Management of Spasticity using Botulinum Neurotoxin-A in a Child following Encephalitis

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ABSTRACT

We report a 20-month-old boy with spastic tetraparesis (global spastic) as a neurological sequela following encephalitis. The spastic symptoms didn't improve after one month of taking baclofen, diazepam orally, and physical rehabilitation therapy. Due to the Intrathecal Baclofen is not available thereby replaced by BoNT-A injection. The Ashworth scale both of hands and feet improved from grade 4 to 2 after four weeks and able to bend his hand and feet after three months of BoNT-A injections. This concludes, if the intrathecal Baclofen is not available, BoNT-A injections can minimize spasticity.

Keywords: *Spasticity; Botulinum Neurotoxin-A*

INTRODUCTION

The impairment of the central nervous system (CNS) results in the clinical condition known as spasticity. Spasticity can be caused by pathology in the cerebral cortex, brainstem, or spinal column, which can be diffuse or local (Awaad and Rizk, 2012). It is a secondary neurological condition induced by neurological hyperreflexia.(Kobal et al., 2018). Spasticity is assumed to be more common in patients who have suffered midbrain and pons injury (Moeini-Naghani et al., 2016).

Two thirds of patients with cerebral palsy have some degree of spasticity. Due to a higher survival rate for preterm births, a greater number of children with spasticity (Awaad and Rizk, 2012). However, spastic following encephalitis is rarely reported. A study of 93 kids who were hospitalized in Stockholm, Sweden, between 2000 and 2004, found that 60% of those with encephalitis had sequelae at the time of discharge, but spastic incidents were not reported. These symptoms included some minor ones including fatigue, but in 24% of cases, they included cognitive impairment, dysphasia, motor impairment, ataxia, or epilepsy (Fowler et al., 2008). In addition, spasticity in cerebral palsy increases the risk occurring of pneumonia and acute kidney injury (AKI) which can increase the risk of death (Prastiya et al., 2018).

Spasticity causes inactivity and reduced functional capacity. Inaction can lead to decubitus, cardiac problems, respiratory infections, thrombophlebitis, fixed contractions, bladder and bowel problems, osteoporosis, and social isolation. Finally, the effects of inactivity can result in further loss of strength and function. Because spasticity impairs mobility, self-care, hygiene, sleep patterns, sexual performance, mood, and self-confidence, the patient's quality of life may suffer (Awaad and Rizk, 2012).

Spasticity management is difficult because, to determine treatment strategies and goals, it is necessary to evaluate the benefits and drawbacks that patients gain from their spasticity. Physical and occupational therapy are traditional treatments for spasticity; however, they only have a minor effect on the patient's spasticity (Awaad and Rizk, 2012). Different diseases can cause specific complications in the context of pediatric neurorehabilitation. Several of these complications, including deep vein thrombosis, autonomic dysreflexia, and heterotopic ossification, can be serious and even fatal (Greenwood, 2004). To reduce spasticity, oral medications can be used; however, many have undesirable side effects including, sedation, drowsiness, fatigue, and confusion (Moeini-Naghani et al., 2016). Therefore, there is a new treatment for spasticity. Injections of botulinum neurotoxin-A (BoNT-A) have proven to be less difficult, more effective, and less painful for patients. The purpose of this paper is to

evaluate the efficacy of BoNT-A injections in the treatment of spasticity in a child with spastic tetraparesis after encephalitis.

CASE PRESENTATION

A 20-month-old boy patient arrived at the emergency unit of Dr. Soetomo Hospital, Surabaya, Indonesia, after being referred from a clinic with chief complaints of seizures three times at the clinic and twice at the emergency room of Dr. Soetomo Hospital, accompanied by fever, dyspnea, and decreased consciousness. The first seizure happened four hours before admission, about less than five minutes, duration seizure stopped after administered diazepam per rectal, but 30 minutes-1 hour later the seizure returned in less than five minutes, but the patient did not regain consciousness between intermittent seizures. The patient complained of fever one day before admission, with the highest temperature being 41°C. The patient also complained of diarrhea (3-5 times per day), vomiting, and cough for three days before admission, took any medication from the public health centre such as paracetamol, zinc, and ambroxol, but since the first day of admission, there had been no diarrhea.

