Effective Botulinum Toxin injection point for treatment of headache

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Effective Botulinum Toxin injection point for treatment of headache

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석사, 박사과정을 거쳐 이 논문을 완성하기까지 부족한 저를 이끌어 주시고 연구자로서의 첫 발을 내딛게 해주신 허경석 지도교수님께 다시 한 번 깊은 감사의 말씀을 드립니다. 논문의 작성과 심사에 아낌없는 조언과 도움을 주신 김희진 교수님, 임상적 관점에서 소중한 조언을 해주신 안형준 교수님께도 깊은 감사를 드립니다. 또한 논문 심사와 대학원 과정 동안 많은 도움을 주신 원성윤, 이재기 교수님 감사합니다.

그리고 저의 연구와 실험에 큰 도움을 주신 최유진 선생님을 비롯한 해부학교실 조교 선생님들께도 감사드립니다.

학부 때부터 늘 저를 격려해 주시는 이근우 학장님과 논문 공개발표시 많은 조언과 관심을 보여주신 김광만 교수님, 심준성 교수님, 대학원 과정동안 많은 격려를 해주신 유형석 교수님, 문석준 교수님, 박원서 교수님께도 감사의 말씀을 드립니다.

개원의로 또 대학원생으로 임상진료와 학업을 동시에 한다는 것이 쉽지 않은 과정이었음에도 박사과정을 잘 끝마칠 수 있도록 저를 도와주었던 우리 연세웰치과 직원들에게 감사를 표합니다.

어린 시절 인내와 끈기의 가르침을 주신 아버지, 항상 아들을 믿

고 응원해 주시는 어머니, 항상 저희 가족을 사랑으로 보살펴 주시는 장모님, 이 아빠에게 언제나 웃음과 희망을 주는 건명, 강민 사랑스러운 두 딸과 뱃 속의 셋째에게, 마지막으로 대학원 과정동안 헌신적인 내조를 해준 사랑하는 나의 아내 남수연에게 이 논문을 바칩니다.

감사합니다.

2015년 06월

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The underlying causes of migraine are often nerve and muscle disorders, which has led to botulinum toxin type A (BoNT-A) injection gaining traction as a viable treatment option. However, previous injection sites on the temporalis muscle for treating migraine were determined by observing the trigger point of migraines, and it is unsure whether these are the most anatomically effective sites for injection (Whitcup et al., 2014).

This study performed an extensive analysis of published research on the morphology of the temporalis muscle in order to provide an anatomical guideline on how to distinguish the temporalis muscle and temporalis tendon by observing the surface of the patient's face. Furthermore, it was found that Sihler's staining could be applied to the temporalis muscle in order to identify accurate and effective BoNT-A injection sites for treating migraines.

Twenty-one hemifaces of cadavers (16 males, 5 females; mean age, 81.0 years; age range, 63 - 93 years) were used in this study. The experiment was divided into two steps: (1) morphologically analyzing the temporalis region of the cadavers and (2) applying Sihler's staining to the temporalis muscle and tendon.

The posterior border of the temporalis tendon was classified into three types according to its location relative to five reference lines: in Type I the posterior border of the temporalis tendon is located in front of reference line L2 (4.8%, 1/21), in Type II it is located between reference lines L2 and L3 (85.7%, 18/21), and in Type III it is located between reference lines L3 and L4 (9.5%, 2/21).

The vertical distances between the horizontal line passing through the jugale (LH) and the temporalis tendon along each of reference lines L0, L1, L2, L3, and L4 were 29.74±6.87 mm (mean±SD), 45.06±8.84 mm, 37.76±11.18 mm, 42.50±7.59 mm, and 32.14±0.47 mm, respectively; the corresponding vertical distances between LH and the temporalis muscle were 55.02±8.25 mm, 74.99±9.90 mm, 73.97±10.12 mm, 55.24±13.25 mm, and 47.56±11.41 mm.

Sihler's staining shows that the anterior and posterior branches of the deep temporal nerve run through the anterior and posterior fibers of the temporalis muscle, respectively.

