

# Clinical analysis of 86 botulism cases caused by cosmetic injection of botulinum toxin (BoNT)

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## Abstract

This study was conducted to analyze the clinical characteristics of and treatment strategies for botulism among patients receiving cosmetic injection of botulinum toxin (BoNT).

A total of 86 botulism patients caused by cosmetic injection of BoNT were enrolled in our study. All of the patients were diagnosed according to their history of cosmetic BoNT injection, clinical symptoms and signs, and other auxiliary examinations (including those on renal and liver functions, blood index detection, and chest X-ray). All of the patients received comprehensive treatments and botulinum antitoxin serum injection.

The main symptoms of botulism patients included headache, dizziness, insomnia, fatigue, blurred vision, eye opening difficulty, slurred speech, dysphagia, bucking, constipation, and anxiety. These clinical symptoms occurred 0~36 days after BoNT injection, especially from 2nd to 6th day after the operation. Furthermore, the usage dose of BoNT was negatively related to latent period. Finally, patients all discharged from our hospital 1~20 days after treatments, and their symptoms relieved or disappeared.

Botulism is a severe side effect for BoNT injection. Injecting botulinum antitoxin serum may be an effective approach to improve clinical outcomes of botulism cases.

**Abbreviation:** BoNT = Botulinum toxin.

**Keywords:** botulinum toxin, botulism, cosmetic

## 1. Introduction

Botulinum toxin (BoNT) is a proteinaceous exotoxin that is produced in the growth and reproduction of anaerobic *Clostridium botulinum*, a gram-positive and spore-shaped rod bacteria.<sup>[1,2]</sup> BoNT, as a neurotoxin, is the strongest biotoxin among all known natural and synthetic toxins. Investigations have demonstrated that BoNT could affect the cholinergic motor nerve endings to disturb the release of acetylcholine via the antagonism of calcium ions, thus inhibiting shrink of muscle fibers, causing flaccid paralysis of muscles and developing temporary denervation<sup>[3,4]</sup> (Fig. 1). Specially, the paralysis of respiratory muscle represents the main cause of deaths among botulism patients.

BoNT was initially used as a biological weapon, because it could destroy nerve systems of organisms, leading to dizziness, dyspnea, muscle weakness, and some other symptoms.<sup>[5]</sup> Later, it was medically used to treat facial spasm and other muscle movement disorders. On the basis of its function of focal muscle

paralysis, BoNT has been successfully applied in clinic for treating various diseases caused by skeletal muscle spasms since 1979, such as strabismus, facial tic, refractory headache, chronic migraine, and hyperhidrosis.<sup>[6-8]</sup> Moreover, Jean Carruthers, an ophthalmologist in Canada, found that the frown lines of patients disappeared after the injection of BoNT for blepharospasm treatment, and this discovery promoted a novel cosmetic practice that revolutionized aesthetic treatment.<sup>[9]</sup> Since then, growing studies have indicated that BoNT could be employed as a cosmetic procedure. Furthermore, in 2002, the Food and Drug Administration (FDA) of USA approved the use of BoNT in cosmetology field, and then, BoNT injection has gradually become a major and common aesthetic services all over the world.

Currently, yearning for youthful look is an obsession for most women, so cosmetic injection of BoNT has swept the world for this purpose. However, the majority of people have little knowledge about adverse effects of BoNT on human bodies. It has been reported that frequent application of BoNT in short time or overdose might lead to botulism, which could endanger the physical and mental health of people, even their lives. The main clinical symptoms of botulism include muscle weakness, blepharoptosis, facial palsy, and rising difficulty. Figure 2 has been removed from the article prior to publication. The authors were not able to get patient consent for the use of this image. In the current study, we reported 86 botulism patients caused by cosmetic injection of BoNT who were admitted in our hospital from April 2009 to June 2013.

## 2. Clinical materials and methods

### 2.1. Study subjects

All of the subjects enrolled in our report were females, aged between 17 and 63 years (Table 1). They all developed botulism

