Novel Therapy Severe Post-Herpetic Neuralgia Successfully Treated with Botulinum Toxin A: Serial Cases

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ABSTRACT
This study discusses Post Herpetic Neuralgia (NPH), a common complication after shingles. NPH is characterized by pain that persists for 3 months after healing of the herpes zoster lesions. Studies show an association between increasing age and the incidence of NPH, with approximately 9-34% of herpes zoster patients experiencing NPH. The incidence is higher in the age group over 60 years. NPH causes chronic neuropathic pain and affects the patient's quality of life. The treatment of NPH is unclear, but multimodality therapy and botulinum toxin (BTX) may have good results. BTX works by reducing the release of pain and inflammatory mediators. Several studies have shown pain relief after using BTX in NPH patients. This study reported a series of post-herpetic neuralgia cases in a man, aged 59 years, a woman, aged 54 years, and a woman, aged 50 years. From anamnesis, complaints of pain in the back after the lesion onset were reported. Patients have similar complaints of pain, such as burning, pricking, and discomfort. Complaints of this pain vary between 1 and 3 months after the herpes zoster skin lesions have healed. This causes the patient to have difficulty sleeping at night and interferes with the patient's daily activities.

Keywords: Novel Therapy, Severe Post-Herpetic Neuralgia, Botulinum Toxin A

INTRODUCTION
Post Herpetic Neuralgia (NPH) is the most common complication of herpes zoster [1]. NPH is defined as pain that persists for 3 months after the herpes zoster lesion has healed. Several existing studies have found that there is a significant relationship between increasing age and the incidence of NPH. [2,3]
From the available data, it was found that 9-34% of herpes zoster patients will experience NPH [1]. The incidence of Herpes zoster is approximately 5.23 cases per 1000 persons, and the incidence of NPH is 0.4 cases per 1000 persons. NPH most often occurs in the elderly, and the incidence of NPH will increase sharply with age, where 3-4% occur at the age of 30-59 years, 21% at the age of 60-69 years, 29% at the age of 70-79 years, and 34% at the age of more than 80 years [4]. This occurs due to a decrease in cellular immunity. At the skin and genital polyclinic at Sanglah Hospital, Denpasar, it was found that there were 23 new cases of shingles during 2021 with 10 cases of NPH and 50% were aged over 50 years.
Pain in NPH is a type of neuropathic pain which manifests itself in the form of allodynia, hyperalgesia, intermittent pain in the form of a stabbing or cutting feeling or spontaneous pain, namely in the form of a burning feeling [5]. This pain can last continuously for years and can seriously interfere with quality of life such as interfere with sleep and daily activities thereby interfering with patient productivity. [5]
Adequate therapy for patients with NPH is needed to minimize this poor prognosis. So far there is no definite algorithm in the management of NPH patients. A multimodality approach, including a combination of topical and systemic medications, relaxation, and psychosocial interventions is sometimes needed produce better outcomes [6,9]. There are several alternative

therapies for NPH, Botulinum toxin (BTX) is one of the modalities that has the potential to have beneficial effects in the treatment of NPH. BTX is a neurotoxin protein produced by anaerobic bacteria of the genus Clostridium. There are around seven types of BTX that have been identified, but BTX-A and BTX-B are the types most widely used in the medical world [10]. BTX works by inhibiting the release of pain mediators from peripheral nerve endings and reduces inflammation so that it has the potential to treat NPH pain. Several studies have been conducted on NPH patients which showed significant improvement in pain intensity post BTX injection. The safety profile of using BTX-A for the treatment of neuropathic pain is generally good [11]. Therefore, it is important to learn more about the potency of botulinum toxin in neuropathic cases post herpes in the form of this literature review.

The following will report a case of post-herpetic neuralgia treated with botulinum toxin A injection. This case is reported because NPH cases are quite common but difficult to treat and to better understand the management of NPH with botulinum toxin A.

CASE SERIES

First Case

A man, 59 years old, Balinese, Indonesian citizen, married, with medical record number 21001622, came to the IGD of RSUP Prof. Dr. I. G. N. G. Ngurah on June 16, 2021 at the referral of Sp. KK with Neuralgia Post Post Herpetic.

Anamnesis is obtained by autoanamnesis with the patient and heteroanamnesis with the patient's family. The patient came with the main complaint of watery rashes. Complaints of watery resilience in patients since the previous 4 weeks. Initially, the patient admitted that he had a watery discharge that felt painful in that area and was diagnosed with shingles since he had been treated at Sp.KK. The patient was admitted to treatment 3 days after the appearance of the lesions and was given acyclovir 5x800 mg for 7 days but was not taken regularly according to the dosage. In addition, 3x1 tablets of mefenamic acid were given, 2x1 tablets of sedatives, and compressed fluids for infusion. Complaints of pain are said to be reduced but still felt intermittent in the area of the lesion. The patient then had time to go to another Sp.KK (after the lesion was dry) with complaints of pain in the former lesion and was given gabapentin 2x300 mg, amitriptyline 1x125 mg, and neurotropic vitamins but the pain has not improved. History of drug allergy and application of traditional oils was denied. Past medical history: vertigo, hypertension since August 2022. History of drug use: amlodipine 1x5 mg, acyclovir 5x800 mg, gabapentin 2x300 mg, mefenamic acid 3x500 mg, vit B6 1x1 tablet, amitriptyline 1x125 mg. History of other diseases such as diabetes, heart disease, or asthma was denied. History of drug allergy was denied.

Physical examination revealed good general condition with compost mentis awareness (Glasgow coma scale (GCS) E4V5M6). Vital signs obtained blood pressure 120/80 mmHg, pulse rate 72 times per minute, respiratory rate 16 times per minute, and axillary temperature 36.6 C. Anthropometric examination revealed a body weight of 65 kg with a height of 170 cm, and a body mass index of 22.4 kg/kg m2 (usual nutritional status). In general status, the head is normocephalic, there is no anemic conjunctiva and icteric sclera in both eyes. Examination of the ears, nose and throat did not reveal any abnormalities. There were no enlarged lymph nodes in the neck and axillae. Thoracic examination revealed single, regular heart sounds (BJ1 and BJ2), no murmurs and gallops and vesicular breath sounds, no crackles and wheezing was found in both lung fields. Abdominal examination revealed bowel sounds within normal limits, no enlargement of the liver and spleen, and no abdominal distension. On examination the extremities were warm and no edema was found.

Dermatological examination on the thoracoabdominalis anterior et posterior dextra and axila dextra multiple hyperpigmented patches with clear boundaries geographic shape measuring

1x3cm-8x10cm confluent as high as T1-T2. There were no atopic stigmata, mucosal abnormalities, hair abnormalities, nail abnormalities, sweat gland abnormalities, lymph node enlargement, or nerve enlargement. Visual Analog Scale (VAS) got a score of [8].

