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Impact of Botulinum Toxin Consultation Shutdown Due to the Covid-19 Pandemic on Spasticity Treatment: A Review of the Literature

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Review Article

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Abstract

Introduction: The COVID-19 pandemic has imposed an additional pressure on health systems worldwide, creating an increased challenge to chronic patient management due to consultation shutdown. Spastic patients were especially vulnerable to inadequate care. This review aims to describe the impact of botulinum toxin (BT) consultation interruption due to the COVID-19 pandemic on spasticity treatment.

Methods: A literature search was conducted in the database of Medline, PubMed, Embase, Google Scholar and Scopus. Keywords for the search included "COVID-19" AND "Botulinum Toxin" AND "Spasticity".

Results: A total of 6 studies reporting the impact of BT consultation suspension on spasticity due to the COVID-19 pandemic met inclusion criteria. All studies were observational and included a small sample. Consultation interruption was variable between studies and ranged from 36-75 days, originating a mean treatment delay of 23-129 days due to re-scheduling difficulties. The majority (72-93%) of patients in all studies perceived worsening of spasticity with BT consultation suspension. Effects seem to be worse with longer treatment delays and concerning the mobility and passive function treatment objectives. Some studies reported a worse quality of life in patients with BT treatment delay whilst others did not find this association.

Discussion: Although a year has passed since the start of the COVID-19 pandemic, there is a scarcity of studies reporting the impact of BT consultation interruption on the treatment of spastic patients. An increased inter-treatment delay originates a reduction in the effectiveness at the end of the treatment cycle due BT washout. On average, a 1% worsening of symptoms occurs with one day of delay. Thus, a small delay of a few weeks can lead to worsening of symptoms which may take several treatment cycles to return to previous stable benefit level. The impact of BT consultation suspension on quality of life is controversial and further studies are necessary to clarify this question.

Conclusions: The COVID-19 pandemic has had a major negative impact on the BT treatment of spasticity. Thus, consultation shutdown severely affected these patients and needs to be avoided.

Keywords: Botulinum Toxin; Coronavirus; COVID-19; Spasticity

Introduction

Spasticity is an upper motor neuron lesion manifestation characterized by involuntary muscle hyperactivity with a velocity-dependent hypertonia [1]. Spasticity can decrease active or passive movement, increase disability and impair function [2]. This can be associated with several complications including pain, spasms, contractures and deformities, originating decreased activity and participation [3]. Spasticity management is essential in preventing the development of tendon contractures and limb deformities, improving functionality and quality of life [3].

Botulinum toxin (BT) is a neurotoxic protein produced by the *bacterium Clostridium botulinum*, which is used in the treatment of various clinical conditions such as spasticity, dystonia, chronic migraine and sialorrhea [4]. TB inhibits the release of the neurotransmitter acetylcholine in the neuromuscular junction, decreasing muscle contraction. Thus, it represents an effective and safe treatment for focal or regional spasticity. However, injections have to be administered repeatedly, every 3 to 4 months, in order to maintain therapeutic effect [5].

COVID-19 is caused by the novel coronavirus SARS-Cov-2. Although initially described in China, quickly it assumed pandemic proportions affecting millions of people in the world. The COVID-19 pandemic has imposed an additional pressure on health systems worldwide, originating non-urgent consultation shutdown in order to reduce infection risk and reallocate medical resources for the management of infected patients [6]. This has created an increased challenge to chronic patient management, with spastic patients being especially vulnerable to inadequate care.

To the present date, no systematic review has described the repercussions of the COVID-19 pandemic on the BT treatment of patients with spasticity. Thus, this review aims to describe the impact of BT consultation interruption due to the COVID-19 pandemic on spasticity treatment.

Methods

The present review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. A literature search was conducted in the database of Medline, PubMed, Embase, Google Scholar and Scopus. Keywords for the search included “COVID-19” (or coronavirus, or SARS-Cov-2) AND “Botulinum Toxin” AND “Spasticity”. All clinical study types were included and no language publication or sample characteristic restriction was imposed.

