

A Case Study on the Use of Trihexyphenidyl, Korean Medical Treatment for the Control of Sialorrhea in Patients with Amyotrophic Lateral Sclerosis(ALS)※

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Key words :
 Amyotrophic lateral sclerosis(ALS);
 Sialorrhea;
 Oriental medical treatment;
 Trihexyphenidyl

[Abstract]

Objectives : Sialorrhea in amyotrophic lateral sclerosis patients is a cause of death due to aspiration pneumonia as well as reduces the patient's quality of life. We report the changes that appeared in the sialorrhea treated by using trihexyphenidyl and Korean medical treatments.

Methods : We treated amyotrophic lateral sclerosis patient with sialorrhea by using trihexyphenidyl a known antiparkinsonian agent and Korean medical treatments such as acupuncture, pharmacopuncture and herbal medicine. The salivation rate was checked with visual analogue scale(VAS).

Results : There was a more than 50 % decrease in salivation in this case. Owing to the constipation, trihexyphenidyl was stopped after which only Korean medical treatments were provided. Over which a lasting decrease in salivation could be seen.

Conclusions : Existing treatments would cause several considerable side effects and have difficulty in being applied in domestic clinics. In this respect, we suspect that our findings could open up new clinical guideline possibilities. We should solve the limitations of this case study and conduct more studies.

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I. Introduction

Amyotrophic Lateral Sclerosis(ALS) is a progressive and fatal neurodegenerative disorder involving primarily the motor neurons in the cerebral cortex, brainstem and spinal cord. With in 2~4 years, it causes progressive and severe muscle weakness, eventually causing death due to respiratory muscle palsy¹⁾. Symptoms of bulbar dysfunction are common in ALS, presenting as an initial symptom in nearly half(45 %) of the patients, and presenting in almost 81 % of the patients at the time of death^{2,3)}. ALS patients with bulbar dysfunction frequently develop dysarthria and difficulty in swallowing that cause sialorrhea at a relatively early stage in the disease. Such sialorrhea reduces the patient's quality of life due to social problems, such as embarrassment, discomfort, difficulty in speaking, as well as increasing the risk of aspiration pneumonia⁴⁾.

Recently, several different treatments for sialorrhea in ALS have been introduced. Treatment options for sialorrhea range from conservative (observation, postural control, biofeedback, spit-cup) to more aggressive measures such as pharmacotherapy, botulinum toxin (BTX) injection, radiotherapy, and surgical treatment. Salivary gland irradiation and surgical ablation are effective and permanent, but they can result in an irreversibly dry mouth and exacerbation of dysphagia and dysarthria. Some studies reported acute deterioration of bulbar function after botulinum toxin treatment for sialorrhoea in ALS⁵⁾. As these method have various side effects and there is difficulty in applying them in domestic clinics, additional discussions are needed.

Domestic studies on ALS patients have been conducted by Kim et al⁶⁾, Ryu et al⁷⁾, Choi et al⁸⁾, Cheon et al⁹⁾, Park et al¹⁰⁾, Ryu et al¹¹⁾, Kwon¹²⁾ etc. However, studies on ALS patients with sialorrhea are inadequate. Especially, since there have been no studies so far using Korean medical treatments such as acupuncture, pharmacopuncture, herbal medicine and western medicine treatments. So we need to make effective and practical clinical guidelines as soon as

possible.

We administered *trihexyne* a known antiparkinsonian agent with Korean medical treatments to an ALS patient with sialorrhea in our hospital between 8th March and 26th May 2012. After which, we stopped the *trihexyne* and provided Korean medical treatment only until 2012.6.25. We reported the changes that appeared in the sialorrhea during this period.

II. Case study

1. Patient

Sohn ○○ M/61

2. Chief complaints

dysarthria, sialorrhea, dysphagia, sputum, fasciculation (Rt. leg), both lower limb weakness

3. Onset

2010. 2

4. Past medical history

N/S

5. Family history

N/S

6. Medication history

Ambrect Tab. 2T#2, Busron Tab. 10 mg 2T#2, Oropherol Soft Cap. 100 mg 2T#2, Platless Tab. 1T#1, Livaro Tab. 2 mg 1T#1, Aronamin C plus Tab. 2T#2

7. Present illness

① 2010. 2

After playing tennis, dysarthria developed.

② 2010. 4

Visiting Korea University Hospital. B-CT, MRI→ None specific.

