Developments in Post-Stroke Spasticity Care with Early Use of Botulinum Toxin A: A Review

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ABSTRACT

Spasticity is one of the most common and disabling complications of stroke. Most of these patients notably experience both muscle-based and non-muscle-based pain. This negatively affects their quality of life as well as aggravates caregiver burden. Post-stroke spasticity (PSS) may furthermore lead to several complications related to limited mobility, both motor (eg, contractures) and non-motor (cognitive decline, depression) if left untreated. It is thus crucial to address this with safe and effective means such as botulinum toxin therapy as early as possible. We aim to demonstrate the utility of botulinum toxin (BoNT) in PSS treatment and how early intervention may be preferable to late spasticity control for patients. Literature search and evaluation were done using the traditional evidence hierarchy. Early intervention with botulinum toxin A (BoNTA) demonstrated a more marked reduction in both spasticity and spasticity-related pain with longer required intervals to reinjection.

Keywords Botulinum Toxin, Early Use/ Intervention, Poststroke Spasticity, Pain

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INTRODUCTION

Spasticity is one of the most common and disabling complications of stroke.[1] It is defined as an upper motor neuron (UMN) lesion-induced disruption of sensory-motor control, manifesting as intermittent or persistent involuntary muscle activation.[2,3] This almost always occurs in the paretic limbs.[2,4,5] Both a neurogenic (ie, overactive muscle activation) and rheologic (ie, shortening of muscle and soft tissues) component contribute to movement resistance in UMN lesions such as that in stroke.[6] There is usually a delay in the emergence of this spastic muscle hyperactivity suggesting activation of neuroplasticity processes post-stroke.[1,7]

Post-stroke spasticity (PSS) occurs in more than one-third of patients within a year from ictus, and predominantly involves the paretic limbs.[8] The time to development of clinically significant PSS, measured by a Modified Ashworth scale (MAS) equal to or greater than 1, ranges from 3 to 18 months.[4,7] However, PSS can be detected as early as two weeks with the help of neurophysiological methods.[7] The prevalence of spasticity evolves through the phases of stroke; with PSS occurring in 4%-27% of those in the acute phase (1-4 weeks post ictus), 19%-26.7% of those in the subacute phase (1-3 months post ictus), and 17%-42.6% in the chronic (>3 months post ictus) phase.[9]

Most patients with PSS experience pain and along with this are nonmotor complications such as cognitive decline, fatigue, depression and lower quality of life.[2,10] There is a correlation between the severity of PSS pain and that of cognitive impairment, depression and suicidality.[10] Hence the need for treatment is evident.[1]

PSS is demonstrably a common complication of stroke which may result in disability, functional impairments and contractures, especially if left untreated.[4,2] It negatively impacts the quality of life of stroke patients, and in turn also worsens the caregiver burden.[4,2] Furthermore, the costs of having a stroke quadruple if spasticity ensues.[4] A prospective observational study showed that patients with MAS ≥2 at follow-up had significantly lower Barthel Index scores, lower quality of life, and more pain; with pain developing within 12 weeks post-ictus and almost exclusively in patients with an increase in muscle tone.[11] A majority (72%) of the patients with PSS developed pain whereas only a minority (1.5%) of patients without spasticity experienced pain.[10] A cross-sectional study showed that the majority (80%) of the patients with upper motor neuron disorders believed that their pain was related to spasticity, and this suggests that pain management should be considered as a part of the spasticity treatment plan.[12]

Each stroke patient with spasticity has a distinct symptomatology and presents in different ways making the therapeutic treatment planning very challenging.[6] Setting goals is done utilizing clinical scales measuring impairment such as MAS, tone assessment scale and Tardieu and Modified Tardieu scales; and activity limitation including modified Rankin scale (MRS), functional independence measure (FIM), disability assessment scale and Barthel Index.[2,13]

There are non-pharmacologic and pharmacologic treatment measures for PSS. Non-pharmacologic primarily involves rehabilitation medicine, including physical therapy exercises, use of casts, orthoses and physical agents; and constraint-induced movement therapy (CIMT).[2,3,14] Another non-pharmacologic management for PSS is extracorporeal shock wave therapy (ESWT), which uses a rapid sequence of sonic pulses believed to break actin-myosin functional linkages in muscles.[2,14] Lastly, surgery is usually reserved for severe cases and complications of chronic spasticity.