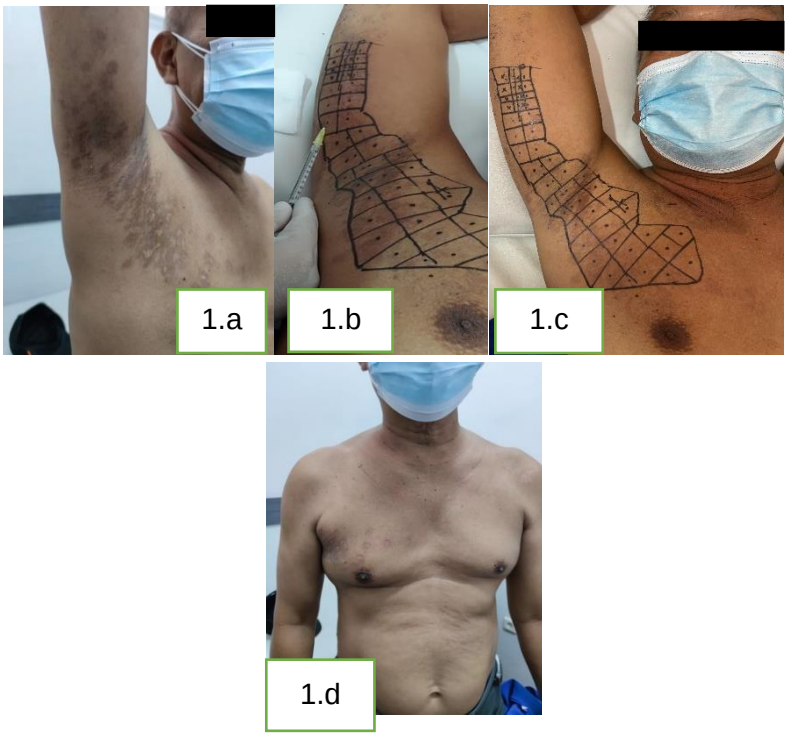

Figure 1.a-d multiple confluent hyperpigmented patches. 2.b Intradermal botulinum toxin injection technique.

The working diagnosis in the patient is neuralgia post herpetic. Management in patients is BTX-A with 0.1 cc containing 5 IU. vitamin B complex 1 tablet every 24 hours intraorally, and complete blood count, SGOT, SGPT, BUN, SC and GDS.
Complete Blood Results WBC 3,97, NE% 48,00, LY% 29,50, MO% 11,10, EO% 10,10, BA% 1,30, NE 1,91, LY# 1,17, MO # 0.44, EO# 0.40, BA# 0.05, RBC 3.53, HGB 11.30, HCT 34.00, MCV 96,30, MCH 32,00, MCHC 33,20, RDW 12,70, PLT 238,00, MPV 9,00, NLR 1,63. SGOT 24,7, SGPT 24,90, GDS 88, BUN 19,90, Creatinine 1,07, e-LFG 63,85.

Second Case
Female patient, 50 years old, Balinese ethnicity, Indonesian citizen with medical record number 18010960, on February 21 2022 came for control to the skin and genital polyclinic Sanglah General Hospital Denpasar with a history of herpes zoster on the right abdomen
From the anamnesis, there were complaints of pain in the right abdominal area since 10 days ago and it got worse 3 days before coming to the skin and genital polyclinic at Sanglah Hospital, Denpasar. Pain is felt continuously throughout the day. Patients complain of pain such as burning, pricking, and discomfort. This causes the patient to have difficulty sleeping at night and interferes with the patient's daily activities. The appearance of this pain 10 days ago was accompanied by the appearance of nodules filled with fluid on the right back and right armpit accompanied by fever. The patient then received therapy from a doctor in the form of:acyclovir 800 mg every 4.5 hours intra orally for 7 days, mefenamic acid 500 mg every 8 hours intra orally, compress NaCl 0.9% every 8 hours on erosion lesions and vitamins B1, B6, B12 every

24 hours intra orally. It is said that the watery nodule starts to break and becomes a scab and then becomes a wound and the wound heals on its own, it is said that the pain is increasing and sleep at night is still disturbed because of pain in the former shingles wound.
The patient had never had the same complaint before. The patient had chickenpox as a child. The patient has a history of lymph node cancer since 4 years ago at Sanglah Hospital every month. History of diabetes, high blood pressure in the patient and his family was denied. The patient is a pensioner. Prior to the appearance of the nodule complaints, the patient reported feeling tired because the patient was taking care of traditional ceremonies at his home
On physical examination, the patient's weight was 68 kg, height 165 cm, general condition was good and awareness of compos mentis. The patient's blood pressure is 100/70 mmHg, pulse rate is 88x/minute, respiratory rate is 20x/minute, axillary temperature is 36 c. Examination of the oral and genital mucosa was normal. Examination of nails and hair revealed no abnormalities.
Dermatologic status of the right abdominal location was found in fluorescence: Multiple hyperpigmented macule-patches, well demarcated, geographic shape, size varies from 0.5 cm x 0.5 cm to 1 cm x 3 cm, discreetly scattered, some confluent, high-level distribution dermatome T11-T12.

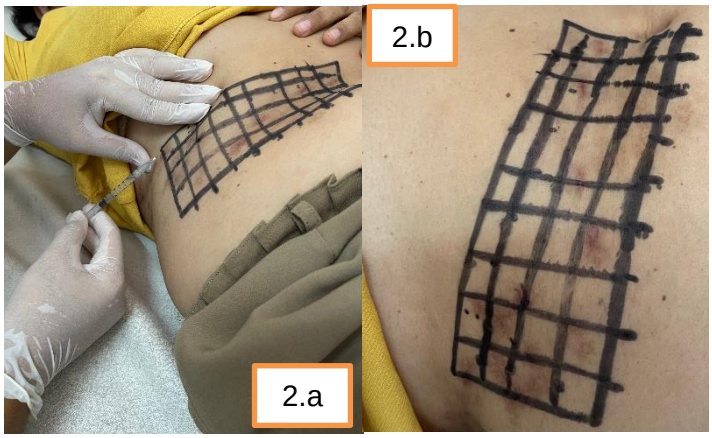

Figure 2.a-b Multiple hyperpigmented macules, well defined, geographic shape, size varies from 0.5 cm x 0.5 cm to 1 cm x 3 cm.

The working diagnosis in the patient is a follow-up for herpes zoster abdominal dextra at T11-T12 and herpetic neuralgia. The patient is given botulinum toxin therapy with 0.1 cc containing 5 IU intradermal. with additional drugs in the form of vitamins B1, B6, B12 every 24 hours intraorally. Patients and companions are also given KIE regarding the diagnosis, causes, plans, goals and targets of treatment, dosage, benefits and side effects of the drugs given.

Third Case
Female patient, 50 years old, Balinese, Indonesian citizen, with medical record number 21027836, on 15 December 2021 came for control at the skin and genital polyclinic at Sanglah Hospital Denpasar with a history of herpes zoster in the left thigh area
From the anamnesis, there were complaints of pain in the left thigh area since 13 days ago and it got worse 5 days before coming to the skin and genital polyclinic at Sanglah Hospital, Denpasar. Pain is felt continuously throughout the day. Patients complain of pain such as burning, pricking, and discomfort. This causes the patient to have difficulty sleeping at night and interferes with the patient's daily activities. The appearance of this pain 10 days ago was accompanied by the appearance of nodules filled with fluid on the right back and right armpit

accompanied by fever. The patient treated with acyclovir 800 mg every 4.5 hours intra orally for 7 days, mefenamic acid 500 mg every 8 hours intra orally, compress NaCl 0.9% every 8 hours on erosion lesions and vitamins B1, B6, B12 every 24 hours intra orally. It is said that the watery nodule starts to break and becomes a scab and then becomes a wound and the wound heals on its own, it is said that the pain is increasing and sleep at night is still disturbed because of pain in the former shingles wound.

