a 71.4% improvement after BTX treatment on measurements in the movement laboratory (3DGA) (Table 4). For hand ability (dystonia improvement in hand function), we used the GAS scale, and 66.7% of patients achieved improvement, as shown in Table 3. Tables 3 and 4 show improvements in several aspects of daily living and functionality after BTX application, respectively, divided into spasticity and functionality. Table 4 shows the improvement in dystonia. The ethics committee of the SARAH Network of Hospitals approved our study protocol, and the requirement for patient consent was waived by the committee. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Discussion**

In neurorehabilitation, BTX A as adjunct therapy can be a useful therapeutic resource for the treatment of hypertonia [11,12]. In addition to spasticity, numerous motor and non-motor disorders can complicate clinical courses and hamper the rehabilitative process in patients with neurological impairment. Worsening adverse events and neutralizing antibody formation can occur after repeated BTX injections [11]. In our hospital, there was a significant improvement (87%) in hygiene and wearing clothes (100%). Patients reported a significant beneficial effect lasting up to 4-6 months. The main adverse effect was mild temporary target muscle paresis for 5–10 days. In most cases, muscle paresis did not lead to functional disability. There were no other important adverse effects, except for one case of cutaneous allergy not causally related to BTX. Two other patients reported muscle soreness for more than a few hours after the intramuscular injections, but we did not classify it as an important adverse effect. In our unit, we work as a multidisciplinary team for spasticity and other neurological disorders that can be treated with BTX. The staff team is composed of neurologists, physical therapists, and nurses. All patients were attended to together and had their cases discussed as teams. Multidisciplinary work minimizes complications and optimizes assertive behaviors.

Previous studies suggest that oral baclofen may be effective in many patients with spasticity, regardless of the underlying disease or severity, and that it is at least comparable with other antispasmodic agents. However, adverse effects, such as muscle weakness, nausea, somnolence, and paresthesia, are common with oral baclofen, affecting between 25% and 75% of patients, limiting its usefulness [35]. The first
intervention in our service is generally oral drug treatment. We used baclofen, tizanidine, levodopa, and biperiden as first-line therapies for spasticity, dystonia, and other movement disorders and conservative pain treatments. Before BTX, the medical treatment for focal spasticity involved oral antispasticity drugs, which had decidedly non-focal adverse effects, and phenol injections. Phenol injections were difficult to perform, could cause sensory complications, and had effects of uncertain duration and magnitude, such as pain on injection, bleeding, and infection [37]. There could be damage to the skin and necrosis of surrounding muscles, blood vessels, and soft tissues. Accidental intravascular injections can cause tinnitus and flushing. Neuritis could manifest after partial destruction of a somatic nerve with subsequent regeneration; the resultant dysesthesia or hyperesthesia may be worse than the original pain [37]. Furthermore, few neurologists had expertise in BTX injections, as they were mostly rehabilitation specialists. BTX can produce focal, controllable muscle weakness with predictable duration, without sensory adverse effects [29]. The safety of BTX-A is impressive, with minimal (mainly local) adverse effects [33], and focal spasticity management should be multidisciplinary, patient-centered, and goal-directed. The routine measurement of impairment and activity is strongly endorsed. BTX injection should only be provided as part of an integrated approach to focal spasticity management [32], and when patients have focal disorders or they do not tolerate the side effects of oral antispasticity, we start to evaluate BTX as an optional therapy. Even so, patients were selected for this intervention due to important functional disabilities, such as difficulty in wearing orthoses, basic hygiene, and serious pain disorder.

The effectiveness of intramuscular BTX injection for the treatment of spasticity in hemiplegic patients is superior when performed with needle electromyographic guidance than without electromyography [30].

Injections of BTX into the affected arm of hemiplegic patients improve abnormal trunk lateral flexion. This shift of the center of mass of the upper body towards the midline improves various gait parameters, including gait speed [36]. In relation to gait impairment, patients who were subjected to detailed walking electromyography study in the laboratory could help the team to identify focal muscles that were acting out of phase and be treated with BTX; they showed significant improvement.

Pain relief was also a common demand for patients and there was great benefit with the use of botulinum toxin, which has certain properties that might have a beneficial effect on chronic pain [31]. The use of a movement laboratory was very positive in the management of these patients, and aided the attending team with regard to the correct muscle choice for intervention, as well as with the best dosage for each case.

**Conclusion**
Most patients have improved functionality on the GAS scale after treatment with BTX, which is used as an adjunct therapy in subjects already in rehabilitation programs. The main rehabilitation objectives with the GAS scale were achieved in most patients.

Pain improvement (which can be very limiting to the rehabilitation process) was observed in the majority of patients, and no major side effects were observed with the application of this treatment.

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Tables

Table 1: Subjects characterization
| Walking classification          | N (%)   |
|--------------------------------|---------|
| Limited household walker       | 6 (14%) |
| Household walker               | 14 (33%)|
| Limited community walker       | 11 (26%)|
| Community walker               | 11 (26%)|
| Total                          | 42 (100%)|

Table 3: Percentages of overall spasticity and pain improvement in segments measured using the GAS scale

|                  | UPPER LIMBS | LOWER LIMBS | CERVICAL |
|------------------|-------------|-------------|----------|
| Spasticity (%)   | 66.7%, n    | 66.7%, n    | N/A      |
| pain (%)         | N/A*        | N/A*        | 100%     |

n: 63.
* Lack of data in medical records

Table 4: Percentages of functional/symptomatic improvement in spasticity measured using the GAS scale
UPPER LIMBS | LOWER LIMBS | MOVEMENT LABORATORY (3DGA) | CLAW FINGER
---|---|---|---
PAIN | 90.9% | 61.5% | | 76.9%
Range Of Movement (ROM) | 66.7% | 66.7% | |
DEFORMITY | 66.7% | 66.7% | |
ORTHOSES | 100% | 87.5% | 75%
LIMB FUNCTION | 66.7% | 50% (TRANSFER) 60.9% (WALK) | 71.4%
HYGIENE | 87.5% | 50% | |
DRESSING | 100% | 100% | |
PHYSIOTHERAPY Flexibility | 100% | 100% | |

DYSTONIA (GAS SCALE / VAS SCALE)

Table 5: Dystonia improvement measured using the GAS scale

| | UPPER LIMBS | CERVICAL |
---|---|---
TREMOR | 50% | 75%
PAIN | 100% | 100%
DEFORMITY | N/A* | 100%
HAND FUNCTION | 50% | N/A**

* Lack of data in the medical records
**: Hand function is not measurable with cervical topography

Declarations

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Code availability: Not applicable

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TFH wrote the manuscript and analyzed data. AAG analyzed data, contributed to analytical tool and revised the manuscript. GOK, VSA, SFO and CEF collected all the data. VVAM conceived and designed the paper, also revised it for scientific content. All authors read and approved the manuscript.

**Figures**

**Figure 1**

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Figure 2

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