Critically Appraised Topic

The Use of Botulinum Toxin Injections for the Treatment of Restless Legs Syndrome

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Clinical Scenario: Ella is a 58 year old female who was diagnosed with Restless Leg Syndrome 6 months ago. Ella has been taking 3mg of Requip a day at suppertime for the last 3 months, and 100mg of Tramadol for leg pain every 4-6 hours as needed. Patient explains that she is still having sleepless nights due to the urge to move her legs with or without sensations when in bed Ella explains that the Tramadol does help her pain but she often finds herself awake walking around her house to stop the sensation of movement to her lower extremities. Patient explains that she rarely has the symptom of the urge to move her lower extremities during the day time, but she if often exhausted, moody and unable to complete all the tasks she is planning to complete at her job. Ella's restless nights are also putting a strain on her marriage. Ella's husband is tired of her always walking him up by her interrupted sleep, making him often exhausted at work. Ella saw her primary provider a month ago asking for a sleep aid since she had no luck with over the counter agents. Ella was prescribed Ambien CR 6.25mg PO at bedtime for insomnia. Patient did not like how the medication made her feel. She explained she did sleep a little better but should felt more aggressive and drowsy during the day. Patient has no known food, environmental or drug allergies.

Clinical Questions: Would an intramuscular injection of botulinum toxin in the legs relieve the uncomfortable sensations that patients have restless leg syndrome?

Articles:

Fatta, B. N., Peckham, E. L.,Hallett, M. (2008). Double-blind, placebo-controlled pilot trial of botulinum toxin a in restless leg syndrome. *Neurology*, 71(12), 950-951.

Rotenberg, J. S., Canard, K., Difazio, M. (2006). Successful treatment of recalcitrant restless legs syndrome with botulinum toxin a. *Journal of Clinical Sleep Medicine*, 15 (2), 275-278.

Summary and Appraisal of Key Evidence:

In the article by Fatta, Nahab and Hallett six patients were enrolled from June to July of 2007, who had a at least a moderately severe case of Restless Leg Syndrome. Diagnosis was based in the International Restless Legs Syndrome Study Group (IRLSSG).The patients were enrolled in this study to assess the effectiveness of an intramuscular injection of Botulinum toxin on reducing RLS symptom improvement, reduced medication use and reduction in daytime sleepiness, compared to the injection of a placebo of sterile saline. After injection the participants were injection they were scaled on the IRLSSG scale at weeks 2 and 4 and compared to baseline results. On week 2 placebo treated patients noted a 5.0 +/- 5.1 point improvement on the IRLSSG compared to the BTX-A injected group that only had a 1.0 +/- 3.5 improvement. On week 4 the BTX-A group has a increase of 5.0 +/- 6.0 improvement from baseline compared to the placebo group that had a 2.7 +/- 5.9 improvement from baseline. Weaknesses of this study involve the number of participants, the length of time monitoring for effectiveness and adverse

effects, the race of the participants was not included, the perception of pain can vary per individual when being assessed, 5 patients were on a dopamine agonist and one patient was on clonazapam before the study, and the age range was limited. The strengths of the study included: equal ratio of male to female participants, those receiving the BTX-A injection all received the same dose at the same locations, patient's were graded so they all had similar levels of RLS, none of the patients has received BTX-A injections before, and all patients underwent the same evaluation to assess whether they could be participants in the study.

The level of evidence of this article is 2a with a grade B since the study involved a non-randomized control group, had a well matched group, having participants similar based on their IRLSSG rating for RLS, and the study had less than 30 participants.(Levels, 2002). The study demonstrated homogeneity with other studies. The study also demonstrated a high quality prognostic cohort study because greater than 80% of the outcomes were measured in participants.(Levels, 2002). Internal validity is valid in the sense that all BTX-A injections were the same dose, given in the same locations and results were scaled on the IRLSSG for all participants. External validity is questionable because race, weight, geographical status was not assessed as well as other comorbidities. The threats of the study involve a small testing population, and an insufficient duration of time to measure long term effects. The opportunity this study can provide based on results is treatment for patients of RLS symptoms without using opioids or benzodiazepines for relief of symptoms.