The seizure type of patient was generalized tonic-clonic seizure. The seizures were usually affecting both legs and arms. The patient has never had any seizures before. There was a history of febrile seizures in the paternal family history. The patient was treated in the intensive care unit for 10 days using a ventilator, then his consciousness improved, and he was moved to a pediatric ward with stiff hands and feet (spastic tetraparesis).

The patient was born and delivered by cesarean section with an indication of fetal macrosomia, gestational age of 39 weeks, birth weight of 3600 grams, birth length of 55 cm, and immediately cried. His immunization history was one bacille Calmette-Guérin (BCG); three polio; three diphtheria-tetanus-pertussis (DTP); three Haemophilus influenza type B (HiB); three hepatitis B (HepB); and one measles-rubella (MR). The patient drank breast milk from birth until two months old, formula milk was given since the age of two months, complementary feeding since the age of six months, and family food since the age of one year. Prior developmental history was normal: social smiling by about six weeks, head-lag disappeared when being pulled into a sitting position by four months old, learned to roll over onto his back and sit with arms supported by around six months old, then crawled, and finally walked at one year old. He could do some babbling at six months and speak a few words by one year old. There was no prior travel history, head injury, tuberculosis contact, animal contact, swimming, camping, or hunting.

The patient's body weight was 16 kg, his body height was 90 cm, his body mass index (BMI) was 19.75 kg/m^2, and his head circumference was 48 cm. The weight-for-age Z (WAZ) score was above +3SD, the length-for-age Z (LAZ) score was above +2SD, the weight-for-length Z (WLZ) score was above +2SD (overweight), the BMI-for-Age Z score was above +2SD (overweight), and the head circumference based on Nellhaus chart was normocephalic.

The first condition, Glasgow Coma Scale of 8 (eye opening: 3, verbal: 1, motor: 4), BP: 90/60 mmHg, HR: 145 bpm, RR: 48 tpm, T: 38.9ºC (fever), and SpO_2: 98%. There was dyspnea, chest retraction, and bilateral rhonchi. The anterior fontanels were closed and unbulged. There were no rash at all, parotitis, stomatitis/perioral lesions, otitis, jaundice, retinitis, or orchitis. The neurological examination revealed equal pupils, round, and reactive to light. There were hyperreflexia of physiology reflexes, bilateral positive Babinski reflexes, bilateral positive Chaddock reflexes, and bilateral clonus. There was no hand or foot spasticity or meningeal sign (negative Brudzinski's and Kernig's sign). After 10 days, consciousness had improved and there was no longer any dyspnea. Patient moved to a pediatric ward with Glasgow Coma Scale 15 (eye opening: 4, verbal: 5, motor: 6), BP: 90/60 mmHg, HR: 115 bpm, RR: 28 tpm, T: 36.9^0C, and SpO_2: 98%. Four extremities had spastic tetraparesis without lateralization, according to the neurological examination. The Ashworth scale was 4 for both hands and feet (Figure 1).

Figure 1. The Ashworth scale both of hand and feet before BoNT-A injections was 4.

The laboratory test revealed Hb 11 g/dl, a WBC of 8.200/µL, thrombocytopenia (78.000/µL), eosinophils 3% (normal), neutrophil 40.3% (normal), lymphocyte 55% (increased), procalcitonin 0.45 ng/ml, CRP 0.1 mg/L, serum Glucose 118 mg/dl, AST 54 U/L, ALT 52 U/L, Albumin 3.7 g/dl, BUN 7 mg/dl, Creatinine 0.14 mg/dl, Sodium 139 mEq/L, Potassium 3.9 mEq/L, Cl 100 mEq/L, and Ca 8.6 mEq/L. Artery blood gas analysis revealed pH 7.36, pCO_2 58 mmHg, pO_2 81 mmHg, HCO_3 21.2 mmol/l, Beecf -0.9 mmol/l, and SO_2 96%. Cerebrospinal Fluid (CSF) analysis (taken on the 10^{th} day of illness) revealed a WBC count of 6/µL (MN 5, PMN 1), an RBC count of 0, glucose of 71 mg/dl (normal), total protein 61.4 mg/dL (increased), a Nonne negative, and a Pandy negative. The blood and urine cultures revealed sterility. The sputum culture revealed *Escherichia coli ESBL*, sensitive to Amikacin, Levofloxacin, and Meropenem. The CSF culture revealed sterility. The chest radiograph revealed pneumonia.