The patient had never had the same complaint before. The patient had chickenpox as a child. The patient has a history of chronic heart failure and routinely visits the heart polyclinic at Sanglah Hospital every month. History of diabetes, high blood pressure, drug allergies, and malignancy in the patient and his family was denied. The patient is a pensioner. Prior to the appearance of the nodule complaints, the patient reported feeling tired because the patient was taking care of traditional ceremonies at his home

On physical examination, the patient's weight was 68 kg, height 165 cm, general condition was good and awareness of compos mentis. The patient's blood pressure is 100/70 mmHg, pulse rate is 88x/minute, respiratory rate is 20x/minute, axillary temperature is 36.3 oC, Visual Analog Scale (VAS) score is 5. In the general status of the patient, the head is normocephalic, on examination of both eyes there is no visible hyperemic conjunctiva in both eyes, anemia and jaundice are not seen, and the pupil reflex is good and symmetrical. No enlarged cervical lymph nodes were found. Examination of the ears, nose and throat did not reveal any abnormalities. Chest examination revealed a single heart sound (S1 and S2).irregular there are murmurs. In the lungs, vesicular breath sounds were found without crackles or wheezing. On abdominal examination, bowel sounds were within normal limits, no distension was found and there was no enlargement of the liver and spleen. On examination of the extremities, all four extremities felt warm and no edema was found. Examination of the oral and genital mucosa was normal. Examination of nails and hair revealed no abnormalities.

Dermatologic status at the location of the left femur was found in fluorescence: Multiple hyperpigmented macule-patches, well defined, geographic shape, size varies from 0.4 cm x 0.5 cm to 4 cm x 5 cm, some confluency, distribution as high as dermatome L2-L3.

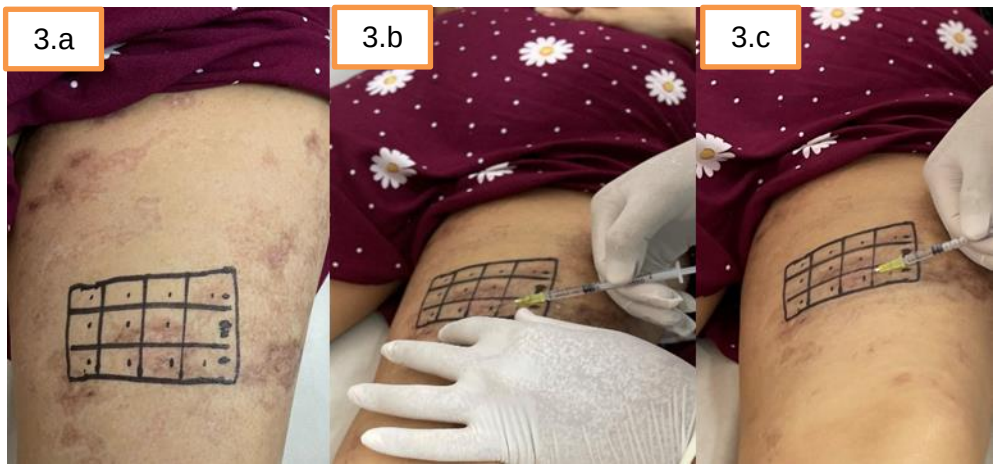

Figure 3.a-c macular-patchy hypopigmentation multiple, well defined, geographic shape, size varies from 0.4 cm x 0.5 cm to 4 cm x 5 cm. Figure 3.b intradermal injection of botulinum toxin

The working diagnosis in the patient is follow-up of herpes zoster thoracalis on the right as high as L2-L3 and herpetic neuralgia. The treatment given to the patient is laser biostimulation with power 450 mW for 20 minutes three times a week, Gabapentin 300 mg tablet every 8 hours intraorally, Paracetamol 750 mg tablet every 8 hours intraorally. Patients and

companions are also given KIE regarding the diagnosis, causes, plans, goals and targets of treatment, dosage, benefits and side effects of the drugs given.
As an additional examination, a Tzanck examination, gram (base erosion), culture (base erosion), and blood tests are carried out. Tzanck's examination revealed the presence of multinucleated datia cells. Gram-based examination of the wound found leukocytes 10-20/large field of view and gram-positive cocci found >50 field of view. A basic culture examination of the wound was also carried out and awaiting the results. A complete blood count (DL) showed an erythrocyte count of 5.15 103/µL (4.0-5.2); hemoglobin 14.9 g/dL (12.0-16.0); hematocrit 45.41% (36-46); platelets 213 103/uL (140-440); leukocytes 6.24 103/µL (4.0-11.0); neutrophils 4.78 103/µL (2.5-7.5); lymphocytes 0.796 103/uL (1.0-4.0); monocytes 0.608 103/uL (0.1-1.2); eosinophils 0.012 103/uL (0-0.5) and basophils 0.042 103/uL (0-0.1). Liver function examination obtained SGOT results of 22.4 IU/L (11-27); SGPT 20.3 IU/L (11-34), current blood sugar 113 mg/dL (70-140) and albumin 2.99 g/dL (3.4-4.8). Examination of kidney function obtained a BUN of 17 mg/dl (8-23) and creatinine of 0.67 mg/dL (0.5-0.9). Electrolyte examination obtained sodium levels of 137 mmol/L (136-145), potassium 3.57 mmol/L (3.5-5.1) and chloride 94.2 mmol/L (94-110).
From the history, physical examination, and supporting examinations in laboratory tests, a working diagnosis of post-herpetic femoral left post-herpetic neuralgia was found at L2-L3.
The treatment given to the patient is botulinum toxin A injection with 0.1 cc containing 5 IU intradermal. with additional drugs in the form of vitamins B1, B6, B12 every 24 hours intraorally. Patients and companions are also given KIE regarding the diagnosis, causes, plans, goals and targets of treatment, dosage, benefits and side effects of the drugs given.