- ③ 2010. 8
Asan hospital admission. (for 4D) EMG, Genetic testing → ‘Motor neuron disease’ diagnosed.
- ④ 2011. 4
Visiting Seoul National University Hospital. EMG, Genetic testing etc. → ‘ALS’ diagnosed.
- ⑤ 2011. 8
Visiting Asan Hospital. Several test → ‘ALS’ diagnosed.
- ⑥ 2011. 11. 29~12. 28, 2012. 1. 2~1. 19
Gwang-Ju Oriental Medical Hospital, Wonkwang University admission treatment.
- ⑦ 2012. 1. 26
Admission(by wheel chair)

8. Examination views

- ① EKG : normal
- ② LAB : MCHC 37.4 ↑, Eos% 14.6 ↑, Eos# 1.0H, Baso% 1.1 ↑, ALT 43 ↑, ALP 79.0 ↓, Glucose 106.0 ↑
- ③ Motor Grade : Shoulder 5-/5-, Elbow 5/5, Wrist 5-/5-, Finger 5-/5-, Hip 3/3, Knee 4/4, Ankle 3/4, 1st toe 3/4
- ④ Neurological examination
Mental state : Alert
Pupil reflex : 2+/2+
Knee jerk reflex : →→
Biceps reflex : →→
Babinski sign : -/-

9. Korean medical diagnosis

Wei symptom(痿證)

10. Treatment method

a. Trihexyne tabs

Trihexyne a known antiparkinsonian agent and manufactured by Tai guk pharmaceuticals was used, between 2012. 3. 8 and 2012. 3. 19 *Trihexyne* (0.5 mg) was administered to the patient 30 minutes

Table1. *Trihexyne* Administration

Date	12. 3. 8~19	12. 3. 20~ 5. 26	12. 5. 27~
Dose	0.5 mg/d	1 mg/d	Stop

after eating breakfast, however salivation of the patient increased. *Trihexyne*(1 mg) was administered in the same way between 2012. 3. 20 and 2012. 5. 26. During this period the patient had complained of slight constipation so the administration of *trihexyne* was stopped (Table 1).

b. Acupuncture & pharmacopuncture

① Monday, Wednesday, Friday

Sa-am acupuncture lung tonification(太白SP₃ · 太淵LU₉ · 少府HT₈ · 魚際LU₁₀) was conducted on both sides by single-use 0.25×40 mm needles(DongBang acupuncture, Inc Korea). The SP₃ and LU₉ acupoint needles were electrically charged at 2 Hz and also stimulated using infra red for 15 minutes.

0.1 cc of Scolopendrid pharmaco-puncture(Korean pharmacopuncture institute) was injected equally at acupoints of *Hagwan*(ST₇) · *Jichang*(ST₆) · *Cheondol*(CV₂₂) · *Daechu*(GV₁₄) · *Amun*(GV₁₅) · *Pungbu*(GV₁₆) · *Gyeonjeong*(GB₂₁).

After checking for allergic reactions using a skin test, 0.1cc of bee-venom pharmaco-puncture(Korean pharmacopuncture institute) was administered equally on the acupoints of *Joksamni*(ST₃₆) · *Susamni*(LI₁₀) · *Hapgok*(L₄) · *Guheo*(GB₄₀) · *Pungsi*(GB₃₁).

② Tuesday, Thursday, Saturday

Scalp acupuncture in motor area was conducted by single-use 0.3×40 mm needles(DongBang acupuncture Inc, Korea) for 15 minutes. Bulbar palsy treatment was conducted by stimulating the soft palate and applying acupuncture in Geumjin, Okaek acupoints by single-use 0.4×0.75 mm needles(DongBang acupuncture Inc, Korea). After which, bamboo salt was spread over the procedure region.

0.2 cc of Hominis placenta pharmacopuncture(Korean pharmacopuncture institute) was injected equally at acupoints of *Sinsu*(BL₂₃), *Jangmun*(LR₁₃), *Amun*(GV₁₅).