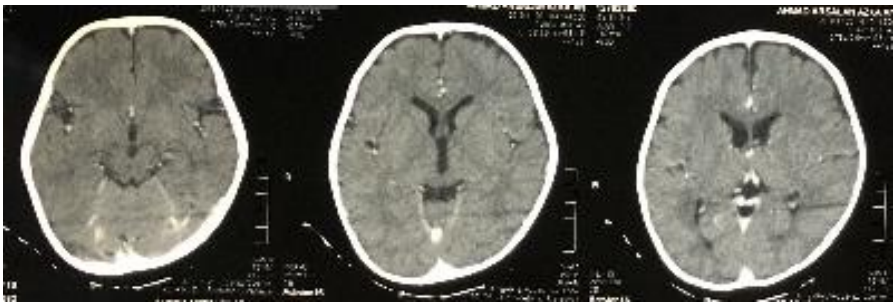

Figure 2. The head computed tomography (CT) scanning with contrast revealed encephalitis, taken on 2^{nd} day of illness.

The head CT scan with contrast revealed encephalitis (a patchy low-level enhancement), but no brain edema/infarct/hemorrhage/mass. He was diagnosed with encephalitis, pneumonia, and being overweight. The patient was administered ceftriaxone injection during five days, phenytoin injection, and thermoregulation, but after the result of sputum culture came out, replaced with levofloxacin intravenously during two weeks. The patient was intubated on a ventilator for nine days at Intensive Care Unit (ICU). The patient was extubated on the tenth day in the ICU, his consciousness improved, he had no dyspnea, and he was transferred to a pediatric ward. On the 15th day of treatment, the temperature returned to normal, and the sputum culture was sterile, but the spastic tetraparesis appeared as a neurological sequela, so the patient was taken baclofen and diazepam orally. The patient was

referred to the rehabilitation department to keep the muscle strength, prevent contracture, and restore movement and function.

The spasticity didn't improve after one month of taking baclofen, diazepam orally, and physical rehabilitation therapy. To treat his spasticity, BoNT-A was injected into his upper and lower extremities. A 100-unit dosage (equal to 6-7 U/kgBW) was injected directly into the muscles, divided into 10 U (equal to 0.6-0.7 U/kgBW) for each tibialis posterior muscle, soleus muscle, gastrocnemius muscle, biceps brachii muscle, and flexor digitorum muscle.

Four weeks after the procedure, the stiffness in the hands and feet decreased. Additionally, improved were the scissor legs. The Ashworth spasticity scale improved from grade 4 to 2 (Figure 3a). Physical therapy for muscle exercise was maintained. After three months of therapy, both initially atrophic soleus muscle and lower arm muscles are improved. The patient was able to bend his hands and feet (Figure 3b).

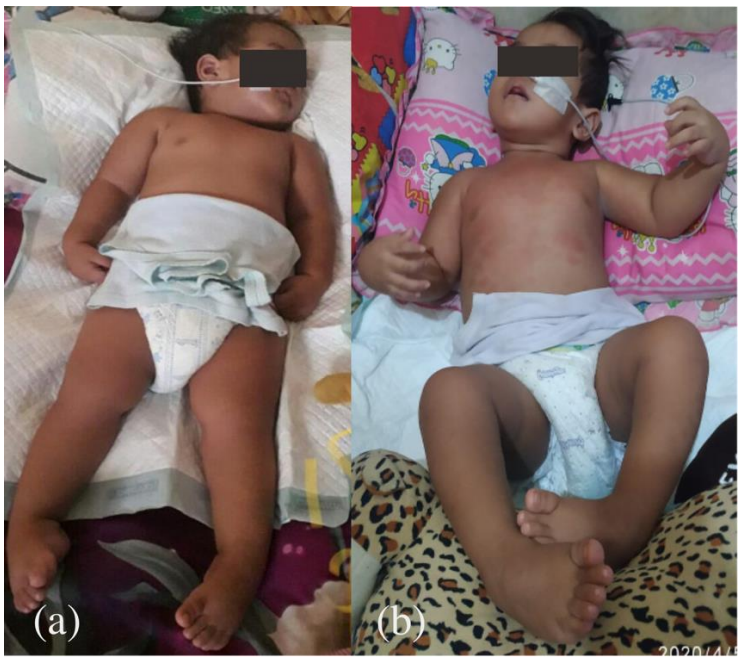

Figure 3. The Ashworth scale both of hand and feet improved from grade 4 to 2 after four weeks of BoNT-A injections (a). The boy was able to bend his hand and feet after three months of BoNT-A injections (b).