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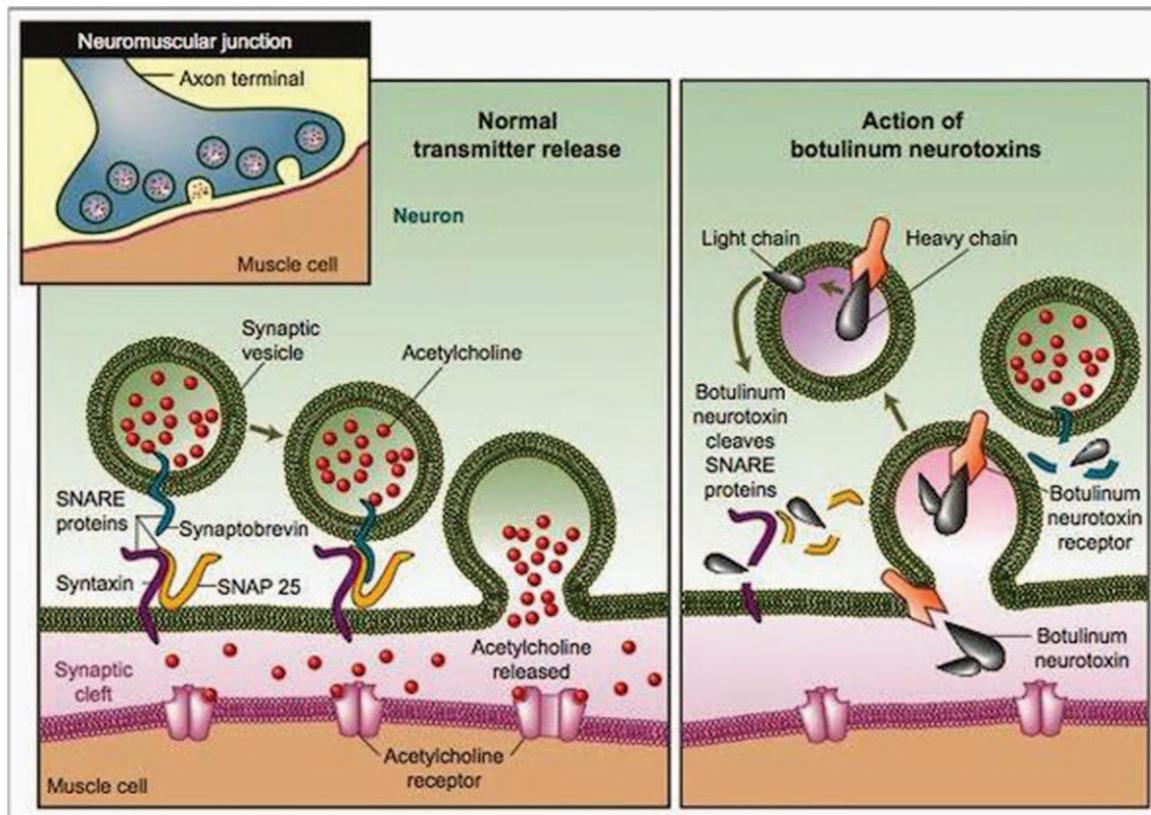


Figure 1. The effect of BoNT on acetylcholine.

after BoNT injection in upper arm, forehead, gastrocnemius muscle, masseter muscle, or some other sites to achieve “rejuvenation.” Some of them only received BoNT injection in 1 site while some others in several sites. All of 86 patients were directly injected with A-type BoNT with no history of drug or food allergies. Patients presented rising difficulty, blepharoptosis, weak convergence reflex, facial palsy, limb myasthenia, cyanotic lips, and tachypnea. The study was approved by the Ethics Committee of our hospital. Written informed consent was obtained from each participant. The patients agreed to show their images for publication.

**2.2. Diagnosis modality**

On the basis of chief complaints, the patients’ poisoning statuses and degrees were determined according to the history of cosmetic

BoNT injection, clinical symptoms, and signs as well as other auxiliary examinations. The classification standards were as follows: mild botulism: developing dizziness, headache, fatigue, blepharoptosis, and/or blurred vision, not affecting normal life; moderate botulism: apart from the above listed symptoms, dysphagia and/or bucking were observed, and nasal feeding was adopted accordingly; and severe botulism: apart from all of the above-mentioned symptoms, respiratory failure appeared and mechanical ventilation was applied.

**2.3. Auxiliary examinations**

Auxiliary examinations used for patients’ diagnosis included those on renal and liver functions, blood index detection, chest X-ray, and abdominal ultrasound.

**2.4. Differential diagnosis**

On the basis of the patients’ chief complaints and their clinical symptoms, the differential diagnosis was conducted to discriminate BoNT botulism from myasthenia gravis, Guillain-Barre syndrome, cerebrovascular diseases, cervical vertebra diseases, and polymyositis.

**2.5. Therapeutic methods**

All of the patients received comprehensive treatments, including nerve nutrition, systemic support and symptomatic treatment, and the injection of botulinum antitoxin serum. The concrete steps and standards are listed as follows.

| Age, y | Case no. | Incidence rate (%) |
|--------|----------|--------------------|
| ≤20    | 2        | 2.33               |
| 21–25  | 12       | 13.95              |
| 26–30  | 29       | 33.72              |
| 31–35  | 21       | 24.42              |
| 36–40  | 10       | 11.63              |
| 41–50  | 10       | 11.63              |
| >50    | 2        | 2.33               |

BoNT = Botulinum toxin.

