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Botulinum Toxin for the Treatment of Leg Spasticity in Children with Cerebral Palsy

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Abstract

Cerebral palsy affects 3 out of every 1000 children in the United States. It is multifactorial and not fully understood. What is known is that most of the cerebral palsy cases are congenital and the majority of motor dysfunction is classified as spastic. Over the last 25 years botulinum toxin has been a part of the first line treatment in children with spasticity. The purpose of this literature review is to determine if botulinum toxin is as safe and effective compared to a placebo or therapy alone in children. Key words and mesh terms were used in AccessMedicine, Cochrane Review, Pubmed, CINAHL complete, and Ebsco databases to find studies within the last five years that focused on pediatric participants with cerebral palsy and lower limb spasticity. Narrowing the search down brought 12 articles that were not sponsored by drug companies, realized their own limitations, and were focused on pediatric patients with lower extremity spasticity. Areas that were focused on include gait and motor function, safety of botulinum toxin, duration of injection, and combination therapy. The data shows botulinum toxin when used as part of a comprehensive rehabilitation program is most beneficial by delayed surgeries, reduced pain, and improved range of motion which improved gait in children under the age of seven. However, the dose, injection site, and repetition of injections should be individualized to each patient to minimize adverse events and be the most effective.

Keywords: botulinum toxin, cerebral palsy, spasticity, lower limb spasticity.

Botulinum Toxin for the Treatment of Leg Spasticity in Children with Cerebral Palsy

Botulinum toxin is produced by a bacterium called *Clostridium botulinum*. This toxin acts to prevent acetylcholine release in the neuromuscular junction blocking neuromuscular signals. Without the stimulation from the acetylcholine, the muscle decreases in tone and becomes weak. Botulinum toxin has been used in multiple facets including cosmetic, dermatologic, and neurological areas. Botulinum toxin type A (BoNT-A) is the most well-known subtype of this toxin and can be used for wrinkles, movement disorders, bladder dysfunction, and pain (Murray, C., & Solish, N., 2021). Over the last 25 years, BoNT-A has been considered the first line treatment in cerebral palsy patients with focal spasticity (Sätilä, H., 2020). Is this treatment still considered safe and effective for children with cerebral palsy?

Statement of the Problem

According to the CDC, cerebral palsy (CP) affects 1- 4 out of every 1000 children worldwide and is the most common motor disability in children. In the United States, CP affects 3 out of every 1000 children. The cause of CP has been found to be multifactorial and is not fully understood. The majority of CP cases are congenital rather than being acquired. CP can be classified based on the type of motor dysfunction including spasticity, dyskinesia, ataxia, or mixed. The most common of these is spasticity which makes up 80% of children diagnosed with CP. The term spasticity is used to describe muscles that have increased tone and are stiff. These stiffened muscles can create abnormal movements and a decreased range of motion. Secondary problems such as equinus deformities and balance difficulties can occur due to the movement disorders. Treating spasticity early can help prevent and correct deformities with the bones and joints (Cerebral Palsy, CDC 2020).

Research Question

In children with cerebral palsy and leg spasticity, is botulinum toxin as safe and effective compared to a placebo or therapy alone?

Methodology

A literature review of scholarly articles was conducted through databases in the North Dakota School of Medicine and Health Sciences which include AccessMedicine, Cochrane Review, Pubmed, CINAHL complete, and Ebsco. Key words and mesh terms were used to find literature discussing botulinum toxin and its use in spastic cerebral palsy. This search resulted in 953 articles. This was refined by excluding adults (anyone over 18 years of age) and upper extremity spasticity; leaving 96 articles. Most of the research and articles were published in the early 2000s since botulinum toxin became widely used in the 1990s for treatment of movement disorders. Due to the limited number of articles written in the last 3 years, the review on literature was increased to include articles published in the last 5 years. This left 90 articles in the search. Narrowing the search was done by selecting the articles that were not sponsored by drug companies and the articles that realized their own limitations which left 12 articles.