BoNT-A should be injected into the temporalis muscle at least 45 mm vertically above the zygomatic arch. This will ensure that the muscle region is targeted and so produce the greatest clinical effect with the minimum concentration of BoNT-A. In order to easily identify the temporalis muscle in a clinical setting, the second finger should be placed on the bottom corner of the zygomatic arch; the tip of the thumb will then be located 45 mm from the zygomatic arch.

Key words : Migraine, Botulinum toxin type A, Temporalis, Injection site, Sihler stain

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I . INTRODUCTION

Headaches can be clinically classified into primary and secondary types. Primary headaches occur without underlying organic diseases and can be further classified into migraine, tension-type headache, and cluster headaches. Among the three classifications, migraines have the strongest hereditary associations. Patients suffering from migraines often show hypersensitive reactions to light, sounds, and touch, and during severe episodes this can lead to photophobia, acousticophobia, and olfactophobia. Although migraines are not life-threatening, they can severely impair the everyday lives of affected patients.

The underlying causes of migraines are often nerve and muscle disorders,

which has led to botulinum toxin type A (BoNT-A) gaining traction as a viable treatment option (Carruthers and Carruthers, 2001; Göbel et al., 2001; Heckmann et al., 2001). BoNT-A reportedly has fewer side effects than the drugs that are commonly used to migraines. Furthermore, a single BoNT-A treatment can last up to 4 months, in contrast to the fairly short-term effects of orally administered drugs and lidocaine injections (Dodick et al., 2004; Chan et al., 2009).

The US Food and Drug Administration (FDA) recognized the safety and effectiveness of BoNT-A by approving 31 injection sites for BoNT-A on October 2010. Among them, four injection sites on each side of the temporalis muscle were suggested. These injection sites were approved after observing the clinical ramifications of BoNT-A injections originally aimed at treating tension-type headaches. However, anatomical research focused on the neural distribution of the head and neck area is needed to form the basis for accurate and specific BoNT-A injections.

The specific mechanism by which BoNT-A relieves pain has not yet been identified (Robertson et al., 2012; Cernuda et al., 2014), but it can be hypothesized that the relief of muscular tension, and transcytosis and the retrograde transport of BoNT-A suppresses the diffusion of neurotransmitters across the peripheral nerve (Ramachandran and Yaksh, 2014). These mechanisms suppress both peripheral and central sensitization, providing relief for patients suffering from peripheral and central neuritis. Since BoNT-A acts on nerve endings, an extensive and accurate anatomical understanding of the nerve endings of the targeted muscle is critical for obtaining maximum relief with the minimum concentration of BoNT-A.

Invasive anatomical procedures are of limited use when attempting to find effective BoNT-A injection sites due to the risk of damaging the muscle and the target nerve endings. In contrast, Sihler's staining, which dyes myelin

sheaths, provides a minimally invasive and effective method of tracking nerve endings within a targeted muscle (Won et al., 2011; Yang et al., 2013).

Since migraines often occur in the temporal region, the temporalis muscle is the main target for BoNT-A injections aimed at treating migraines. The application of Sihler's staining to the temporalis muscle will facilitate accurate and extensive observations of the neural distribution and nerve endings of the deep temporal nerve.

The morphology of the temporalis muscle restricts the ability to identify effective injection sites by simply observing the associated neural distribution, and the pharmaceutical application of BoNT-A in the tendon region is highly ineffective. Sihler's staining must therefore be accompanied by morphological investigations of the temporalis muscle and temporalis tendon.

This study performed an extensive analysis of published research on the morphology of the temporalis muscle in order to provide an anatomical guideline on how to distinguish the temporalis muscle and temporalis tendon by observing the surface of the patient's face. Furthermore, it was found that Sihler's staining could be applied to the temporalis muscle in order to identify accurate and effective BoNT-A injection sites for treating migraines.