Table 2. Herbal Medicine Treatment

Date	Herbal medicine
2012. 3. 10~13	<i>Scolopendra</i> 8 g, <i>radix ginseng</i> 4 g, <i>fructus crataegi</i> 4 g, <i>fructus amomi rotundus</i> 4 g, <i>fructus amomi xanthioidis</i> 4 g, <i>radix platycodi</i> 6 g, <i>radix glycyrrhizae</i> 8 g, <i>radix aconiti lateralis preparata</i> 6 g, <i>cortex magnoliae officinalis</i> 4 g, <i>radix puerariae</i> 10 g, <i>semen glycine</i> 10 g, <i>fructus schisandrae</i> 6 g, <i>batryticatus bombycis</i> 2 g, <i>holotrichia</i> 2 g, <i>herba cirsii</i> 4 g, <i>arillus longan</i> 4 g, <i>semen raphani</i> 4 g(1 time/d)
2012. 3. 14~6. 10	6 g of <i>radix platycodi</i> was changed to 2 g in the previous prescription(1 time/d).
2012. 6. 11~22	<i>Cortex acanthopanacis</i> 12 g, <i>semen raphani</i> 8 g, <i>herba cirsii</i> 10 g, <i>cortex cinnamomi</i> 6 g, <i>fructus hordei germinatus</i> 6 g, <i>fructus amomi rotundus</i> 10 g, <i>semen benincasae</i> 6 g, <i>radix ginseng</i> 4 g, <i>fructus chaenomelis</i> 10 g, <i>thallus laminariae</i> 4 g, <i>fructus ziziphi jujubae</i> 4 g, <i>rizoma zingiberis recens</i> 4 g(1 time/d)
2012. 5. 28~6. 15	<i>Maziren powder</i> (3 times/d)

Table 3. Progress and VAS Change

Date	Progress	VAS
2012. 3. 8~10	No change	7
2012. 3. 11~15	Slightly more	8
2012. 3. 16	The most	10
2012. 3. 17~26	Slightly less than 3. 16 (3. 20 <i>Trihexyne</i> 0.5 mg → 1 mg)	9
2012. 3. 27	Same as first	7
2012. 3. 28	Less than beginning for the first time	6
2012. 3. 29~31	More decreased	5
2012. 4. 1~19	More decreased	4
2012. 4. 20~24	More than before	6
2012. 4. 25~28	Same as first	7
2012. 4. 29~5. 2	Less than before	5
2012. 5. 3~8	More decreased	4
2012. 5. 9~10	More than before	6
2012. 5. 11	More decreased	5
2012. 5. 12~26	More decreased (5. 26 <i>Trihexyne</i> stop)	4
2012. 5. 27	Same as before	4
2012. 5. 28~6. 25	The least and last	3

c. Herbal medicine

2012. 3. 10~6. 10 prescription named ‘*Okong* decoction(蜈蚣湯)’ was administered 30minutes after eating breakfast.

2012. 6. 11~6. 22 prescription named ‘*Ogapi* decoction(五加皮湯)’ was administered in the same way.

2012. 5. 28~6. 15 ‘*Mazain* powder(麻子仁散)’ was administered three times a day due to constipation (Table 2).

11. Assessment & Result

The salivation rate was checked with visual analogue scale(VAS). The patient rated himself by marking the VAS ruler representing the subjective amounts of sialorrhea (range from 0 to 10, where 0 represents no drooling and 10 represents constant drooling) at 8pm everyday.

We measured VAS(Table 3), (Fig. 1).

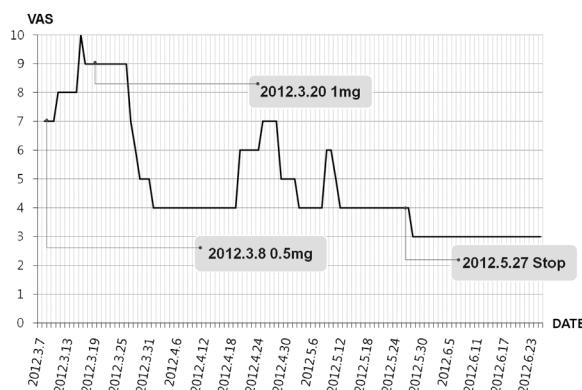


Fig. 1. Sialorrhea VAS change

III. Discussion

The worldwide incidence of ALS is reported to range between 0.4 and 2.6 / 100,000 individuals per year, reviewed in Beghi et al¹³⁾. There is no difference between race, geography and socioeconomics¹⁴⁾. The symptoms of ALS include spasticity, muscle weakness and wasting, impaired speaking, swallowing and breathing as well as sialorrhea. Survival time is significantly reduced when the disease starts with bulbar symptoms or at an older age.