**Table 2**  
Dosage distribution of 86 BoNT-poisoned patients.

| Dosage, IU | Case no. | Percentage |
|------------|----------|------------|
| ≤100       | 14       | 16.28      |
| 101–200    | 28       | 32.56      |
| 201–300    | 18       | 20.93      |
| 301–400    | 7        | 8.14       |
| 401–500    | 2        | 2.33       |
| >500       | 2        | 2.33       |
| Unknown    | 15       | 17.44      |

BoNT = Botulinum toxin.

**2.6. Nerve nutrition: patients took neurotrophic drugs**

**2.6.1 Systemic support**

Dysphagia patients received nasal feeding or intravenous nutrition to maintain the water-electrolyte balance.

**2.6.2 Symptomatic treatment**

Patients should pay attention to rest and psychological counseling. For those patients with moderate to severe botulism, their signs would be monitored closely. Severe patients would accept tracheal intubation and mechanical ventilation.

**2.6.3 Botulinum antitoxin serum**

Patients with negative skin test were given 10,000 IU antitoxin serum via intramuscular injection, once every 12 hours; patients with positive or weak positive skin test were given 10,000 IU via desensitization injection, once a day. For all the patients, once the conditions were improved or stopped exacerbating, the injection dose could be reduced. The amount of antitoxin serum should be about 30,000~50,000 IU.

**3. Results**

**3.1. Clinical information of 86 patients with botulism**

In our investigation, the patients were injected with different dosages of BoNT, ranging from 6 to 1000 U (Table 2). The clinical symptoms of botulism occurred within 0~36 days after injection, mainly between 2nd and 6th day after the operation (Fig. 3). What is more, according to Spearman analysis, the injection dose of BoNT was negatively correlated with botulism

onset time. The detailed symptoms of the patients and the numbers of corresponding events were as follows: headache, 18 cases; dizziness, 68 cases; insomnia, 33 cases; fatigue, 74 cases; blurred vision, 72 cases; eye opening difficulty, 62 cases; slurred speech, 37 cases; dysphagia, 61 cases; bucking, 35 cases; constipation, 15 cases; anxiety, 36 cases; nasal feeding, 21 cases; and prejudices in normal life, 26 cases (Table 3). Fatigue and blurred vision were the most frequently observed symptoms.

**3.2. Auxiliary examinations**

To exactly identify the poisoning statuses of patients, several auxiliary examinations were performed. The majority of patients (80 cases) had normal kidney function. The examination on liver function found mild abnormality in 8 cases, with a slight increase in amylase. Ten patients presented raised platelet count and neutrophil number. Five cases developed tachycardia and 9 had lung infection showed in X-ray chest radiograph. All patients got normal abdominal viscera via ultrasound detection.

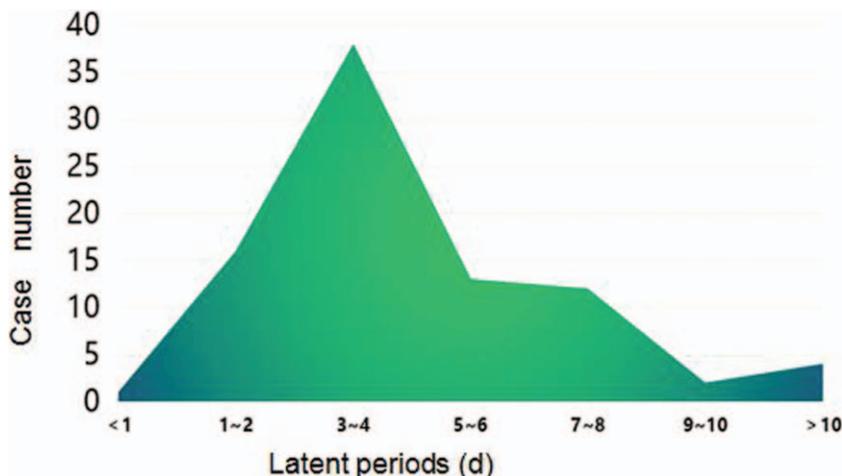
**3.3. Treatment outcomes**

After treatments, the patients received comprehensive examinations again. The discharge criteria were as follows: subjective

**Table 3**  
Clinical symptoms of 86 BoNT-poisoned patients.

| Symptoms                 | Case no. | Incidence rate (%) |
|--------------------------|----------|--------------------|
| Headache                 | 18       | 20.93              |
| Dizziness                | 68       | 79.07              |
| Insomnia                 | 33       | 38.37              |
| Fatigue                  | 74       | 86.05              |
| Blurred invasion         | 72       | 83.72              |
| Difficult eyes open      | 62       | 72.09              |
| Unclear articulation     | 37       | 43.02              |
| Dysphagia                | 61       | 70.93              |
| Drink bucking            | 35       | 40.70              |
| Constipation             | 15       | 17.44              |
| Anxiety                  | 36       | 41.86              |
| Nasal feeding            | 21       | 24.42              |
| Prejudice in normal life | 26       | 30.23              |

BoNT = Botulinum toxin.