Pharmacologic treatment may be in oral form such as baclofen, tizanidine, dantrolene and diazepam, and other benzodiazepines; or injectables such as alcohol and botulinum neurotoxin (BoNT).[2,3,14] Rehabilitation approaches are very diverse and aim to prevent secondary complications instead of targeting the abnormal muscle activity, while surgical approaches address the musculoskeletal deformities that ensue in chronic cases of PSS.[3,13] Injectables have the advantage of a more localized effect compared to oral forms, especially in focal and multifocal PSS. Between BoNT and phenols, the former selectively inhibits muscle contraction avoiding unsought sedation and general weakness, and the effect is reversible 3 to 4 months post-injection.[3,14,15] Recent randomized controlled trials showed possible advantages of adjunctive therapy with CIMT or ESWT after BoNT administration.[2,14]

BoNT is produced by the anaerobic Clostridium botulinum bacteria and interferes with neural transmission by blocking acetylcholine release in the neuromuscular junction.[16,17] Two serotypes, BoNT type A or BoNTA (onabotulinum toxin A or Botox®, abobotulinum toxin A or Dysport® and incobotulinum toxin A or Xeomin®) and BoNT type B or BoNTB (rimabotulinum toxin B or Neurobloc®/Myobloc®) are proven safe and effective in treating conditions with cholinergic overactivity, including muscle hyperactivity which include spasticity, dystonia, tremors, spasms, autonomic hyperactivity such as hyperhidrosis, drooling, overactive bladder and cosmesis like wrinkles.[14,15] After injection, BoNT spread is rapid and driven by the dose, dilution, needle size and injection technique.[15,17] The blockage of neurotransmitter release is irreversible, while the neuromuscular function can be recovered by nerve terminal sprouting and new synaptic connections which occurs after two to three months.[16]

BoNT therapy is a safe and effective treatment option for PSS; reducing muscle tone and pain experienced by the patients.[1,2,17] It is common practice, however, to delay BoNT treatment until spasticity is already bothersome to the patient.[6]

The author's aim here is to show the role of BoNT in PSS care and how early intervention may benefit patients over the standard care of late spasticity management. Conventional evidence hierarchy was used to search and appraise literature. Randomized control trials (RCTs) and systematic reviews were preferentially pursued, followed by lower-level practice-based evidence to address clinical issues discussed in this review.

Botulinum Toxin A in Pain Reduction

Meta-analyses of RCTs that examined the use of BoNT for muscle-based (ie, spasticity and dystonia)

or non-muscle-based (ie, central neuropathic pain, painful diabetic neuropathy, trigeminal neuralgia and complex regional pain syndrome) pain syndromes showed lower pain scores in the group that received BoNTA treatment.[16,17,20] This was attributed to neuromuscular blockage halting contraction leading to subsequent relaxation of the painful spastic muscle. The reduction in pain level is also ascribed to biological responses of the body with BoNTA, more specifically the inhibition of release of substance P, calcitonin gene-related peptide (CGRP), glutamate and lower transient receptor potential vanilloid (TRP1), all of which are local neuropeptides that mediate neuromuscular junction and muscle fiber actions. These two mechanisms lead to a reduction of pain-inducing substances such as prostaglandins and consequent lower pain rating.[17,18] Moreover, the absence of any difference between the magnitude of pain relief between muscle-based and non-muscle-based pain suggests that there might be independent toxin-induced pain relief processes from either muscle or nerve hyperactivity.[20]

In a cross-sectional study that aimed to explore the association between the experience of pain and spasticity, 80% of patients deemed that their pain was spasticity-related. Furthermore, 62% claimed that the pain they experienced was reduced by BoNTA treatment.[12] The Adult Spasticity International REgistry (ASPIRE), a multicenter, prospective observational registry of patients being treated with onabotulinum toxin A, showed that BoNTA significantly reduced patient-reported spasticity-related pain.[21] This is a vital finding since spasticity-related pain has been associated with poor quality of life and diminished occupational productivity.[10,21]

Approximately three-fifths of post-stroke patients develop shoulder spasticity, of which three-fifths experience pain around the area involved; the severity of shoulder pain was associated with the degree of spasticity.[22] In two large-scale, international clinical trials involving patients with upper limb spasticity receiving abobotulinum toxin A injection – the Upper Limb International Spasticity Study-II (ULIS-II) and Adult Upper Limb (AUL) open-label study – it was shown that shoulder pain relief was the primary treatment goal of those requiring BoNT injections. In both ULIS-II and AUL, those in the shoulder population attained significant improvements in passive and active function, respectively, as well as pain and range of motion.[22] This further alludes that spasticity causes shoulder pain in these patients and exemplifies that the abobotulinum toxin A injection improves outcomes in adults with spasticity.