DISCUSSION

Post-herpetic neuralgia (NPH) is the most common complication of herpes zoster. NPH is variously defined as any pain that occurs 1, 3, 4 or 6 months after the onset of the herpes zoster lesion; [11] However, most of the current definitions focus on pain that occurs within 3 months after the herpes zoster eruption has disappeared [4,11].
Pain is the main symptom of herpes zoster, where 84% of patients will feel pain before the appearance of the lesion, and 89% of patients will feel pain when the eruption occurs.12 Several studies divide herpes zoster pain into 3 phases, namely 1. Acute phase: pain phase that occurs simultaneously with skin lesions and persists for up to 30 days, 2. Subacute phase: pain persists between 30 days to 120 days after the onset of skin lesions; 3 The chronic phase (NHP) where pain persists for more than 3 months after healing of the herpes zoster skin lesions [6].
From several clinical studies, 12-15% of herpes zoster patients will experience NPH.11,13 Both the frequency and duration of NPH increase with age. 40% - 50% of patients who suffer from herpes zoster are patients over 60 years of age, and 10% - 20%between This patient has NPH.14 Results of a multicenter study in America conducted by Shingles *Prevention Study* showed that in patients over 60 years, 12.4% of patients still felt pain until 3 months later, and 41% still felt it until 6 months [15].
There is a significant correlation between age and the incidence of NPH. NPH is more common in the elderly and rarely in immunocompetent people younger than 50.6,11 The main risk factors for NPH besides increasing age are the presence of prodromal pain, the severity of pain during the acute phase of Herpes zoster, more extensive skin rashes, more extensive sensory disturbances in dermatomes affected by Herpes Zoster and a state of immunosuppression.6,16
The first case was a man. A man, aged 59 years, ethnic Balinese, from anamnesis obtained 10 days before coming to the skin and genital polyclinic at Sanglah Hospital suffered from herpes zoster. Previously there were complaints on the skin in the form of clustered watery nodules on the right back and right armpit; great pain when the skin lesions appear is also felt, and the

lesions increase from the right back to the right armpit. After 3 months, the patient complained of still feeling pain even though the skin lesions had healed.

The second case was a female patient, aged 54 years, of Balinese ethnicity. From the anamnesis, she found complaints of pain in the left thigh area from 13 days ago. She worsened 5 days before coming to the skin and genital polyclinic at Sanglah Hospital, Denpasar. Pain is felt continuously throughout the day. Patients complain of pain, such as burning, pricking, and discomfort. This causes the patient to have difficulty sleeping at night and interferes with the patient's daily activities. The appearance of this pain 10 days ago was accompanied by nodules filled with fluid on the right back and right armpit accompanied by fever. The patient then received therapy from a doctor in the form of acyclovir 800 mg every 4.5 hours intra-orally for 7 days, mefenamic acid 500 mg every 8 hours intraorally, compress NaCl 0.9% every 8 hours on erosion lesions and vitamins B1, B6, B12 every 24 hours intraorally. It is said that the watery nodule starts to break and becomes a scab and then becomes a wound, and the wound heals on its own; it is said that the pain is increasing and sleep at night is still disturbed because of pain in the former shingles wound.

Third Case 50 From the anamnesis, there were complaints of pain in the left thigh area since 13 days ago, and it got worse 5 days before coming to the skin and genital polyclinic at Sanglah Hospital, Denpasar. Pain is felt continuously throughout the day. Patients complain of pain, such as burning, pricking, and discomfort. This causes the patient to have difficulty sleeping at night and interferes with the patient's daily activities. The appearance of this pain 10 days ago was accompanied by the appearance of nodules filled with fluid on the left thigh accompanied by fever. The patient then received therapy from a doctor in the form of acyclovir 800 mg every 4.5 hours intra-orally for 7 days, mefenamic acid 500 mg every 8 hours intraorally, compress NaCl 0.9% every 8 hours on erosion lesions and vitamins B1, B6, B12 every 24 hours intraorally. It is said that the watery nodule starts to break and becomes a scab and then becomes a wound, and the wound heals on its own; it is said that the pain is increasing and sleep at night is still disturbed because of pain in the former shingles wound.

The pathogenesis of NPH is the presence of neuronal injury that affects both the central and peripheral components of the system nerve. Virus replication in the dorsal ganglion causes a response of inflammation, swelling, bleeding, necrosis and neuronal cell death. The virus then spreads centrifugally along the nerves to the skin, causing inflammation and damage to the peripheral nerves.6,10 Sometimes, the virus spreads centripetally towards the spinal cord (affecting sensory and motor areas) and the brainstem. This causes sensitization or dedifferentiation of peripheral and central nervous elements [14].

The virus destroys the large ganglion cells, and what is left are fine cells. The impact is that temporal summation does not occur, so the modulation process in the posterior horn does not run normally, and as a result, no process between the endogenous analgesic system and pain intake enters the posterior horn. This can result in symptoms of hyperalgesia (severe pain produced by a stimulus that normally produces mild pain). Impulse signals arrive simultaneously at the core thalamus, and most of it is delivered by fine fibers, which are fibers that conduct pain impulses [11,12,16]. The simultaneous arrival of many impulses is perceived as severe pain consistent with neuralgia, a central sensitization caused by the ectopic activity of afferent nerve fibers. Persistent isometric discharge of nerve fibers induces central sensitization in which N-methyl-D-aspartate plays a major role and causes a persistent perception of pain. Damage to these nerve fibers persists in NPH patients [16,17].

NPH is often about dermatome region thoracic (>50%) followed by division ophthalmic in the trigeminal region and other cranial nerve regions (10-20%), cervical region (10-20%), then dermatome lumbar (10-20%) and sacral (2-8%).19,20 NPH patients usually complain of constant pain (described as burning, deep, throbbing), intense pain intermittent (pain like being stabbed, shot) and/or pain evoked by a stimulus such as allodynia. Allodynia (pain evoked by

a normally painless stimulus) is pain present in up to 90% of NPH patients. Other sensory complaints can also include sensitivity to changes in temperature and numbness to the lesions [18,19]. Pain like this can cause sleep disturbances, depression, anorexia, weight loss, and chronic fatigue and interfere with daily activities such as dressing, bathing, shopping, cooking, housework and traveling [17].

In the first, second, and third cases, the patient complained of pain at the site of the herpes zoster, which had healed in the dermatomes at the T1-T3, T11-T12, and L2-L3 levels. All three cases had similar pain and symptoms, such as prickling, burning, and tingling sensations. The patient also complains of discomfort when the skin is touched by hands or air; this interferes with the patient's daily activities. Patients experience sleep disturbances and stress due to the pain they feel.

NPH includes neuropathic pain caused by primary damage or dysfunction in the nervous system [3]. pain rating scales are commonly used to assess pain intensity, namely verbal *Rating Scale* (VRS), *Visual Analogue Scale* (YOU) day *Numerical Rating Scale* (NRS). In VRS, there is a range from "no pain" to "severe pain". On VAS, pain intensity along the 10 cm line is accompanied by facial expressions. The marks at both ends of the line on this VAS can be numbers or descriptive statements. One end represents no pain, while the other represents the worst possible pain. The NRS measures pain intensity from 0 to [10.15,19,21]

The B complex vitamins (B1, B6 and B12) play a fundamental role in the nervous system structurally and in maintaining proper nervous system function. There is increasing evidence in the literature to show that B-complex vitamins contribute to nerve repair, both in accelerating the regeneration of nerve tissue and in restoring nerve function by various mechanisms. Research conducted by Martins Gazoni concludes Existing studies, although rare and heterogeneous, have shown that the vitamin B complex has an analgesic effect. B complex vitamins are considered safe and low-cost and a good choice for analgesic therapy [30].

Today, research and development of drugs is growing rapidly. However, until now, no single therapy has effectively treated NPH. NPH is still an important problem in the health sector because parents often suffer from NPH, and the administration of drugs to the elderly often causes side effects, so attention is needed in choosing a combination of therapies [10].