Literature Review

Comparing Gait and Gross Motor Functions

Children with spastic CP have stiffness and resistance in the muscles when passively stretched; this is called hypertonic stiffness (Skoutelis et al., 2020). There are two main factors for this; the factor that is focused on more is the reflex-mediated stiffness. With reflex-mediated stiffness, or spastic stiffness, the involuntary response of the muscle is due to hyperexcitability of the stretch reflex. Within the clinic this reflex-mediated stiffness leads to stereotyped movements, abnormal joint positions, and abnormal passive range of motion. This is classified as

dynamic contracture due to muscle shortening. Dynamic contractures along with muscle weakness, impaired motor control, fatigability, and impaired balance all cause impaired muscle stretching. Muscle stretching is needed for normal muscle growth. Children with spastic CP overtime have decreased range of motion due to secondary changes in structure, morphology, and stiffness in muscles. Spastic muscles are weaker, inelastic, thinner, shorter, and have longer tendons when compared to normal muscles. These changes in the muscles lead to the secondary changes in CP patients called static, or fixed, contractures. In children with CP, we are trying to prevent or reduce the possibility they develop these contractures (Skoutelis et al.).

A classification system was created to group individuals with CP to their varying degrees of limitations and abilities of movement. The widely used system is called the Gross Motor Function Classification System (GMFCS). There are five levels to help distinguish independence and mobility (Barkoudah et al., 2021). Level I, the individual can walk, climb stairs without assistance of a railing, and can run or jump. These individuals have limited speed, balance, and coordination. Level II individuals can walk in most settings but may have difficulty with long distances or uneven ground or incline, climb stairs using a railing, and have minimal ability to run or jump. These individuals may use hand-held or wheeled mobility devices over long distances. Individuals in level III can walk with hand-held devices in indoor settings, climb stairs with railing and supervision or assistance, and use wheeled mobility for long distances. Level IV individuals require physical assistance or powered mobility in most settings and may walk for short distances in home with physical assistance or a body support walker after being positioned. These individuals use wheelchairs outside of the home. Level V are the most limited individuals in mobility. They have a difficult time maintaining head and trunk posture and controlling leg

and arm movements. These individuals are transported in wheelchairs in all settings (Barkoudah et al.).

Varying studies use gross motor function measure (GMFM), goal scores, and physician global assessment to rate changes in motor function. The GMFM is a standardized evaluation specifically for children with CP that is conducted by a pediatric therapist to assess the five areas of gross motor function. Blumetti et al., (2019) explains the areas evaluated in GMFM are 1) lying and rolling, 2) sitting, 3) crawling and kneeling, 4) standing and walking, and 5) running and jumping. Another evaluation of motor function includes a goal score, which is a subjective assessment from either the patient or their caregiver. The physician global assessment is used to evaluate the response to treatment as determined by a physician's judgement (Blumetti et al., 2019).

When assessing gait, video gait analysis and physician rating scale are more commonly utilized. Both assessments can be slowed down to be analyzed and have been found to be more accurate when used consistently according to Blumetti et al. Video gait analysis records the patient walking, and the movement is analyzed by software. Physician rating scale also uses a video of the patient walking that can be slowed down and evaluated by an observer, usually a physician.

Within the Cochrane library, Blumetti et al. reviewed 12 randomized controlled studies for BoNT-A injections versus a placebo in children with CP from birth to age 19. Four of these studies were able to be analyzed together in the meta-analysis to assess gait as a primary outcome. Physician rating scale was used in two of the studies while video gait analysis was used in the other two. These studies showed BoNT-A improved gait in both a short (2-8 weeks) term follow up with a p value of 0.006 and medium (12-16 weeks) term follow up with a p value of <

0.001. Long term follow ups were excluded for gait measurement in these studies (Blumetti et al., 2019). Physician rating scale may not be as accurate at grading improvement of gait compared to video gait analysis, especially with the variability between different observers. It would be recommended to have the same observer for all follow ups to provide consistency in analysis.