Ⅱ. MATERIALS & METHODS

1. Materials

Twenty-one hemifaces of cadavers (16 males, 5 females; mean age, 81.0 years; age range, 63 - 93 years) were used in this study. All of the cadavers were donated by Yonsei Medical Center. None of the cadavers had any damage or previous surgery in the temporal region. The experiment was divided into two steps: (1) morphologically analyzing the temporalis region of the cadavers and (2) applying Sihler's staining to the temporalis muscle and tendon.

2. Methods

2.1. Morphological analysis of the temporalis muscle and tendon

The skin, subcutaneous tissue, and superficial and deep temporal fasciae of the temporalis muscle were first removed, which allowed the temporalis tendon and temporalis muscle to be clearly identified. This study used several anatomical points as standard markers to measure the width, height, and length of the temporalis muscle.

In order to provide a clear clinical guideline for BoNT-A injection in the temporalis region, the jugale and zygomatic arch were used as structural anatomical markers to morphologically delineate the temporalis muscle. The reference points and lines shown in Fig. 1 were established prior to making the measurements described below.

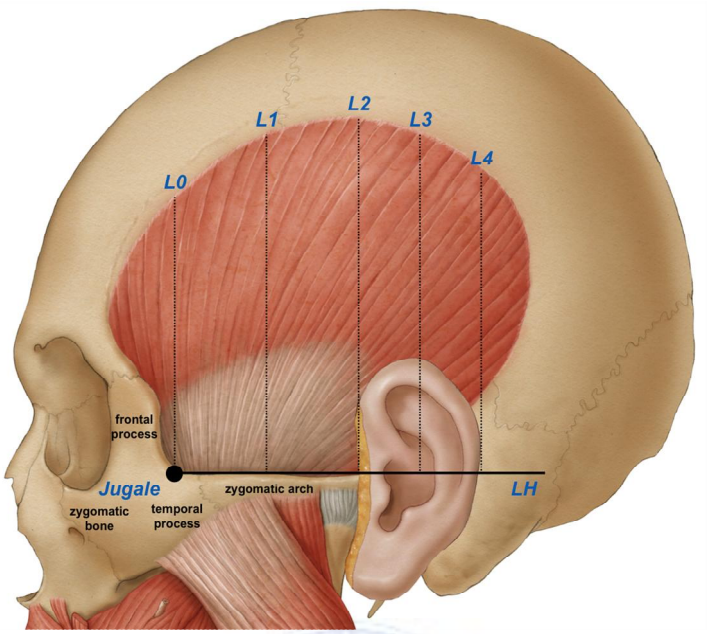

Fig. 1. Reference points and lines based on surface anatomical structures. Jugale: A landmark on the skull at which the temporal and frontal processes of the zygomatic bone meet. LH: The horizontal line passing through the jugale. L0: The vertical line passing through the jugale. L1: The line evenly dividing L0 and L2. L2: The vertical line passing through the anterior outer margin of the ear. L3: The line evenly dividing L2 and L4. L4: The vertical line passing through the posterior outer margin of the ear.

Horizontal line LH was used as a standard for measuring the vertical distances separately to the temporalis muscle and temporalis tendon using vertical lines L0 - L4 as defined in Fig. 1. All measurements were made using a protractor and digital calipers (CD-15CP, Mitutoyo, Kawasaki, Japan) capable of measuring to the nearest 0.01 mm.

2.2. Sihler's staining for identifying the neural distribution of the temporalis

muscle

Sihler's staining was applied to reveal the neural distribution of the temporalis muscle. Sihler's staining involves the seven steps described below. Although the duration of staining varies according to thickness, it usually takes up to 5 months.

Fixation

The temporalis muscle that had been dissected from the cadaver was placed in 10% unneutralized formalin for 1 month. The duration of formalin fixation varied according to the specimen size and thickness. The formalin did need not to be replaced unless it became polluted.

Maceration

The fixed specimens were washed for 1 hour in running water, and then stored in 3% potassium hydroxide solution (3% aqueous potassium hydroxide solution containing 0.2 ml of 3% hydrogen peroxide per 100 ml). The fixed specimens became partially transparent after 3 to 4 weeks of storage, during which time the potassium hydroxide solution was replaced daily.