In 2006, Canard and Marc conducted a study on three individuals that met the diagnostic criteria for RLS. Response of the study was assessed clinically, by the Epworth Sleepiness Scale or by the need for medication use of the participants. The participants in the study used various interventions for treatment of their RLS such as: C-pap machine, aspirin, Tylenol, gapapentin, opioids, and bendiazapines In the study three participants were followed for up to a period of two years after the use of BTX-A injections. All participants had injections to lower extremities in several locations, and one participant received an injection in his gastrocnemii and in his lumbar paraspinal muscles. The total amount of BTX-A injected in the participants ranged from 70-320 units/cc. All patients found relief from symptoms of RLS within days of injection. One individual found relief of symptoms of RLS for 12 weeks after 3 subsequent injection cycles. One patient was able to reduce gapapentin usage by 50%. Another individual was able to stop taking gapapentin and opiates for RLS symptoms, had complete relief of lower extremity symptoms and continues to receive BTX-A injections every three months. Weaknesses of the study involve: the limited number of participants, unequal male to female ratio, different doses of BTX-A were given to different participants, BTX-A was given in different locations depending on the participants, participants were on various medications and practiced various interventions to reduce RLS symptoms during the study, and a set time period for evaluation was not established . Strengths of the study involved all patients having to go through the same evaluation process before the study began, all participants met the diagnosing criteria for RLS, and participants were followed for up to 2 years based on success of injections.

The level of evidence of the study is 4 with a grade of C because there is a poor quality of the prognostic studies and a limited number of participants.(Levels, 2002). A poor quality cohort study was conducted because the study failed to clearly measure exposures and outcomes in the participants, and sufficient and long-term follow-up was not completed on all individuals of the study.(Levels, 2002). Internal validity is compromised because the dose and location of the BTX-A injection varied per

participant, how the participants were selected, how the results were recorded and how the analysis of success was determined. External validity is also compromised for this study because race, weight, and geographical status, comorbidities and age range were not considered due to lack of strict protocol for design of the study. The threats of the study include that it was only conducted on three participants, the study was not well controlled, and results for each case were recorded in different time periods. The opportunity this study provides is that the results from the study could be beneficial to patients that suffer the movement and sensation symptoms from RLS. Patients of RLS could benefit from an injection every few months to provide relief from their symptoms without taking opioids or benzodiazepines.

Clinical bottom Line:

1. The group members from both studies are similar in that they share the diagnosis of RLS, but may share different levels of the disease since the levels of the disease in the second study were not completed. Due to the small number of participants in the studies, limited long term study or incomplete results of long term use of BTX-A injections indicate a poor quality of research. During the studies conducted no adverse effects were reported and majority of patients had symptom relief with injections.

2. First line therapy for RLS is dopaminegerics, but they may be problematic regarding long term use. Other medications that patients with RLS turn to for symptom relief includes: opioids, benzodiazepines, and antiepiletics, which can be costly, cause addiction and provide adverse effects. (Ondo, 2008).

3. Internal validity was more complete with the study completed by Fatta, Nahab and Hallett, due to analyzing RLS status and outcomes of BTX-A injections on the IRLSSG scale. Both studies had external validity compromised since, race, weight, comorbidities and geographical statuses were not assessed.

4.The use of BTX-A injections in practice once proven effective and safe could provide relief to patients that have the condition of RLS, reduce noncompliance of medication regime, reduce polypharmacy(especially in the elderly), reduce opioid and benzodiazepine addiction and dependence and increase quality of life in these patients.

References:

Levels of evidence-March 2002. (2002). Retrieved from http://www.eboncall.org/content/levels.html

Ondo. W. G. (2009). Restless legs syndrome. *Neurological Clinics*, 27(3). Retrieved from

http://www.mdconsult.com/das/article/body/189638121-4/jorg=clinics&source=MI&sp=22273743&sid=969344144/N/703226/1.html?issn=0733-8619