Function was included in 8 of the studies reviewed by Cochrane. These were divided into two groups. One group looked at standard measures and the other looked at individual measures. Standard measures focused on gross motor function measure. Cochrane showed there were no differences in BoNT-A versus a placebo for short, medium, or long (>24 weeks) term follow ups when the studies utilized standard measures such as GMFM. However, the individual measures using goal attainment scale or physician global assessment showed differences in short and medium follow ups (Blumetti et al., 2019).

When using the GAS and PGA there are a variety of potential results, including the potential for a placebo effect in which they may believe the patient received the BoNT-A injection when they did not. To reduce the variety of possible subjective findings, standardized measures should be used to ensure clear cut evaluations of patients that can be reproduced or reevaluated by another individual. Using individual measurements for each patient would be much harder to reproduce or equalize across the study populations.

A small retrospective study by Read et al. (2017) included 17 ambulatory participants with bilateral lower limb spastic CP. The participants were either in the GMFCS I or II category based on their independence and mobility status. To be included in this study the children did not receive BoNT-A prior to their baseline assessment, had received 3 cycles of BoNT-A for their ankle equinus gait, did not use orthotics, and were assessed before and after each injection using

2D video gait assessment. Injections were given on mean 7.7 months apart with post assessment done on mean 12.6 weeks after the injection (Read et al., 2017). This study was used to assess changes in gait with multiple injections.

Read et al. showed post vs pre improvement in gait with the first treatment cycle. The second and third post vs pre gait showed no significant improvement. However, gait quality was maintained between the second and third treatment. These results are analogous to other studies showing the most improvement is seen after the initial BoNT-A injection.

Since Read et al.'s study was retrospective there was not a control group that received a placebo or withheld an injection preceding measuring patients' gait. The authors acknowledge this cannot exclude whether their outcomes were from the natural course of gait of patients with CP or if it was because of the BoNT-A injections. In addition, some participants received physiotherapy, additional injections in the hip abductor, or lower limb casting (Read et al.2017).

Similarly, Choi et al. (2019) performed a retrospective study. However, Choi et al.'s study was more inclusive of children with CP because the focus was the functional gain of the patient. This study included a total of 919 injections of BoNT-A in 591 children with lower limb spasticity. Ages ranged from 2-13 years old but what makes this a more inclusive study is that GMFS levels I-V were included. Since Choi et al. was assessing functional improvement, children who were non-ambulatory were included within the study, specifically 26.4% of the participants were considered non-ambulatory.

GMFM was used to assess short and midterm follow-up. The ambulatory groups showed improvement at both the 1-2 month and 3-6 months assessments. The non-ambulatory groups only showed improvement in the first follow up at 1-2 months. The gross motor changes in this retrospective study were associated with the patient's age at injection along with injection type

(Choi et al.). The non-ambulatory children with CP might not show an improvement in the GMFM scores but reduction in spasticity may reduce pain, prolong hip surgery, or improve daily therapy goals. Other rating scales and studies should be considered in pediatric CP patients who are non-ambulatory as the gross motor functions are vastly different between the GMFS levels I and V.

In another study, Multani et al., (2019), they reviewed Cohort studies, systematic reviews, and evidence statements. Multani et al. found that children with CP younger than 4 years of age had the most clinical improvement with BoNT-A injections. Their study also shows BoNT-A has little or no benefit for CP patients after 6 years of age. Multani el al. points out that gains are more positive in the short term, however, there aren't enough long-term studies done to verify long lasting gait improvement or patient independence. This appears true in non-ambulatory pediatrics with CP. BoNT-A injections did not appear to prevent operations for hip displacement or change in the morphology. It only prolonged when the patient had to undergo the procedures (Multani et al., 2019).

