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Using botulinum toxin to treat diabetic foot pain

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WHAT DID THE AUTHORS STUDY? Botulinum toxin type A (BoNT/A) is made naturally by certain bacteria. BoNT/A works by paralyzing specific kinds of nerve cells. BoNT/A can be used to treat many illnesses that affect either nerves or the muscles with which they communicate. In the article “Botulinum Toxin for Diabetic Neuropathic Pain: A Randomized Double-Blind Crossover Trial,” Dr. Yuan and associates describe how BoNT/A might be used to treat the kind of nerve pain that develops in some people who have diabetes.¹ The study compares whether injecting BoNT/A into the skin is better at reducing neuropathic pain than injecting a placebo (saline, salt water) into the skin.

HOW WAS THE STUDY DONE? Dr. Yuan and colleagues looked carefully at 20 people who had neuropathic pain due to type 2 diabetes. Each person had been diagnosed with diabetes for at least 3 years. Patients with neuropathy experienced either paresthesias (prickling, tingling, or numbness) or a specific kind of pain (burning, itchy, shooting, etc.) in both of their feet up to the ankle or mid-shin. Doctors assessed the pain by 1) physical examination, 2) a specific questionnaire for pain, and 3) a specific test of nerve function. The nerve test is called a *nerve conduction velocity* test. It is designed to see how well patients’ nerves can transmit electrical signals. If the nerve is damaged, as happens in diabetes, the signals carried by the nerves are either slower or weaker than normal.

As in all studies, there are reasons to include specific participants. This makes sure that the group is alike and that the results are solid. For instance, only people with proven polyneuropathy due to diabetes were included. Since a specific treatment was being studied, only people who had not changed to other pain medications could be included. Otherwise, the doctors would not have known whether the study treatment improved the pain or if improvement was a result of changing to these other medications. Because alcoholism and kidney problems can both cause neuropathic pain, patients with these medical conditions could not be included.

Patients were randomly chosen to receive either BoNT/A or saline injections. The injections were

given at 12 evenly spaced sites in the skin on the tops of their feet. A nurse prepared the needles secretly in another room, so neither the patients nor the doctors knew whether they were injecting the toxin or the placebo. This is called a double-blind study. This was done so that the results of the study would not be affected by either the patients’ or the doctors’ expectations.

Three different tests of neuropathic pain symptoms were done before treatment. The tests were then repeated after the 1st, 4th, 8th, and 12th weeks of the study. This was done to see how well the treatments were working. The authors used a well-known pain scale (visual analog scale) as one measure of improvement. They also used a Chinese version of the Pittsburgh Sleep Quality Index, which is filled out by the patient. It is also filled out by the patient’s sleep partner. This provides the researchers with a number representing sleep difficulty. A higher number means worse sleep.

Third, the researchers used the Short Form-36, a questionnaire used to assess general quality of life. Another injection was given after the 12th week. This time patients were given whichever treatment—BoNT/A or saline—they had *not* been given in the first injection. In other words, each patient received *both* the treatment *and* the placebo. Called a *crossover design*, this allowed Dr. Yuan and colleagues to compare each patient’s response to both BoNT/A and placebo. Using this kind of study, they were able to show how the group did *as a whole*. Also, they could see how well each person responded to the pain treatment. This is a common study design that improves the strength of the study’s conclusions.

WHAT DID THE AUTHORS FIND? At the end of the study, Dr. Yuan and colleagues compared the change in scores between the treatment (BoNT/A) and placebo groups at the four time-points. After 4, 8, and 12 weeks, significant reductions in visual analog scale (pain) were seen in the BoNT/A group compared to the placebo group. Overall, 44.4% of the BoNT/A group vs 0% of the placebo group reported improved pain. These findings support the theory

that BoNT/A injections into the skin can help to relieve neuropathic pain in people with diabetes. However, the findings are not definite, and a larger study is needed.²

WHY ARE THE FINDINGS IMPORTANT? In 2003, the National Center for Chronic Disease Pre-

vention and Health Promotion predicted that one in three Americans born after the year 2000 would develop diabetes in their lifetime.³ In general, more than 25% of people with diabetes are estimated to suffer from diabetic neuropathy. This means there are many people who could benefit from new, effective treatments for neuropathic pain.