Sialorrhea is a disabling problem in bulbar-onset ALS, although it is not a direct cause of death, it causes reduced quality of life such as sanitary problems, discomfort, embarrassment, difficulty in swallowing, speaking and increased risk of aspiration pneumonia. *Trihexyne* composed of trihexyphenidyl is an anti-parkinsonian agent of the anti-muscarinic class. Trihexyphenidyl is used for the symptomatic treatment of Parkinson's disease in mono and combination therapy. The exact mechanism of action in parkinsonian syndromes is not precisely understood, but it is known that trihexyphenidyl blocks efferent impulses in parasympathetically innervated structures like smooth muscles, salivary glands, and the eyes. To function, it binds to the M1 muscarinic receptor and possibly the dopamine receptor. It is known that the effectiveness of trihexyphenidyl is treating the extrapyramidal side effects and reducing the frequency and duration of oculogyric crises as well as of dyskinesic movements and spastic contractions and excessive salivation etc¹⁵⁾. Taking advantage of these facts, we make use of it for treating sialorrhea in ALS patient, but on the other hand, we cannot use it consistently and in quantity because of its side effects. It is known that side effects of anticholinergic agent such as *trihexyne* are divided into two types: peripheral and central. Peripheral side effects include blurred vision, dry mouth, decreased GI motility, decreased secretions, tachycardia, and urinary bladder retention. Central side effects include sedation, decreased concentration, forgetfulness, confusion, and psychotic symptoms¹⁶⁾. Thus, we should

use anticholinergic drugs carefully and find other treatments.

ALS belongs to the category of *Wei* symptom(痿證) in Korean medicine. The five types of *Wei* symptom were described as “*Wei* symptoms include five types (痿證有五色). Heat in the lung dries lung parenchyma and leads to *Wei Pi*(肺熱葉焦者爲痿癱). Heat in the heart dries heart *Qi* and leads to *Mai Wei*(心熱氣燥者爲脈痿). Heat in the liver leads to *Jin Wei*(肝氣熱者爲筋痿). Heat in the spleen leads to *Rou Wei*(脾氣熱者爲肉痿). Heat in the kidney leads to *Gu Wei*(腎氣熱者爲骨痿).” in 《圖解校勘舍岩道人鍼法·痿證門》¹⁷⁾. We judged that above ALS patient with sialorrhea, dysarthria and dysphagia was similar to type of 痿癱. Based on this, the Sa-am acupuncture lung tonification treatment(太白·太淵 補, 少府·魚際 瀉) was selected to treat 痿癱.

Stimulation of the soft palate and application of acupuncture in the Geumjin, Okaek were carried out with the purpose of improving the symptoms of bulbar palsy such as dysarthria, dysphagia, sialorrhea.

Pharmacopuncture such as Scolopendrid, bee-venom, hominis placenta pharmacopuncture was used for enhancing immunity, strength and treating muscle weakness and pain caused by joint contracture.

It is known that characteristic of scolopendrid is sour(辛), warm(溫), and very dry(猛燥). It can be used to treat disorders such as wind(風), cold(寒), dampness(濕)¹⁸⁾. Sialorrhea is considered a type of dampness. Taking advantage of dry character of Scolopendrid, we make use of *Okong* decoction for treating sialorrhea.

In this case study, there appeared to be a reduced sialorrhea in the ALS patient after using *trihexyne* tab. and Korean medical treatment. There was a more than 50 % decrease in salivation in this case.

In the early stages of the study, salivation increased because the patient didn't receive a high enough dose of *trihexyne*, as well as being diagnosed as suffering with another ongoing neurodegenerative disease.

No serious adverse side effects of *trihexyne* were encountered except slight constipation in the treatment period.

Owing to the constipation, *trihexyne* was stopped after which only Korean medical treatments were

provided. After which patient progress was monitored. Over which a lasting decrease for a month in salivation could be seen.

Existing studies show that invasive treatments have many side effects and overdose or long-term use of anticholinergic drugs cause serious side effects^{5,16}. Even though we cannot definitively confirm that the Korean medical treatment might directly affect sialorrhea, it shows effect on lasting decrease in salivation. It is important to show that the Korean medical treatment could be a complementary treatment to existing treatments which have many side effects.

The limitations of this study include there was only one patient, uncontrolled design, and lack of blinding. As it judges a change of salivation only with VAS, there is also insufficient data to make an objective and/or a subjective evaluation.

Existing treatments would cause several considerable side effects and have difficulty in being applied in domestic clinics. In this respect, despite some limitations, we suspect that our findings could open up new clinical guideline possibilities.

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