Safety of botulinum toxin

An observational study from Swinney et al. (2018) was used to document if severity of CP has a relationship with adverse events during or after the BoNT-A injections. Participants were separated into different groups based on their GMFCS levels I-V. Swinney et al. defined systemic reactions as "lower respiratory illness, generalized weakness, dysphagia, and death". A total of 591 children with only a diagnosis of CP were followed after BoNT-A injections. In this sample size, there were a total of 2,219 injections. The children had multiple injection visits with the median being four injections. Within this group, the injector would directly observe for

adverse events at the time of the injection and then follow up reporting of adverse events reported by a parent or a caregiver (Swinney et al.).

During the injection, the most common adverse events included pain, distress, nausea or vomiting. Comparing GMFCS levels, there was only a significant difference in distress while receiving the BoNT-A injection. GMFCS level III showed more distress compared to level I (Swinney et al.). Level III individuals are more likely to have increased hypertonia compared to level I individuals. The stiffness of the muscles may affect distress as the injections are given.

In addition, level V had less distress during the injections compared to level I. Swinney et al. notes conscious sedation, topical anesthetic creams, or occasional general anesthetic were used for the patients. This could also account for the differences in response to the injections. It was never stated which participant received higher forms of anesthetic during injections or if it was randomized. Comparing distress among participants in this study is difficult due to the lack of consistent anesthetic used prior to injections and may have caused inconsistent findings.

Follow ups were conducted between days 21-35 post injection. The most common adverse events included bruising, upper respiratory infections, local weakness, pain, and flu-like illness. The study shows GMFCS level III had less local weakness and pain compared to level I. Comparing systemic adverse events with GMFCS level I, there was a significant increase in levels IV and V. GMFCS V showed increased generalized weakness and higher rates of lower respiratory tract illnesses. There was one death reported which occurred in a patient who received the injection as part of palliative care and two hospitalizations that were unclear if BoNT-A was a contributing factor. Overall, the study shows an adverse event of 5.9 per 100 injections during the initial procedure and 22.8 per 100 adverse events discovered during follow

up. Most of the adverse events are mild and transient such as distress, bruising, or localized weakness (Swinney et al.).

Swinney et al. relied on observation during the injection to determine pain and distress. It was not specified what counted as pain or distress during the injections. Observations that may have been classified as pain or distress could include the child speaking up saying they had pain, the child grimacing, or yelling. Follow up was vague, which consisted of a questionnaire the caregivers answered and not all participants had a face-to-face meeting to see the injection site. Pain is subjective and hard to rate not only by the participants but by the parents or caregivers.

In addition, the study was comparing GMFCS groups for a potential increase of adverse events with increasing levels on the GMFC scale. As the levels increase the more advanced the condition the patients have and the more likely they are to have comorbidities. Even though the study screened the patients for only being diagnosed with CP, it is possible other conditions developed during the study. This makes it more likely that the levels IV and V would have more complications.

Going even further than Swinney et al., Paget et al. (2018) examined what other factors the patients had that would explain a higher rate of adverse events. To begin, prior to injection EMLA cream or nitrous oxide sedation is used. Some of the children do get additional sedation such as midazolam, but only a few. Nowhere within the study is it documented as to what methods were used to determine what anesthetic the participants did or did not receive.

Taking a closer look at the variables showed that children with a history of dysphagia, gastrostomy, or a history of aspiration pneumonia were more likely to have systemic adverse events. Children in levels of GMCFS IV and V are more likely to have these predisposing factors, however, not all the children in these classifications have dysphagia or aspiration

pneumonia. Even though there is minimal risk of adverse reactions we still want to minimize the possibility of systemic adverse events. Therefore, a thorough history on all patients is important to help minimize adverse events (Paget et al. 2018). The limits of this study include not all the factors that could contribute to increased systemic adverse effects were included in evaluation.