Results

Study flow diagram is shown in Figure 1. A total of 13 studies reporting BT consultation interruption due to the COVID-19 pandemic were found using the keywords described in the methodology section. Five of these studies [7-11] were clinical recommendations focusing on the return of BT consultation after shutdown and patient prioritization selection, being excluded from the review. One study [6] only focused on BT treatment of migraine and was excluded. Another study [12], although reporting a delay of 2-6 months of BT administration in the treatment of spasticity due to consultation interruption, did not report the impact of this delay on patients’ symptoms and was also excluded. Thus, a total of 6 studies reporting the impact of BT consultation suspension on spasticity due to the COVID-19 pandemic met inclusion criteria for the review and are shown in Table 1.

No high evidence studies were found (randomized control trial or systematic review) and only observational studies are available. Almost all studies were cross-sectional and monocentric, with only one case-control and one multicentric study. In all studies, sample size was small (< 150 patients), mean patient age was lower than 65 years and BT dosage was not very high (mean unified dose units < 320 U). BT Consultation interruption period was variable between studies, ranging from 36 to 75 days, and was related to individual countries’ public health measures. Mean treatment delay ranged from 23 to 129 days due to difficulties in re-scheduling patients.

➢ Patients’ Perception of Consultation Interruption on Spasticity

Evaluation of patients’ perception of BT consultation interruption on their spasticity was different between studies, with some using a qualitative likert scale whilst others used a quantitative visual analogical scale. The majority (72.2-93%) of patients in all studies perceived worsening of their spasticity with BT consultation suspension. Although patients reported a worsening of pain, involuntary movement, active and passive function, range of motion and mobility, Santamato, et al. [18] have pointed to a greater affection of mobility and passive function (self-hygiene) with BT therapy suspension. Also, Freitas Ferreira, et al. [14] and Samadzadeh, et al. [17] found that symptom perception seemed to be worse with longer treatment delays. Dressler, et al. [13] reported that 66% of patients perceived BT therapy more important than before due to the treatment interruption due to the COVID-19 pandemic.

➢ Impact on Quality of Life

The impact of spasticity treatment delay on quality of life due

to the COVID-19 consultation interruption is controversial. Of the six studies included, only four evaluated the quality of life of spastic patients. Dressler, et al. [13] found a reduction on quality of life perception of 40.2±19.5 % in the visual analogical scale. Gumussu, et al. [16] found that in patients with spasticity due to spinal cord injury, 42% reported increased difficulty in walking, 42% reported increased difficulty in wheelchair sitting and 46% experienced lack of sleep due to increased spasticity after consultation delay. Santamato, et al. [18] found that 70.9% of patients reported a worse quality of life with 53% reporting worse independence and 54.3% requiring increased caregiver assistance. Also, the same authors found that 82.8% of patients presented worse mood, 60.2% worse quality of sleep, 82.5% worse interpersonal relationship and 76.8% worse community life. However, a case-control study carried out by Erro, et al. [15] using the visual analogical scale and the health state description (EQ-5D), a standardized questionnaire for the evaluation of health status, found no significant difference ($p>0.05$) between cases and controls regarding the quality of life aspect.

Santamato, et al. [18] reported that 92.7% of patients did not receive rehabilitation interventions during lockdown, with 33.1% performing some physical activity or self-mobilization and 7.3% accessing telerehabilitation. A significant association between discontinuation of rehabilitation and worsening of independence ($p = 0.003$) was found but not with worsening of spasticity ($p = 0.311$). Freitas Ferreira, et al. [14] reported that 35.7% of patients made up for the absence of BT administration with physiotherapy but the majority (57.1%) adopted no additional adjuvant strategy.