The management of NPH still needs to be more abstract. There is no specific algorithm for treating NPH, so this is a challenge for medical practitioners. Several approaches can be taken in providing therapy to NPH patients. The first approach is a multi-modality approach often used to obtain maximum results. This approach includes a combination of topical and systemic medications, relaxation, intervention psychology and social support. Topical therapy includes anesthetic agents, *capsaicin* and various anti-inflammatory preparations. In contrast, systemic therapy includes opioids, anticonvulsants, antidepressants norepinephrine and serotonin, such as duloxetine and venlafaxine), as well as tricyclic antidepressants (*amitriptyline*, *nortriptyline* and *desipramine*).

In addition, additional therapies are also often used at this time. One of the additional therapies that can be given to patients is botulinum toxin A (BTX-A). Botulinum toxin A (BTX-A) is a neurotoxin produced by the bacteria Clostridium *botulinum*, which inhibits the release of neurotransmitter pain and reduces neurogenic inflammation. Two randomized controlled trials were performed by subcutaneous injection at the site of pain using less than 200 units of BTX-A. Both studies show improvement in score visual *analogue scale* (VAS), sleep and decreased use of opioids. The safety profile of using BTX-A for treating neuropathic pain is generally good. Targeted interventions are preferred if the affected area includes the distribution nerve *root* single. *Pulsed radiofrequency* (PRF) is rapidly applied to a nerve target to alter the neuronal membrane and other pain signaling without damaging nerve tissue.

Botulinum Neurotoxin (BTX) is a neurotoxin protein produced by strain neuro toxigenic from forming bacteria purse and anaerobic of the genus Clostridium (*Clostridium botulinum,*

Clostridium bityrricum, *Clostridium barati* and *Clostridium argentinensis*). BTX is a metalloproteinase that breaks down vesicle-associated *membrane protein* (VAMP), similar to tetanus *neurotoxin* (TeNT) but has a different serology. BTX is synthesized as an inactive form of 1285 amino acids, a single-chain polypeptide weighing 150 kDa, which is cleaved by proteases and linked by strong disulfide bonds. This cleavage forms the mature and pharmacologically active toxin into a light ring (50-kDa). Disulfide bonds link a heavy ring (100-kDa). Non-covalent, and a unique segment composed of the N terminus and the H, is called the "*belt*" that surrounds the L globular domain (Fig. 2.5). Reduction in the single interaction of the S-S bond causes a release of the activity of the L ring metalloprotease.
The H ring consists of two 50 kDa domains (the amino-terminal portion, the HN, and the terminal portion carbon, HC) and the BTX-A1 and -B1 molecules. The C-terminal site of the HC domain (HC-C subdomain, 25 kDA) mediates the interaction of BTX with areas that are not terminus from motor neurons, creating a strong and rapid interaction of the toxin with peripheral cholinergic nerve endings. The HN domain (yellow, in Figure 2.5) is important in translocating the L ring across the endocytic vesicle membrane towards the cytosol. This domain consists of two long and four short parts parallel *α-helices*.
The Food and Drug Administration (FDA) approved using BTX as a treatment for strabismus in 1989. Since then, it has been used to treat neurological disorders such as muscle dystonia and dyskinesia. Indications for the use of BTX have grown in the last decades for the treatment of disorders caused by excessive and inappropriate muscle contractions, facial wrinkles and hyperhidrosis.

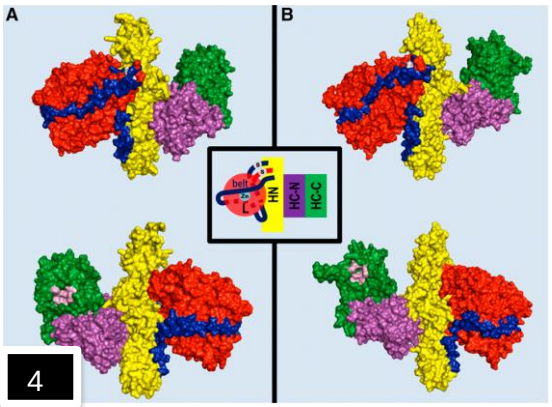

Figure 4. The molecular structure of BTX/A1 and BTX/B1

The crystal structures of BTX-A1 (A) and BTX-B1 (B) are represented as space-filling models of the two opposite surfaces of each toxin molecule showing the organization of three toxin domains: neuron-specific binding HC-C subdomain (green), HC-N subdomain resembling -lectin (purple), translocated HN domain (yellow), and L domain metalloprotease (red). The pink cavity in the HC-C subdomain shown in the bottom panel is the binding site in polsialoganglio. The peptide belt (shown in blue) surrounding the L domain and the interchain disulfide bonds (white in the top panel) connecting the L and HN domains, which stabilize the structure, are also shown.

BTX has seven types of neurotoxins, marked alphabetically (A-G), distinguished by the animal antiserum present in them. Genetic analysis molecular using techniques sequencing the latest generation, find the gene code of various new BTX. These findings can be classified into pre-existing serotypes with different amino acid sequences.
Botulinum toxin A (BTX-A) and B (BTX-B) are the most widely used types of BTX. BTX-A has a molecular weight of about 900,000 and is a double-chain protein. The light chain (*light chain*/LC) is active, whereas the heavy chain (*heavy chain*/HC) is not active (Park, 2017). Some

examples of BTX-A include onabotulinum toxin A (A/His, BOTOXR Allergan), abobotulinum toxinA (A/Abo, Dysport® Ipsen), this incobotulinumtoxinA (A/Inco, Xeomin® Merz), while BTX-B for example rima botulinum toxin B (B/Rima, Myobloc®/Neurobloc® ElanPharmaceuticals). These toxins differ in complexity, purity, potency, and dosageimmunogenisites.19 Both BTX-A and BTX-B are effective in neuropathic pain. Using cisplatin, BTX-B improved allodynia and hyperalgesia in mononeuropathy-induced rats through nerve ligation and polyneuropathy.

BTX is an example of a substrate-targeting bacterial exotoxinintracellular. This toxin evolves into a structured organization designed to deliver metalloprotease domains to the host cell's cytosol, which is achieved by exploiting various physiological functions of nerve endings. Unique bond from to the nerve terminal occurs because of its ability to interact with two independent receptors on the presynaptic membrane polysialoganglioside (PSG) and luminal domains glycosylated of synaptic vesicle proteins that mediate BTX internalization. The mechanism of nerve terminal intoxication by BTX divides into five steps (Figure 2.6): (1) binding to nerve terminals, 2) internalization into the endocytic compartment, 3) low pH promotes translocation of the L chain across the vesicle membrane, 4) release of the L chain in the cytosol with bond reduction disulfide, and 5) cleavage of SNARE to initiate a block of neurotransmitter release and produce paralysis.