Another review looking at adverse events of BoNT-A was done by Multani et al., (2019). Minor adverse events include site injection pain and local muscle weakness. Systemic adverse events were low, between 1-5% in ambulatory children. These included transient bowel or bladder incontinence, pharyngeal or esophageal sphincter paralysis (Multani et al., 2019). In review, it appears that more systemic and harmful effects of BoNT-A injections occur in the general clinical setting due to more variations in dosing and technique. Therefore, it is best to have injections done by a trained provider who can adjust dose, can find the correct injection placement using imaging guidance or landmarks, and knows the higher risk factors for systemic events. Another adverse event that was noted throughout the literature is muscle atrophy. There have not been long term studies for muscle atrophy or fibrosis after BoNT-A injections to measure the degree of muscle recovery or reduction in function due to fibrosis after these patients are adults.

Duration of Effects and Repeating Botulism Toxin Injections

The neuromuscular junction recovers after BoNT-A injection due to sprouts developing from the end plate and the preterminal axon. Satila (2020) reports these sprouts activate the muscle 4 weeks after BoNT-A injection and the original terminal axon regains function after 3 months. The neuromuscular junction can recover many times without loss or destruction of the function, thus the rationale behind repeat injections of BoNT-A.

BoNT-A results in muscle atrophy with the loss of volume peaking between 1-3 months. It is during this time that the muscle begins to recover. Studies have shown that in 1 year the muscles either fully or almost fully return to their original volume. Satila's (2020) review concluded that dose sizes and intervals between injections should be individualized with rehabilitation and other treatments based on each individual patient. Further studies are needed to examine the possibility of any further muscle growth inhibition beyond the 3-month mark. Longitudinal studies of pediatric patients that received BoNT-A have not been completed to assess their quality of life once they reach adulthood.

In another study, Mirska et al. (2019) looked at 60 pediatric patients that ranged from 2 to 16 years old with varying degrees of CP. BoNT-A was injected into the calf muscles with intervals between injections varying from 3-66 months. The patients were assessed with the Modified Ashworth Scale, Physician Rating Scale (PRS), passive range of motion with the ankle extended and the flexed knee joint. In this study, PRS improvements lasted 3 months. This showed that the number of injections did not have any effect on the improvement rate. In addition, this showed the largest gains in gait and muscle tone were achieved in the children under 7 years of age.

Mirska et al. showed the importance of early interventions for children with CP and additional injections that can be repeated every 3-6 months. Less injections would be less traumatic on the patients in addition to their families. If a patient's function can be improved with less needle sticks, there is a chance the children won't dread their appointments and their families can see the improvement more than any pain or distress invoked by the injections.

Combined Therapy in the Treatment of Spasticity

Schasfoort et al, (2018) had a total of 65 children that participated in a single-blind, partly randomized, comparative trial that included 41 of the children receiving BoNT-A injections prior to comprehensive rehabilitation, while the other 24 children only received rehabilitation. Assessments were done at baseline, 12 weeks and then again at 24 weeks. To make note, the ages ranged from 4-12 years with the mean age of 7.3. The study attempted to have the assessors blinded as to which child was receiving the injections. However, the randomization of the children into the two groups did not happen as assigned because families threatened to not participate in the study unless their child was in a preferred group. Therefore, Schasfoort et al. allowed the children to switch groups to pacify the families to have the participants remain in the study, thus placing the study at risk of biases.

There were only 2 findings of significance in this study. The kinematic gait improved with maximum knee angle while walking barefoot after the BoNT-A. The other finding was when the rectus femoris was targeted as the hypertonic muscle, it was better in the patients with comprehensive rehabilitation only. All the other outcomes measured in this study did not show a difference in follow up compared to baseline when rehabilitation was used alone versus when BoNT-A injections were added to the regimen (Schasfoort et al., 2018).

The mean average age of patients was 7 years old. If CP children decline in mobility at 7 years of age this study would not show any benefit of BoNT-A injections with physiotherapy or casting. Early interventions begin at earlier ages and this study should have included a younger population to be more beneficial to the CP population.