DISCUSSION

We report a 20-month-old boy with spastic tetraparesis as a neurological sequela following encephalitis. Based on CSF analysis, the most likely cause for this patient's encephalitis is a virus infection. CSF analysis revealed mild pleocytosis with dominant

mononuclear cells, normal glucose, moderately elevated protein, a negative Nonne-Pandy, and sterile culture on the tenth day of illness. A decrease in CSF glucose concentration indicates a bacterial, fungal, or protozoal etiology. In addition, up to 10% of viral encephalitis patients will have completely normal CSF, especially if the lumbar puncture (LP) is performed early in the illness (Thompson et al., 2012).

The full blood count also showed thrombocytopenia and lymphocytosis which indicated in viral encephalitis. The other primary route of viral entry into the nervous system is viral viraemia and subsequent spread across the blood-brain barrier, which occurs with enteroviruses such as polio and arboviruses such as the Japanese encephalitis virus. Although encephalitis can be caused by a variety of infectious and non-infectious agents, one of the most common causes is direct viral infection. To cause direct infection, the viruses must cross the blood-brain barrier. HSV changes the fronto-temporal areas, resulting in the loss of the typical gyral pattern and later hypodensity (Thompson et al., 2012). However, HSV encephalitis is not compatible with this diagnosis in this patient because the contrast head CT scan revealed no oral mucosa lesions or involvement of the fronto-temporal regions. In approximately one-third of cases, the cause of encephalitis is unknown (Granerod et al., 2010). Recently According to the Health Protection Agency, 60% of cases of encephalitis have no known etiology (Thompson et al., 2012).

The patient developed spastic tetraparesis as a neurological sequela following encephalitis. The longer-term complications of encephalitis include epilepsy, spasticity, and dystonia. In this case, spastic complications occur in the short term after infection. Most viruses primarily infect the brain parenchyma and neuronal cells, but some can also attack blood vessels, resulting in a strong vasculitis component (Thompson et al., 2012).

In this patient, the spasticity didn’t improve after one month of taking baclofen, diazepam orally, and physical rehabilitation therapy. Thus, BoNT-A was injected directly into the muscles. This is not suitable for the treatment of spasticity in children, If the spasticity persists after one month (persistent spasticity) and is global spasticity, starting Intrathecal Baclofen is recommended (Enslin et al., 2020). Because Intrathecal Baclofen is not available in this country, BoNT-A injection is used instead. There is no clear evidence-based guideline or step-by-step approach to treating childhood spasticity.

BONT-A injection was used as treatment in this case. Only types A and B of the seven major BoNT serotypes have been used in children with spastic paralysis because they have different unit potencies, dilution schedules, and side-effect profiles (Multani et al., 2019). BoNT type B (BoNT-B) had a less favorable adverse event profile and a shorter duration of

action than BoNT type A (BoNT-A) in children with spastic dystonia. Thus, serotype A has been used more frequently. Botulinum toxin A dosing guidelines for adults and children have been proposed. Botulinum toxin B is recommended for adults, but research for pediatric patients is ongoing (Schwerin et al., 2004). A study reported the successful use of botulinum toxin A injections into the submandibular or parotid glands alone or in combination with other agents for the treatment of drooling in children with cerebral palsy. The positive results persisted for up to 4 months without any severe side effects or issues with oral function (Jongerius et al., 2004).