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About diabetic neuropathic pain

WHAT IS DIABETIC NEUROPATHIC PAIN? Diabetes prevents the body from processing sugars correctly. It leads to high levels of glucose (a sugar) in the blood. High blood glucose levels and circulation problems (common in people with diabetes) combine to damage nerves. The first nerves affected by diabetic neuropathy are sensory nerves of the feet and ankles. Later, as the nerve problem gets worse, it may spread up the body to involve the arms.

Unlike the pain felt when touching something very hot or sharp, which is triggered by tissue damage, neuropathic pain results directly from damage to the sensory nerves themselves. The damaged nerves attempt to repair themselves, but uncontrolled diabetes interferes with the repair system and the damage worsens. As this cycle continues, the nerves end up becoming overactive and too easily stimulated. Neuropathy and neuropathic pain then occurs, as pain nerves fire even when there is no physical stress.

WHAT DO DIABETIC NEUROPATHY AND NEUROPATHIC PAIN FEEL LIKE? Diabetic neuropathy changes the feeling in affected areas. Symptoms usually begin in the feet and go up the leg if the diabetes is not well-treated. As symptoms reach the mid-calf, they will often also appear in the hands and begin moving up the arms. Sensory symptoms of diabetic neuropathy include less sensation of vibration, temperature, and touch. When a person develops numbness, he or she may injure a foot and not realize it, leading to untreated wounds that become infected.

Neuropathic pain occurs in the same area as the nerve damage. The pain has a shooting, sharp, or burning quality. Some people describe a tingling or prickly feeling. Also, neuropathic pain is very sensitive to things that would normally not be painful. For example, a breath of cool air or a brush with a feather might trigger a stab of pain. Diabetic neuropathy often gets better with walking and worsens when the person is lying in bed or resting. Patients who suffer from this would benefit enormously from a successful treatment.

HOW IS NEUROPATHIC PAIN PREVENTED AND TREATED? The single most important way to pre-

vent diabetic neuropathy and the pain that goes with it is to control the blood sugar. People with diabetes should monitor their own blood sugar. They should also talk with their doctor if they are not able to control it. Hemoglobin A1c is a chemical marker in the blood that reflects how well-controlled a patient's blood sugar has been over the past 3 months. It has been shown that a 1% rise in this chemical was associated with a slowing of nerve conduction, which is a sign of neuropathy.⁴ This result suggests that poor control of blood sugar is directly associated with the development of neuropathy. This can lead to neuropathic pain. Proper diabetes care should include regular checks of blood sugar as well as hemoglobin A1c. Also, sensory examinations of the legs and feet to monitor for neuropathic changes are needed.

There are treatments for neuropathic pain, but none is perfect and many are associated with unpleasant side effects. Most studies show that fewer than 60% of people with this kind of pain experience *partial* improvement.² The only FDA-approved drugs for treating neuropathic pain are duloxetine (Cymbalta[®]), an antidepressant, and pregabalin (Lyrica[®]), an antiepileptic medication. Many pain specialists use drugs like oxycodone (an opioid, like morphine) and amitriptyline (a tricyclic antidepressant) with good results.

It is still unclear why some antidepressants and antiseizure medications are helpful in treating neuropathic pain. In part, this is because we do not understand exactly how neuropathic pain develops. As our grasp of the causes of neuropathy improve, so will the available therapies. Careful studies, such as this study of the use of BoNT/A, are critical in establishing which treatments work for this condition.

FOR MORE INFORMATION

National Institute of Neurological Disorders and Stroke

<http://www.ninds.nih.gov/disorders/diabetic/diabetic.htm>

American Diabetes Association

<http://www.diabetes.org/>

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