Decalcification

The macerated specimens were stored for 4 weeks in Sihler's solution I, which comprises glacial acetic acid, glycerin, and 1% aqueous chloral hydrate mixed in a 1:1:6 ratio. This solution was replaced weekly.

Staining

Adequately decalcified specimens were stained for 3 to 4 weeks in Sihler's solution II, which comprises Ehrlich's hematoxylin, glycerin, and 1% aqueous chloral hydrate mixed in a 1:1:6 ratio. The staining period was varied

according to the specimen size and thickness. A viewing box was used to decide when the Ehrlich's hematoxylin had permeated the specimen sufficiently.

Destaining

Stained specimens are again placed in Sihler's solution I so that they became transparent. This step was necessary since Sihler's solution II dyes both the nerves and muscle tissue purple. The specimens were checked frequently until adequate transparency was achieved. Depending on the specimen, the process took up to 2 hours.

Neutralization

The acidified specimen was neutralized in a 0.05% lithium carbonate solution for about 1 hour before being washed in running water for 30 minutes.

Clearing

The specimen was placed in a thymol crystal containing glycerin solution. The concentration of glycerin was increased in four stages (40%, 60%, 80%, and 100% glycerin), before being finally stored in a 100% glycerin solution.

Ⅲ. RESULTS

1. Posterior border of the temporalis tendon

The ear and reference lines L2, L3, and L4 was used to clearly delineate the temporalis tendon. The posterior border where the temporalis tendon disperses can be classified into the following three types:

1. In Type I, the posterior border of the temporalis tendon is located in front of L2 (Fig. 2). In this type the distance between the jugale and L2 was 49.6±6.0 mm (mean±SD), and it occurred in 1 of the 21 cases (4.8%).

2. In Type Ⅱ, the posterior border of the tendon is located between L2 and L3 (Fig. 3). In this type the distance between the jugale and L3 was 70.2±5.1mm, and it occurred in 18 of the 21 cases (85.7%).

3. In Type Ⅲ, the posterior border of the tendon is located between L3 and L4 (Fig. 4). In this type the distance between the jugale and L4 was 90.0±5.3mm, and it occurred in 2 of the 21 cases (9.5%).

There were no cases where the tendon dispersed beyond L4.

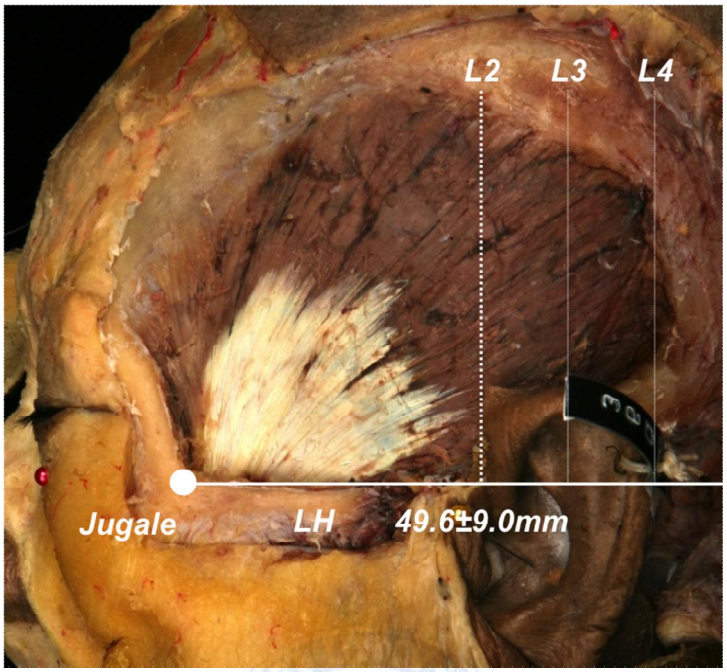

Fig. 2. Type I, in which the posterior border of the temporalis tendon is located in front of L2 (4.8%, 1/21). The distance between the jugale and L2 was 49.6±6.0 mm.