Spasticity can be effectively treated with botulinum toxin A. It is widely used for spasticity control, and numerous studies back up its safety and efficacy. BoNT selectively and reversibly inhibits acetylcholine release at the neuromuscular junction, resulting in less muscle overactivity (Pirazzini et al., 2017). Although there are some general side effects, BoNT injections are known to be relatively safe (Molenaers et al., 2010). Oral medications have more systemic adverse effects, such as drowsiness and sedation, making them difficult to maintain, especially in children. Furthermore, BoNT has beneficial effects on upper limb function and gait kinematics (Moeini-Naghani et al., 2016). Although Clostridium botulinum, an anaerobic microbe, produces the strong neurotoxin known as botulinum toxin, there have been no serious systemic toxin effects associated with its usage in medicine. Concern has been raised about the formation of antibodies, but this can be avoided by spacing injections by 2-3 months.

The botulinum toxin works by preventing the release of acetylcholine at the neuromuscular junction, resulting in functional denervation. It can be administered without electromyography (EMG) or anesthesia, does not cause dysesthesias, and is no more painful than a saline solution injection. The effects are local and can last for 3-4 months or longer. Adverse effects are uncommon and usually related to the injection site, including bruising, bleeding, soreness or redness, or diffusion to nearby muscle groups. Before labeling a patient as unresponsive to botulinum toxin, it is important to consider all possible causes. Reasons could include injection technique, the patient's unique characteristics, or improper toxin storage. Relatively, botulinum toxin has been shown in clinical trials to be more effective, safe, and less painful than other invasive treatments (Keam et al., 2011).

BoNT-A was injected into both the upper (biceps brachii and flexor digitorum muscles) and lower (tibialis posterior, soleus, and gastrocnemius muscles) extremities, and it was effective in reducing spasticity. The most common target muscles in typical hemiplegic posture are the brachialis, biceps, pronator teres, flexor carpi radialis, flexor carpi ulnaris, and adductor pollicis. The larger muscles receive one or two injections, while the smaller muscles are

injected in one location. To prevent diffusion into other muscle groups and the injection of unwanted muscles, ultrasound-controlled small-volume, high-concentration injections are recommended (Multani et al., 2019). Botox injection satisfaction rate was approximately 69.2%. This treatment's goals may be as simple as decreasing pain, preventing secondary medical complications, and increasing range of motion, including contractures (Molenaers et al., 2010).

The patient received a single dose of 100 U BoNT-A, divided into 10 U for each location. Gunawan and Saharso also gave a dosage of 100 U BoNT-A, divided into 10 U for each location (rectus femoris, vastus intermedia, tibialis posterior, soleus muscles, and gastrocnemius muscle) to reduce meningoencephalitis, which causes severe spasticity in cerebral palsy patients. At four to five weeks, muscle tone and motor function both improved, as did the child's ability to bend their knees and hips, adduct their hips, bend their toes, and plantar flex their feet. After the procedure, no adverse effects were observed (Gunawan and Saharso, 2017).

An adequate injection dose for children is typically calculated based on the child's body weight. Many studies have used various dosages to treat spasticity. The dosage can be given in 15 U increments for each muscle or in units per body weight (12 U/kg or 5-28 U/kg) (Choi et al., 2016). Another method of administering Botox is to administer 100 U or 200 U per treated leg. Bjornson used 12 units/kg of Botox-A in 33 children with spastic diplegia in gross motor function classification system (GMFCS) I-III, and improvements in performance goals at 12 weeks, as well as maximum voluntary torque and gross motor function at 24 weeks, were observed (Bjornson et al., 2007).

CONCLUSION

Severe spasticity is a significant barrier to rehabilitation for children with spasticity. If the Intrathecal Baclofen is not available, BoNT-A injections can be used to reduce spasticity. Botox injection improves and enhances muscle performance in a child who has severe spasticity as a result of encephalitis. It improved scissor control and decreased spasticity.

CONFLICT OF INTEREST

The authors declare no conflict of interest exists.

FUNDING

This research was funded privately by the authors.

ETHICS CONSIDERATION

Prior to the study's execution, informed consent was obtained from the patient in accordance with the COPE and ICMJE procedures for publishing ethics. The parents' verbal and written approval was acquired.

AUTHOR CONTRIBUTIONS

RP were involved in concepting, designing, and supervising the manuscript. PIG, RN, and SMS conducted the study and analyzed the data. The final draft of the manuscript will be published to this journal with the approval of all authors, who have read and approved it.

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