**Figure 3.** The clinical symptoms of botulism occurred 0~36 days after injection, mainly between 2nd and 6th day after the operation.

symptoms significantly relieved or disappeared; no respiratory muscle involved; regaining smooth feeding and drinking; recovering the strength of limb muscle and restoring normal sight. Patients were discharged from our hospital within 1~20 days after receiving combined therapies and botulinum antitoxin serum injection.

#### 4. Discussion

BoNT, a zinc-dependent endopeptidase, is a strong, irreversible and fatal neurotoxin, and inappropriate application of BoNT may cause botulism. It has been reported that the toxicity of BoNT is significantly higher than that of potassium cyanide. The lethal dose of BoNT for human beings is only 0.1 µg, and 1 g crystalline toxin could kill over 1 million people.<sup>[10,11]</sup> According to its antigenic difference, BoNT could be categorized into 7 serotypes: A, B, C, D, E, F, and G, among which the A, B, E, and F types are involved in human botulism, while C and D types are responsible for animals botulism.<sup>[12,13]</sup> In addition, BoNT/A is clinically applied most prevalently because of its stability, strongest toxicity, easy preparation, and longest time of maintaining function in low temperature. The patients in our report were all BoNT/A-poisoned cases.

The application of BoNT in cosmetic field has been widely reported worldwide.<sup>[14,15]</sup> Compared with traditional chemical cosmetic methods, such as chemical peeling and face lift, BoNT cosmetology is characterized by little injury, no wound, fast effects, and rapid recovery. Therefore, BoNT injection in cosmetic area has become more and more popular. For cosmetology, the effects of BoNT will occur about 2~3 days after injection and will be obvious 1 week later. Such effect could last for 12~24 weeks and need only 1 more injection half a year later to maintain. Moreover, evidence proves that the injection dose of BoNT is closely related to its effects on muscle paralysis and to wrinkle smooth. Injection with a high dose of BoNT can produce strong paralysis effect with long action time. However, excessive injection of BoNT can also cause side effects due to the involvement of near muscles.

With the wild application of BoNT in cosmetic field, people in need can repeatedly receive such operation in a short period, which may cause botulism due to BoNT overdose. What is more, in many individual medical cosmetology institutions, BoNT uses are frequently arbitrary. The majority of the patients in our report had received BoNT injection in irregular beauty salons. Some of them had taken BoNT in several sites, and some received BoNT injection several times at the same site, resulting in toxin accumulation and consequent botulism. Certain symptoms such as headache, dizziness, insomnia, fatigue, and dysphagia appeared in these cases, but were relieved or disappeared after antitoxin serum treatment and symptomatic therapies. Furthermore, the FDA referred in February 2008 that the safety, effectiveness, and proper dosages of BoNT in certain diseases and populations are still not clear. As a result, the dosages of BoNT should be strictly controlled for whatever disease treatment or cosmetology to avoid the occurrence of side effects.

As BoNT could inhibit acetylcholine release, muscles dominated by cranial nerves and motor nerves will be paralytic among botulism patients, and this phenomenon may be aggravated along with acetylcholine exhaust. Early application of botulinum antitoxin serum and certain symptomatic support treatments, such as active infection prevention, is important for botulism treatment.<sup>[16,17]</sup> The earlier the treatments are performed, the better the effects are. However, cosmetic botulism is insidious,

and often evades from being detected in early examination. Furthermore, as operators and patients frequently possess insufficient or little knowledge about botulism, botulism may occur among people receiving BoNT injection, leading to pulmonary infection and other complications.

In a word, cosmetic botulism is a severe event caused by inappropriate injection of BoNT. The injection dosage of BoNT is positively correlated with botulism severity. Once botulism occurs, timely and appropriate treatments are needed to improve patients' clinical outcomes.

#### Author contributions

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**Validation:** Yanqing Liu, Xin Wang, Xingwang Wang, Kun Wan.

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**Writing – original draft:** Yanqing Liu, Yawei Sun, Xin Wang, Guodong Lin, Kun Wan.

**Writing – review & editing:** Yawei Sun, Xin Wang.

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