Botulinum Toxin in Post-Stroke Spasticity

The safety and effectiveness of BoNTA in improving upper and lower limb muscle tone post-stroke is well-established.[2,15] This ability to reduce muscle tone via chemodenervation (neural component) of injected hyperactive muscles and thereby preclude eventual complications resulting from non-neural components such as contractures is the rationale of BoNTA use in PSS.[2,19] This benefit with the use of BoNTA is sustained even after several treatment cycles, hence it has been a first-line treatment in focal and multifocal spasticity states.[15]

It is a current and well-established practice to initiate BoNT injections in the chronic stroke stage (>6 months, 2.5 years on average) when the muscle overactivity is already obvious and troublesome to the patient, causing functional impairment, disability or pain.[6,7] At this point, non-neural rheologic changes have already ensued.[15] This contrasts with the advocated role of early BoNTA injection in preventing the development of contractures by an earlier international consensus statement [23] followed by a group of experts who sought how to improve current practice in spastic paresis.[24]

The almost exclusive coexistence of paresis with spasticity is taken into consideration in the dosing of BoNT and means that functional improvement may be less appreciated by the patient. Treatment goals in spasticity are thereby geared towards the reduction of pain, prevention of contractures and facilitation of physical rehabilitative interventions.[5] This may be attained with early intervention with BoNT, that is, less than three months post-stroke onset.[2]

Botulinum Toxin with Adjunctive Therapy in Post-Stroke Spasticity

BoNTA is established as an integral part of spasticity management and should be followed with a rehabilitation program.[14] An adjunctive therapy such as CIMT and ESWT may also benefit PSS patients.[14,25,26] A recent systematic review of two RCTs showed that all patients in the BoNT-CIMT

combination therapy showed improvements in their upper limb spasticity compared to baseline results, although not statistically significant.[25] The motor functional activities and ADLs significantly improved in both RCT investigations. However, the available BoNT-CIMT trials have not addressed dosage or treatment methods.[14,25] With long-term, multicenter robustly planned RCTs having a good sample size, it is still necessary to investigate if the BoNT-CIMT combination is more beneficial than standard therapy for reducing PSS. The BoNT-CIMT combination, however, shows promise for enhancing ADLs and motor function recovery.

A recently published meta-analysis demonstrated the effectiveness of ESWT coupled with BoNTA, as a novel therapeutic option, in lowering spasticity, pain severity and spasm frequency in post-stroke, multiple sclerosis and cerebral palsy patients while retaining a satisfactory safety profile.[14,26] These findings need to be further supported by high-caliber studies with a larger participant pool and appropriate study designs.

Early Use of Botulinum Toxin in PSS

Several well-conducted RCTs have observed the safety and efficacy of BoNT treatment in the acute to sub-acute phases (less than 3 months post ictus) of stroke recovery.[27] These studies demonstrated significant reduction of spasticity at weeks 4 and 12 post-injection and that early intervention with BoNT is well-tolerated by and does not hinder the functional recovery of post-stroke patients.[27] Moreover, for the BoNT-naive subset of patients in the early-BIRD study, there was a numerically larger reduction in the mean MAS scores in the early start compared to late start patients from their 2nd to their 5th (last) visit despite a slightly lower baseline.[27] A meta-analysis of early BoNT intervention in post-stroke patients demonstrated a substantial treatment effect on the reduction of hypertonicity when comparing the most affected joint (or overall) at the most improved time-point between weeks 4 and 12 for all six studies.[28] Early use of BoNT may modify or even break the vicious cycle of spasticity and weakness, facilitating motor recovery.[7] Early BoNT injection, through its chemodenervation effects on extrafusal fibers and muscle spindles/intrafusal fibers, may aid physiotherapy in terms of extending the window time for motor re-learning.[18]

Aside from modifying the natural progression of spasticity, another advantage of early BoNT use is a longer time interval before subsequent dose requirements. An exploratory randomized controlled study showed that early injection of abobotulinum toxin A in post-stroke patients both improves muscle tone and delays the time to symptom development or progression, hence delaying the time to re-injection.[4] A large retrospective study on BoNT and patients with PSS revealed a significantly longer time interval to reinjection of 23.1 weeks in the early start group (received first BoNT dose <3 months post-stroke) compared to 14.6 weeks in the late start group (received first BoNT dose >3 months post ictus).[7] Interestingly, in this study, comparatively higher doses of BoNTA were applied in the early intervention group compared to the late intervention group.[7] Figure 1 shows the predicted effect on spasticity of BoNTA injection on early start versus late start PSS patients using the trend of spasticity reduction over the span of five injection visits in the early-BIRD study, overlapped with intervals-to-reinjection demonstrated in the retrospective study. The solid black line shows the reduction of spasticity in post-stroke patients that receive early BoNTA, with the advantage of longer re-injection intervals. The broken gray lines represent the late-start PSS patient projected trend. The unfilled black and gray dots represent the time of re-injection.