BTX binds to acceptors at the nerve endings and enters the nerve endings via receptor-mediated endocytosis. Light chains (LC) bind to exogenous proteins involved in exocytosis and cleave peptide bonds of transporter proteins to block exocytosis and acetylcholine secretion. The C-terminal receptor binding domain, which is the BTX heavy chain (HC), binds to ganglioside receptors and specific proteins on the cell membrane. This binding induces HC-LC endocytosis. In general, acetylcholine binds to acetylcholine receptors on the endplate motor and is necessary for muscle contraction. At this time, the exocytosis of acetylcholine is required in the presynaptic membrane. The normal acetylcholine exocytosis process requires *synaptosomal-associated protein*-25 kDa (SNAP-25), syntaxin, and vesicle-associated *membrane protein* (VAMP)/synaptobrevin in the presynaptic membrane. These proteins are called proteins soluble *N-ethylmaleimide* (SNARE). As a zinc-dependent endoprotease, LC BTX cleaves intracellular SNARE. This cleavage interferes with SNARE-mediated protein transport and release transmitter, blocking muscle innervation, in*junction* neuromuscular and causing flaccid paralysis. LC BTX effects can last from days to months.

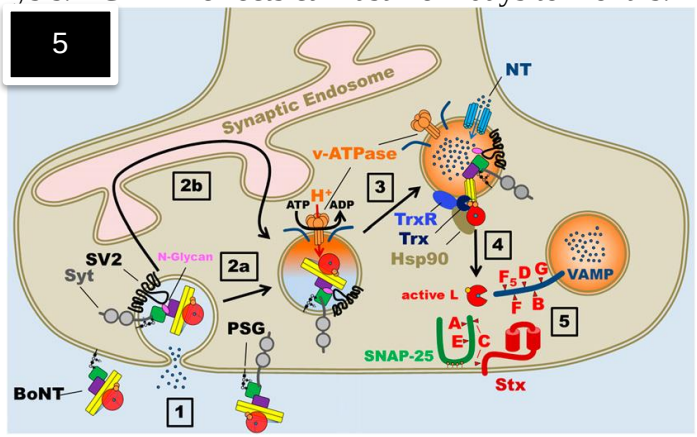

Figure 5 Mechanism of action of botulinum neurotoxin in causing intoxication of nerve terminals.

The first step (1) is the binding of the HC domain (green) to the receptor in polsialoganglio (PSG) from membrane presynaptic (grey and black), followed by binding to the protein receptor. BTX is then internalized within the SV, directly recycled (2a) or within the SV, which

joins the synaptic endosome and re-enters the SV cycle (2b). Acidification (orange) of the cysts, operated by v-ATPase (orange), promotes neurotransmitter accumulation (blue dots) via vesicular neurotransmitter transporters (light blue). Protonation of BTX causes membrane translocation of the L chain into the cytosol (3), which is aided by the HN domain (yellow). The L chain (red) is released from the HN domain by system action reductase thioredoxin (TrxR-Trx, blue and dark blue) and Hsp90, which reduces interchain disulfide bonds (orange) and avoids aggregation of proteases (4). In the cytosol, the L chain displays activitymetaloprotease (5).

BTX also reduces and modifies neuropathic pain in animal models through the following mechanisms. BTX inhibits the secretion of pain mediators (substance P, glutamate, *calcitonin gene-related protein* [CGRP]) from nerve endings and the dorsal root ganglion (DRG), decreases local Inflammation around nerve endings, deactivates sodium channels and increases axon transport (Figure 6).

1) BTX inhibits the release of pain mediators from peripheral nerve endings, DRGs and spinal cord neurons

The effect of BTX on the secretion of sensory neurotransmitters has been demonstrated in various animal models. BTX reduces normal CGRP release and affects the TRPV1 pathway. BTX cleaves the neuronal SNARE and blocks the secretion of neurotransmitters in a sensory ganglion neuron cell culture model. Other studies have shown BTX significantly lowers TRPV1 protein levels. TRPV1 plays an important role in arthritis pain, and a study was conducted to examine the relationship between the antinociceptive effect of BTX and TRPV1 expression in DGR from rats with arthritis pain. BTX or TRPV1 protein levels significantly decreased, so it can be concluded the antinociceptive mechanism of BTX is to reduce TRPV1 expression through inhibition *trafficking* plasma membrane.

2) BTX reduces Inflammation

Cyclophosphamide (CYP) was injected into the rat bladder to induce cystitis because CYP and HCL are injected into the bladder to induce acute injury. The bladder was then removed and compared with Sham's group. CGRP and substance P were significantly increased in the acutely injured group compared to the control group; substance P was also significantly increased in the group cystitis CYP induced. After being given BTX, the neurotransmitter level significantly decreased; this suggests that BTX has an anti-inflammatory effect against chronic Inflammation and acute injury. The anti-inflammatory effect of BTX decreases the release of neurotransmitter peripheral and inflammatory mediators.

This effect of BTX was denied by several researchers who showed no difference in oedema and plasma protein extravasation in groups of mice injected with BTX and without BTX. Other investigators also reported that the BTX group and the control group had no direct effect on acute non-inflammatory pain in the group given BTX on the skin exposed to Ultraviolet B. Administering 20 IU BTX once a week before injection of capsaicin in rat prostate-induced prostatitis showed a significant reduction cyclooxygenase-2 (COX-2) expression in spinal sensory and prostate motor neurons. COS-2 is a key enzyme that plays an important role in Inflammation and pain.

BTX also reduces local Inflammation around nerve terminals. Administration of BTX to a rat model of formalin-induced inflammatory pain showed an effect antinociceptive started 5 hours after BTX therapy and persisted for more than 12 days. Oedema was also reduced, and no local muscle weakness was observed. Formalin-induced glutamate release was also significantly reduced.

3) BTX causes the deactivation of sodium channels

BTX inactivates the sodium channel. Sodium currents stimulate various cellular functions, such as transmission, secretion, contraction and sensation. BTX-A alters the sodium current of the

excitatory neuronal membrane, which differs from anesthetics, tetrodotoxin, and antiepileptics in that it controls the overall sodium current based on its concentration.

4) BTX induces axonal transmission

BTX induces the transmission function of axons from the periphery to the central nervous system (CNS), and administration of BTX in the face and nerve trigeminal causes SNAP-25 truncation in the central nucleus. Additionally, administration of small amounts of BTX on the back of the leg confirms SNAP-25 cut on the ventral *and dorsal horns* of the ipsilateral spinal cord, thus demonstrating a transport function axonal *retrograde* from BTX. BTX effects can also occur on both sides after injection on one side of the body. Diffusion into the blood circulation may affect the central nervous system, but low doses may not cause systemic side effects. BTX is also too big to cross the blood-brain barrier. The possibility of BTX transportation for free retrograde of the injection site is still controversial.