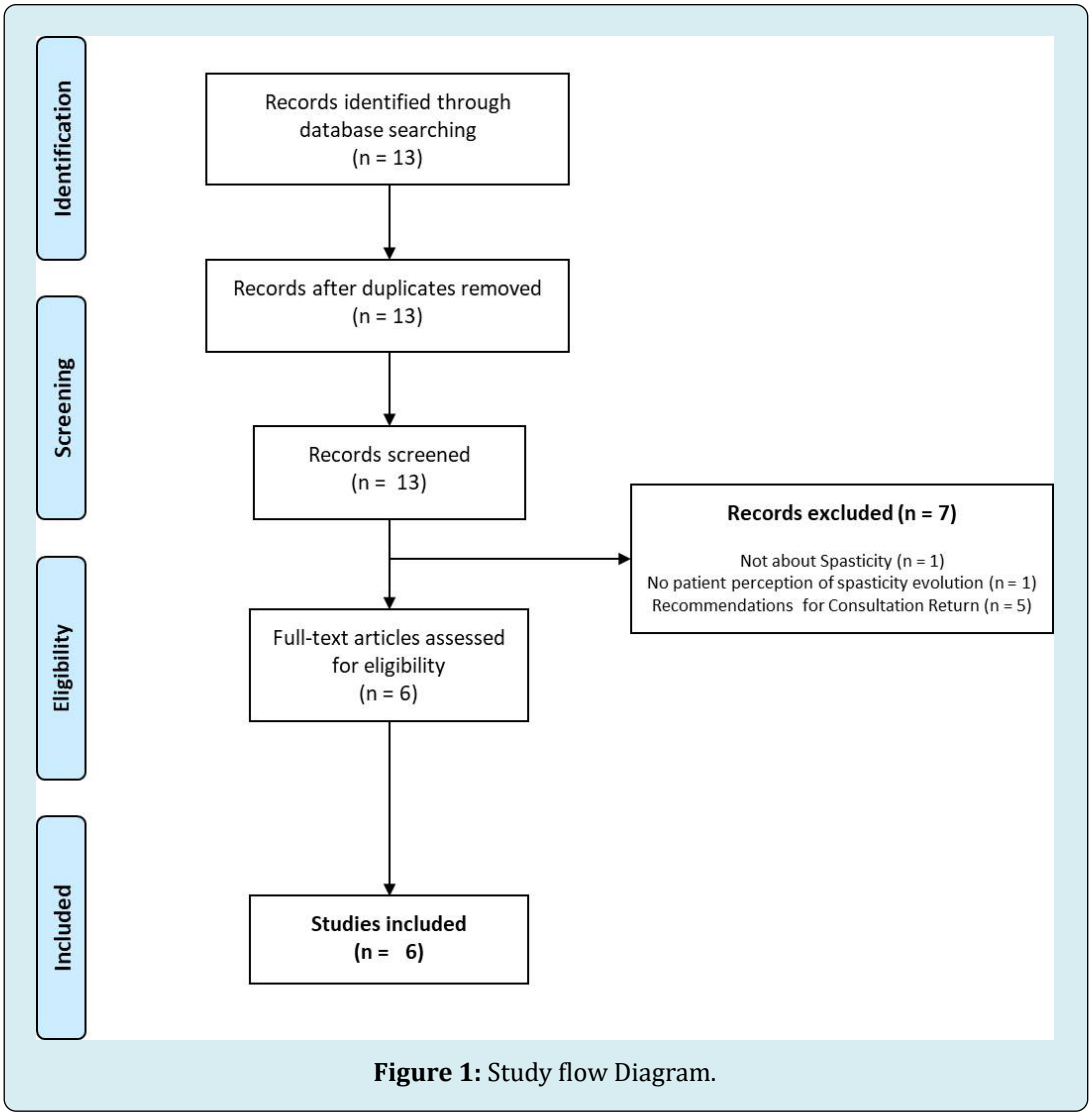

Figure 1: Study flow Diagram.