A recent international, multicenter, non-interventional, prospective, longitudinal study on BoNTA use and upper limb spasticity, which categorized patients into three subgroups (early-start, medium-start or late start), demonstrated that spasticity-related pain, rated using a numeric pain rating scale, improved in all subgroups, most especially in the early start group, that by the fifth visit, no patient reported extreme pain in the said group.[27] The patients in the late start group had almost the same pain scores over time, while the early start group demonstrated reduction in pain rating. Furthermore, a meta-analysis of patients whose onset of stroke was ≤3 months before BoNTA intervention showed a trend favoring pain reduction at week 4, in those that had initial spasticity-related pain.[28,29] Figure 2 shows the predicted effect on spasticity-related pain of BoNTA administration on early start versus late start PSS patients, again using the trend of the early-BIRD study over the course of five injection visits, overlapped with intervals-to-

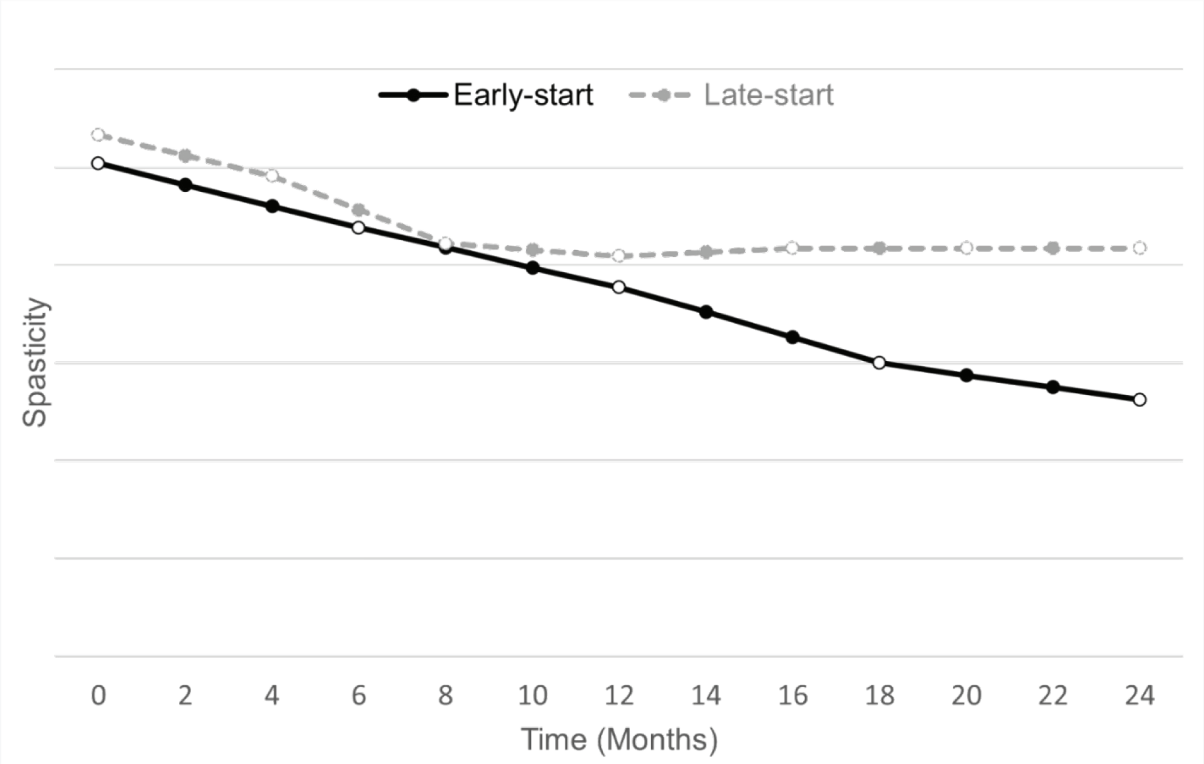

Figure 1 BoNTA re-injection interval with projected effect on Spasticity

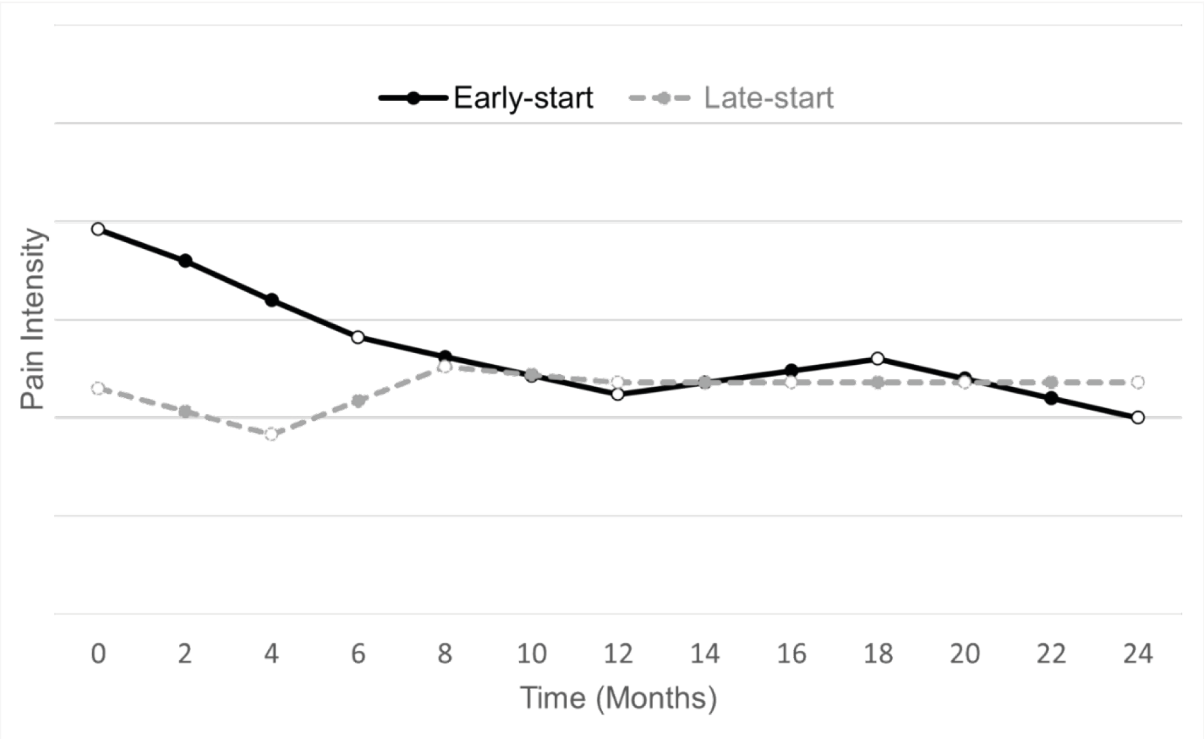

Figure 2 BoNTA re-injection interval with projected effect on Pain

reinjection exhibited in the retrospective study. The solid black line shows the reduction of pain in PSS that received early BoNTA, along with the advantage of longer re-injection intervals. The broken gray lines represent the late start PSS patient projected trend of pain intensity, showing a stable effect in the latter injections. The unfilled black and gray dots represent the time of re-injection.

CONCLUSION

Most patients who develop spasticity post stroke experience muscle-based and non-muscle-based pain and this negatively affects the patient's quality of life and aggravates caregiver burden. Spasticity if left untreated, leads to several complications related to limited mobility, both motor (eg, contractures) and non-motor (cognitive decline, depression). It is therefore imperative to address this with means that are proven safe and effective such as botulinum toxin injection, as early as possible. Adjunctive therapy also benefits PSS patients receiving BoNT such as conventional rehabilitation therapy, CIMT and ESWT. The timing of BoNT administration is a significant factor with several systematic reviews of well-conducted trials demonstrating a favor towards early intervention (<3 months post-stroke) over delayed treatment in terms of its more marked effect in spasticity and spasticity-related pain reduction and a longer re-injection interval.

The researcher recognized that the soundness of predictions of spasticity and pain control and interval-to-reinjection is limited since these were only based on observational studies. Further high-quality prospective longitudinal and RCTs with a larger number of subjects are needed to provide a more robust argument in recommending early BoNTA administration in PSS patients.

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