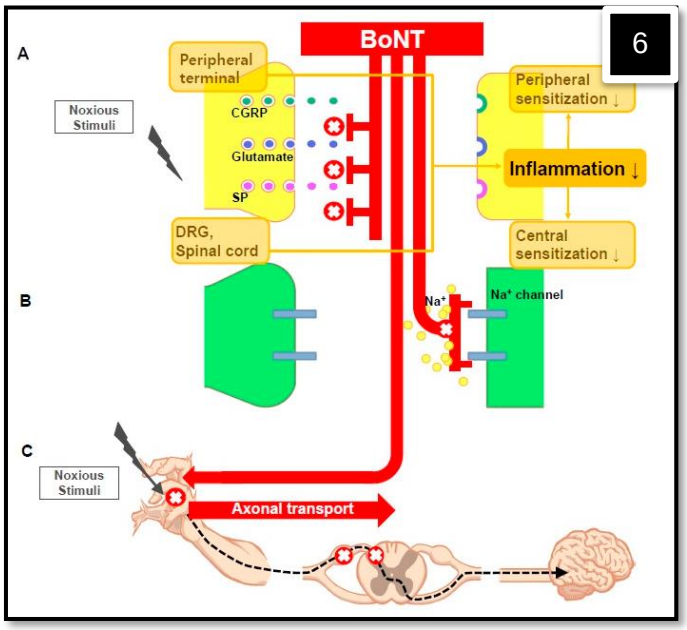

Figure 6 Mechanism of action of BTX in reducing pain.

(A) Stimulus *noxious* induce inflammation by releasing neuropeptides and inflammatory mediators, which can cause peripheral sensitization. This action also occurs in the DRG, the dorsal horn medulla spinal cord and may cause central sensitization. Botulinum toxin (BTX) inhibits the release of pain mediators in peripheral nerve terminals, DRGs, and spinal cord neurons, thereby reducing the inflammatory response and preventing the development of peripheral and central sensitization. Symbol; SP, substance P; CGRP, *calcitonin gene-related protein*; DRG, *dorsal root ganglion*; (B) Hyperexcitability and spontaneous action potentials mediated by Na channels in peripheral sensory neurons contribute to the pathophysiology of neuropathic pain. BTX can control neuropathic pain by blocking Na channels; (C) Some BTX appear to move retrogradely along the axon. SNAP-25 is cleaved in the dorsal horn medulla spinal cord and central nucleus after small amounts of BTX are administered peripherally, thereby increasing the retrograde transport of BTX.

BTX combine several beneficial pharmacological properties to make it a unique drug. These drugs are very potent, and neurospecificity has limited diffusion when injected locally, and their action may suffer reversible along with time. These properties make BTX-A1 a safe therapy and are effective for treating various syndromes characterized by the over function of certain nerve endings.

Giving BTX has special action procedures that must be considered. Each BTX package has a guide for drug use, where the administration is specific depending on the preparation and test method used. They are not interchangeable with other BTX product preparations. Therefore, BTX biological activity units cannot be compared or converted to other botulinum toxin product units as assessed by other specific test methods. BTX (onabotulinumtoxinA) for injection is sterile and vacuum-dried botulinum toxin type A, which is produced by fermentation *strain Hall Clostridium botulinum* type A and intended for intramuscular and intradermal use. Dial purifies BTX from the culture solution, and a series of acids precipitate into a complex consisting of a neurotoxin and some additional proteins. The complex was dissolved in a sterile sodium chloride solution containing Human Albumin and sterile filtered (0.2 microns) before filling and vacuum drying.

The safe and effective use of BTX depends on proper product storage, proper dosage selection, and proper reconstitution and administration techniques. The maximum cumulative dose is generally not to exceed 360 Units at any 3-month interval. Doctors who give BOTOX must understand the anatomy neuromuscular of the area involved and any changes in the anatomy due to previous surgical procedures. BTX injection should be performed cautiously when inflammation is found at the planned injection site or when excessive weakness or atrophy occurs in the target muscles.

BTX is available in 50 Units, 100 Units and 200 Units per single-use vial. Before injection, reconstitute each vial of BTX vacuum-dried with USP 0.9% Sodium Chloride Injection sterile and uncured. Determine the correct amount of diluent in the appropriate size syringe (Table 1), and slowly inject the diluent into the vial. Gently mix the BTX with the saline solution by rotating the vial. Note the date and time of reconstitution on the label. BTX should be administered within 24 hours of dilution. During this period, reconstituted BTX should be stored in the refrigerator (2° to 8° C). This dilution was calculated for an injection volume of 0.1 mL. Decreasing or increasing the dose of BTX is also possible by giving smaller or larger injection volumes from 0.05 mL (50% dose reduction) to 0.15 mL (50% dose increase). An example of dissolving BTX was diluting 100 units of BTX-A in 4 ml of saline solution to obtain a concentration of 25 units of BTX-A per ml.

Table 1. Dilution Instructions for BOTOX vials (50, 100 and 200 units)

50 unit		**100 unit**		**200 unit**	
Solvent addition (ml)	Dosage Result (Units per 0.1 ml)	Solvent addition (ml)	Dosage Results (Units per 0.1 ml)	Solvent addition (ml)	Dosage Result (Units per 0.1 ml)
1	5	1	10	1	20
2	2,5	2	5	2	10
4	1,25	4	2,5	4	5
		8	1,25	8	2,5
				10	2

BTX is put into a sterile syringe of the right size, and the amount of properly dissolved toxin is slightly larger than the dose prescribed. Air bubbles in the syringe are removed, and the syringe is attached to the appropriate syringe. Needle patency should be confirmed. A new, sterile needle and syringe must be used to contact the vial when taking BTX. Diluted BTX should be clear, colorless and free of particles. Parenteral drug products should be inspected visually for particulate matter and discolorations before administration to the patient.

The main property of BTX-A is minimal effect, even in areas close to the injection site. There is a possibility of local diffusion or leakage into the systemic circulation depending on several factors, such as volume and rate of injection, dose, and site of infection. It should be noted that diffusion of BTX from the injection site will be followed by progressive dilution of the large amount in the fluid extracellular. As is well known, a toxin that has been injected and becomes highly soluble can no longer bind to the presynaptic membrane.

The most commonly reported side effect of BTX injection in cases of neuropathic pain is pain during the procedure. One reported mild local skin infection at the injection site one day after the injection. These complaints improved immediately after three days of oral antibiotic therapy. This side effect was reported in a placebo-controlled randomized trial in patients with diabetic neuropathy. The investigators did not state in which group the infection occurred.

The use of BTX-A in trigeminal neuralgia patients showed that three patients had facial wrinkles asymmetrically after the study, and one patient had mild eyelid ptosis. Research by Bohluli et al. 3 2 also found transient facial paresis of the facial nerve branches, which underwent spontaneous resolution in four cases. Only one patient had severe paresis that required physiotherapy and took three months to resolve. One patient who underwent sympathetic block with BTX-A experienced severe nausea and vomiting that began 5 hours after the BTX-A injection, lasted 2 days and resolved spontaneously.

The use of BTX-A for neuropathic pain has minor complications, such as the formation of antibodies and immune-related complications when small amounts of BTX-A enter the bloodstream.11 Several meta-analyses were carried out to look at the side effects of BTX-A administration in neuralgia or NPH patients. A meta-analysis by Meng et al .32 included 12 randomized controlled studies with 495 neuralgia patients. No significant side effects were found by administering BTX-A to the study sample. Overall, 59 of 142 (41.5%) patients in the BTX-A group and 59 of 137 (43.1%) patients in the placebo (saline) group reported injection site pain. A total of 5.5% of patients from the BTX-A group and 7.6% from the saline group showed hematoma at the injection site. A total of 14 patients out of 108 (12.9%) with trigeminal neuralgia experienced mild facial asymmetry after BTX-A therapy. But this complaint itself is limited without requiring additional intervention for treatment. There was no significant difference in the incidence of side effects between the groups receiving BTX-A and lidocaine. This indicates a complaint post actions such as pain and hematoma possibly caused by the injection procedure of the BTX-A component.