Authors	Study Type	Number of Patients	Mean Age (years)	Sex	Disease Duration (years)	Mean BT Dose Treatment (Unified Dose Units)	Conditions Included	Interruption Duration (Days)	Mean Delay of Treatment	Perceived Worsening by Patients	Impact on Quality of Life
Dressler, et al. [13] (July/2020)	Cross-Sectional (Monocentric)	45	61.9±9.8	16M/27F	8.3±5.5	319.3±201.9 [a]	Spasticity, Dystonia, Migraine, Blefarospasm	49	6.6±2.3 weeks	93% reported increases muscle cramps and 82% reported increased muscle pain.	Reduction in perceived QoL in VAS 40.2±19.5.
Freitas Ferreira, et al. [l4] (January/2021)	Cross-Sectional (Monocentric)	28	65.3±11.7	16M/12F	8.9±5.5	207.9±89.0 [b]	Spasticity (Stroke, Multiple Sclerosis, Spastic Herediraty Paraparesis, Cerebral Plasy)	75	4.3±1.6 months	85.7% reported worsening of symptoms Higher treatment delay was associated with worse impact on mobility and passive function.	No Data
Erro, et al. [15] (November/2020)	Case-control (Monocentric)	94 Cases Vs 43 Controls	56.9±17.0 Vs 61.7±14.0	43M/51F Vs 22M/21F	11.4±3.4 Vs 12.3±2.8	263.8±78.8 Vs 269.4±77.5[c]	Spasticity, Dystonia, Migrane, Other	56	73.61±26.54 days	Cases reported a significant greater worsening than controls (VAS increase 5.16±3.09 Vs 1.83±3.34, p<0,001).	No difference between cases and controls in VAS or EQ-5D (p>0,05).
Gumussu, et al. [16] (January/2021)	Cross-Sectional (Monocentric)	24	43.1±13.6	24M/4F	13.8±10.3	No Data	Spasticity (SCI)	No Data	No Data	87.5% reported increase in spasticity.	42% reported difficulty in walking, 42% reported difficulty in wheelchair sitting and 46% experienced lack of sleep.
Samadzadeh, et al. [17] (January/2021)	Cross-Sectional (Monocentric)	94	64±14	No Data	No Data	199±155 [b]	Spasticity, Dystonia, Maigraine	36	23±16 days	Patients reported worsening on VAS of 26±14. Worse symptom perception was associated with longer treatment delay.	No Data
Santamato, et al. [18] (July/2020)	Cross-Sectional (Multicentric)	151	58.42±14.64	90M/61F	7.81±7.34	No Data	Spasticity (Stroke and TBI)	70	No Data	72.2% reported worsening of perceived spasticity with greater worsening of mobility and self-care.	53% reported worse independence and 54.3% required increased caregiver assistance. 70.9% reported worse QoL. 82.8% reported worse mood, 60.2% worse quality of sleep, 82.5% worse interpersonal relationship and 76.8% worse community life.

Table 1: Studies on the Impact of Spasticity Treatment due to Botulinum Toxin Consultation Interruption in the COVID-19 Pandemic Context.
QoL - Quality of Life; SCI - Spinal Cord Injury; TBI - Traumatic Brain Injury; VAS - Visual Analogical Scale.
a Conversion used: 1 U onabotulinumtoxinA = 1 U incobotulinumtoxinA = 0.5 U of abobotulinumtoxinA
b Conversion used: 1 U onabotulinumtoxinA = 1 U incobotulinumtoxinA = 0.33 U of abobotulinumtoxinA
c Conversion used: 1 U onabotulinumtoxinA = 1 U incobotulinumtoxinA = 0.4 U of abobotulinumtoxinA

Discussion

Although a year has passed since the start of the COVID-19 pandemic, there is a scarcity of studies reporting the impact of BT consultation interruption on the treatment of spastic patients. After searching the main electronic publication databases, only 6 low-evidence (5 cross-sectional and 1 case-control) studies were eligible to be included in this review. Thus, evidence level is not very high. Also, patient sample size was small in all studies, limiting external validity and the statistical power of the analysis.

The COVID-19 pandemic has had a major impact on healthcare systems worldwide, affecting negatively both COVID-19 and non-COVID-19 patients. Due to consultation interruption, an increased effort has been carried out in various hospitals in order to implement telemedicine interventions. However, BT administration requires the physical presence of the patient, exposing spastic patients to inadequate care during consultation shutdown. BT therapy is the gold-standard in the management of focal spasticity, with therapeutic effect lasting at least 3 to 4 months [5]. Higher doses (> 600 U of *onabotulinumtoxinA* and *incobotulinumtoxinA* and > 1500 U of *abobotulinumtoxinA*) are associated with a slightly prolonged clinical effect [19-21]. BT preparations are not interchangeable and, in order to compare doses between different BT formulations, these must be converted to a unified dose unit by leaving *onabotulinumtoxinA* and *incobotulinumtoxinA* doses unchanged and dividing *abobotulinumtoxinA* doses by a factor of 3, according to a European consensus [22]. However, this conversion of BT units is still not consensual and a discrepancy exists between different studies, difficulting comparison of results. All studies reviewed found that the majority of patients perceived an increased worsening of spasticity with consultation interruption. However, patients were treated with not very high doses of BT with a maximum mean unified dose of 319 U. If patients has been treated with higher doses, possibly the therapeutic effect would be slightly prolonged and patients could have perceived a lower impact on worsening of spasticity symptoms with treatment delay.