A study by Çağlar et al. (2019) conducted a prospective randomized controlled study with 30 patients between the ages of 2 and 15. Half of them had lower extremity muscles injected

with BoNT-A under ultrasound guidance. The muscle groups were selected based on the spastic muscles used in walking. Splinting was applied after injections and then a rehabilitation program was started. The program was a total of 20 sessions, each lasting 2 hours and taught to the families to continue at home. Even though the control group did not receive BoNT-A, they did undergo splinting and the same rehabilitation program. This same group did not receive local or oral antispastics either.

Patients were assessed on initiation of the study and then again on the fourth and twelfth weeks by using the Modified Ashworth and Tardieu Scales. In contrast to Schasfoort et al. (2018), Caglar et al. found the group that used BoNT-A and the rehabilitation program had improved scores in the Modified Ashworth, Tardieu Scales, GMFCS, Goal attainment scale and visual assessment scale. Though, both groups showed a reduction in pain at 4 weeks after starting the rehabilitation program. The study concluded that BoNT-A injection was effective at reducing the spasticity in patients with CP. However, the most significant finding was that all patients benefited from a rehabilitation program. Therefore, physiotherapy should be implemented in all CP patients (Çağlar et al., 2019).

Bussmann et al. (2020) conducted a study to look at the cost effectiveness of comprehensive rehabilitation alone compared to BoNT-A added to the program. The study was designed to be a randomized control trial measuring motor, gait, and quality of life of ambulatory pediatric CP patients. These were measured at the end of the study at 3 months and then a follow up at 6 months. However, there was pushback from the participants' parents who strongly preferred the trial of BoNT-A before starting the rehabilitation program. Therefore, 60% of the participants were assigned to a group rather than being randomized.

In contrast to other studies, this one concluded that there was no difference in the primary or secondary measures between the two groups at 3 or 6 months. Bussman et al. admits there were problems with the methodology of the study with the major concern being participants not randomized into the groups. Even so, the study still reports there is no added benefit of the BoNT-A prior to the rehabilitation which is not what has been found in other studies. Consequently, the results have not been accepted or recognized in the scientific community. Methodology along with the median age group for this study plays a large role why this study is met with skepticism. Although, it is mentioned there needs to be randomized-controlled trails that also look at dose-response of BoNT-A along with rehabilitation.

Discussion

The evidence presented in this literature review support the idea that botulinum toxin type A will continue to be a first line therapy included in the comprehensive therapy plan in children with spastic cerebral palsy. Botulinum toxin type A is likely to be the most beneficial for children under the age of 7 due to musculoskeletal development and those patients without a history of aspiration or dysphagia. Botulinum toxin type A is safe with weight-based dosing and when injected by experienced individuals who can utilize landmarks or image guidance. Overall, the decision to include botulinum toxin type A injections needs to be individualized based on history of the patient and potential risk factors of each patient. When started with an early intervention, botulinum toxin can decrease spasticity which has positive results on patients' gait and increased range of motion that improve short term goals. These improvements in gait and range of motion have the potential to delay surgical interventions. An abundance of research has been conducted on the short-term effectiveness of botulism toxin type A in children with spastic

CP. However, there needs to be more longitudinal studies to see how these injections given at a young age impact patients' quality of life as they grow older.

Applicability to Clinical Practice

After the literature review, botulinum toxin type A injections should continue to be included as part of the comprehensive therapy program for children with spastic cerebral palsy. Similar to other developmental conditions, it is important for primary care providers to carefully assess children at every well child visit. Early intervention and referrals for these children can improve quality of life for them and their families. The younger the patient can start utilizing botulinum toxin injections and a rehab program, the sooner spasticity can be treated, and the more bone or joint deformities can be prevented and slowed; thus providing a greater quality of life to patients with cerebral palsy.

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