A study showed that herpes zoster was a post-BTX-A complication in a 72-year-old woman with chronic migraine. The patient experienced herpes zoster ophthalmicus five days after therapy; this was thought to be caused by a local stress reaction after tissue damage induced by VZV reactivation.

The dosage for BTX-A injection varies between studies, and no definite dosage has been published for the treatment of NPH. Most patients with neuralgia receive BTX-A doses of 100-200 U. The gift can be subcutaneously, intradermally or intramuscularly. For patients with NPH and trigeminal neuralgia, subcutaneous or intradermal administration is preferred to block peripheral nerve endings. Intramuscular injections are used for other types of chronic neuropathic pain to help relieve muscle spasms.

The location of BTX-A injection in NPH cases needs to be clearly explained. Most researchers call it the “affected area” or “where pain is felt”. Research determines the injection location using the "*follow the pain*”. Injection site determination can also follow a pattern (injection sites spaced 1 cm apart to cover all involved branches) or a checkerboard pattern. For example, 100 IU of BTX-A (5U/route) can be done with 4 ml of sodium chloride (0.9%), then injected subcutaneously in a checkerboard pattern covering all affected areas using a 30 G needle.

Inject subcutaneously, with a distance of 1.5-2 cm between injections. Each injection site was given 5 units of BTX-A. The area of pain determines the total dose, but not to exceed 60 injection points (300 units). The injection was then repeated after 12 weeks. Intradermal administration is known to provide 15 IU BTX-A dissolved in 2% lidocaine, then injected intradermally per 10 cm2 surface area that pain uses a syringe small size.
To reduce injection-related pain, a cream containing lidocaine and prilocaine can be applied to the painful area about 60 minutes before injection. Administration of 50% nitric oxide and oxygen (inhalational sedation) was also administered through a nasal mask starting 5 minutes before and during the procedure. 2% lidocaine gel can be applied to the skin's surface, where BTX-A will be injected intradermally.

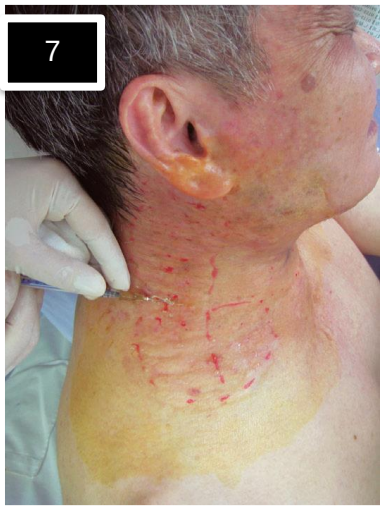

Figure 7 Botulinum toxin-A (BTX-A) injection technique.

The subcutaneous injection technique injects BTX-A into the affected area (marked by the red line) in patients with neuralgia, post cervical herpetic. Subcutaneous injection is carried out using a disposable tuberculin syringe with a radius of 1-2 cm and a volume of 1 ml.
The analgesic effect of BTX-A was first reported in 1985 from a study of BTX-A therapy for cervical dystonia, characterized by the contraction of the neck and shoulder muscles. *Involuntary* resulting in significant musculoskeletal pain. Currently, BTX has received FDA approval for chronic migraine disease. Unfortunately, there are no definite indications for giving BTX to NPH patients. Almost all studies included patients older than 18 years. There is no previous research that includes patients under the age of 18 years, so the administration of BTX-A must consider the patient's age. The duration of NPH varied in each study. The effect of BTX-A shows satisfactory results at the onset of 1 month or at least 3 months after the resolution of the rash. This includes NPH patients who do not respond to drugs such as carbamazepine and phenytoin, but most studies do not mention the criteria for prior NPH therapy. The history of receiving BTX-A therapy before was not mentioned much in selecting patients to receive BTX-A.
There are contraindications listed on the BTX packaging. The contraindications for giving BTX are:

1. Patients are known to have hypersensitivity to Botulinum Toxin. BTX is contraindicated in patients with hypersensitivity to botulinum toxin preparations or components in their mixtures.
2. Infection at the injection site. BTX is also contraindicated for injection when there is an infection at the location to be injected
3. Hemostatic disorders and use of anticoagulant drugs

4. Have motor neuron disease or neuropathic Because of the high affinity of the autonomic nerve terminals, BTX should be administered with caution to patients with preexisting autonomic dysfunction, such as myasthenia gravis.
5. Severe allergic diathesis
6. Comorbid or terminal mental illness
7. Pregnant or breastfeeding. There is no definitive evidence of an adverse effect of therapy on pregnancy. Most studies report pregnancy outcomes after good BTX therapy. However, due to the absence of long-term reports, BTX is placed in risk category C in pregnancy, and the FDA recommends its administration only when the potential benefit equals the potential risk to the fetus.
8. History of alcohol or illicit substance abuse

Some substances that potentially affect the efficacy of BTX-A should not be taken during therapy and should be discontinued at least 10 days before starting therapy. These drugs include spectinomycin, aminoglycoside and substances that inhibit neuromuscular transmission, such as the non-depolarizing muscle relaxants succinylcholine and dantrolene. Anticoagulant drugs must also be stopped at least 10 days before starting therapy, including: 1) oral anticoagulants (dabigatran, rivaroxaban, apixaban, coumarin derivatives); and 2) heparin and low *molecular weight heparin* at an effective anticoagulant dose.

In the first, second, and third cases, the patient received botulinum toxin type A injection therapy with 0.1 points containing 5 IU and routine supplementation of vitamins b1, b6, and b12 every 24 hours until the 12th week. Based on the patient's follow-up control, the analogue visual value can be analyzed. This value is often called the visual *Analogue Score* (VASE). This value can represent the patient's pain after being given the BTX procedure. The VAS values in the three patients, which were obtained after control, were as follows:

Table 2. VAS Score in Post-BOTOX Patients

Patient Number	VAS Score						
	early	2 weeks	4 Weeks	6 Weeks	8 Weeks	10 Weeks	12 Weeks
1	8	2	2	2	2	4	4
2	10	3	3	3	3	5	5
3	7	1	1	1	1	3	3
average	8.3	2	2	2	2	4	4

CONCLUSION

A serial case of post-herpetic neuralgia has been reported in a man, aged 59 years, a woman, aged 54 years, a woman, aged 50 years from anamnesis and complaints of pain in the back area after the lesion onset. Patients have similar complaints of pain, such as burning, pricking, and discomfort. Complaints of this pain vary between 1 and 3 months after the herpes zoster skin lesions have healed. This causes the patient to have difficulty sleeping at night and interferes with the patient's daily activities.

Examination of pain intensity with VAS measurements showed a significant decrease in VAS score from before botulinum toxin injection was given. Other treatments given are vitamins B1, B6, and B12. The prognosis for patients is dubious ad bonam.

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