BT consultation interruption was variable between studies (36-75 days) according to each country's individual lockdown policies. This originated a mean treatment delay ranging from 23 to 129 days, longer than consultation interruption, due to difficulties in re-scheduling patients because of reduced capacity of the re-opened centres in compliance with public health measures. In order to prevent virus transmission and reduce patient risk, BT treatment agendas had to be spaced in order to permit patient distancing, dressing/undressing of protective equipment and room cleaning [7,9], originating constraints in the re-scheduling of suspended patients. This further increases treatment delay with worsening of patient symptoms due to biological washout of BT activity. An increased inter-treatment delay originates a reduction in the effectiveness of BT at the end of the treatment cycle [15]. On average, a 1% worsening of symptoms occurs with one day of delay [15]. Thus, a small delay of only a few weeks can lead to a great worsening of symptoms and relapse on the severity level which may take several treatment cycles to return to previous stable benefit level before the consultation suspension [15].

BT treatment objectives are usually defined according to the World Health Organization's International Classification of Functioning, Disability and Health [23] and include mobility facilitation, improved active or passive function, involuntary movement control, pain control and maintenance of range of motion. The majority of patients, ranging from 72% to 93% according to different studies, reported worsening of spasticity symptoms, with Santamato, et al. [18] pointing to a greater affection in the mobility and passive function domains. Longer treatment delays seemed to be associated with worst symptom perception, according to Freitas Ferreira, et al. [14] and Samadzadeh, et al. [17], related to BT washout with time. Even after 16 weeks, a significant effect can be demonstrated for BT [19]. Re-treatment before the efficacy of the previous injection has completely declined will lead to a continuous staircase-like improvement until a stable level of improvement is reached, increasing patient satisfaction with the therapy [15]. Thus, it is important to not delay BT administration because it may take several treatment cycles to return to the previous stable benefit level. This illustrates the negative impact of the BT consultation interruption on the treatment of spasticity.

Goal Attainment Scaling (GAS) is an individualized outcome measure involving goal selection and goal scaling that is used for monitoring patient progress with BT therapy. GAS permits the understanding of whether the therapeutic goals of BT were being met with previous treatments (before the pandemic consultation shutdown). A GAS T-score of 50 or more indicates a significant change. If patients did not have an expected GAS outcome with the previous BT therapy, symptoms could be felt to be worse due to lack of BT treatment effectiveness and not due to consultation suspension. So, previous GAS is an important aspect to specify in order to correctly interpret study findings. However, only one study [14] included GAS score.

The impact of spasticity treatment delay on quality of life due to the COVID-19 consultation interruption is controversial. Dressler, et al. Gumussu, et al. and Santamato, et al. [1,16,18] found a reduction in the quality of life due to spasticity increase occurring due to BT treatment delay. This depicts the possible negative impact of spasticity limitation

in activity and participation. However, these studies were cross-sectional and this association was not found in the case-control study carried out by Erro, et al. [15] In order to explain this discrepancy, the authors have proposed that over the years, other factors, including the development of coping strategies and better acceptance of their condition, influence health status more than the BT injections [15]. Study methodologies for the evaluation of the quality of life were different between studies, possibly explaining, at least in part, discrepant findings.

Interruption of physical therapy due to the COVID-19 lockdown also affects spasticity and quality of life results. Of the six studies included in the review, only two mentioned adjuvant strategies for the management of spasticity due to BT interruption. However, Freitas Ferreira, et al. [14] did not study the association between absence of physical therapy and symptom worsening and Santamato, et al. [18] did not find a significant association between discontinuation of rehabilitation and worsening of spasticity. Thus, further high evidence studies are necessary in order to clarify the impact of BT therapy suspension due to the COVID-19 pandemic on quality of life of spastic patients.

Conclusion

Evidence from small observational studies suggest that the COVID-19 pandemic has had a major negative impact on the BT treatment of spasticity, with the great majority of patients reporting a worsening of symptoms due to consultation interruption. Effects seem to be worse with longer treatment delays and concerning the mobility and passive function treatment objectives. The impact of BT consultation suspension on quality of life of spastic patients is controversial and further studies are necessary to clarify this aspect. From the available evidence, consultation shutdown severely affected these patients and confirmed the importance of BT therapy in the management of focal and regional spasticity. Thus, interruption of BT consultation needs to be avoided even during hospital lockdowns.

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