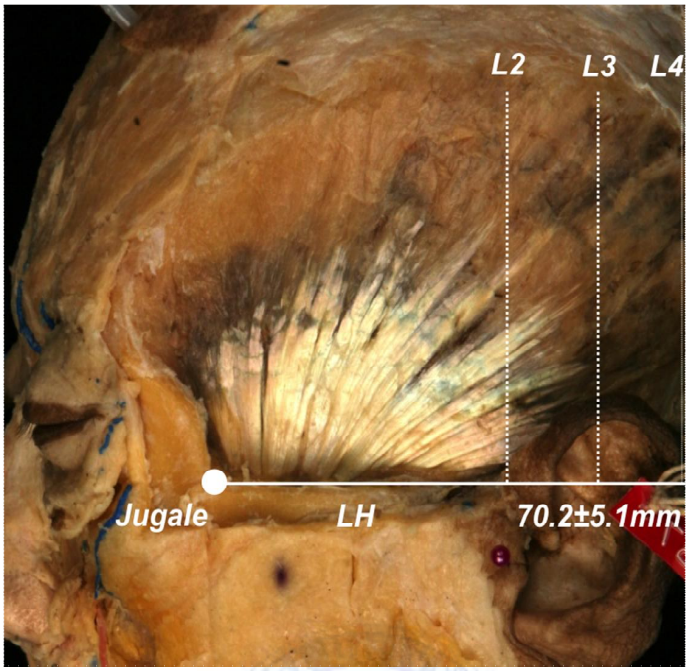

Fig. 3. Type Ⅱ, in which the posterior border of the temporalis tendon is located between L2 and L3 (85.7%, 18/21). The distance between the jugale and L3 was 70.2±5.1 mm.

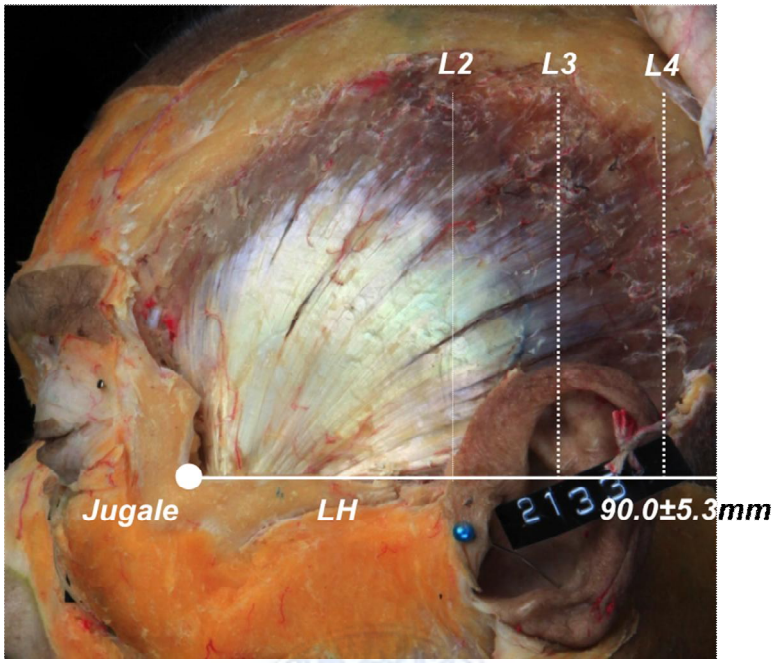

Fig. 4. Type Ⅲ, in which the posterior border of the temporalis tendon is located between L3 and L4 (9.5%, 2/21). The distance between the jugale and L4 was 90.0±5.3 mm.

2. Vertical border of the temporalis tendon and temporalis muscle

The vertical distances between LH and the temporalis tendon along the L0, L1, L2, L3, and L4 reference lines were 29.74±6.87 mm, 45.06±8.84 mm, 37.76±11.18 mm, 42.50±7.59 mm, and 32.14±0.47 mm, respectively; the corresponding vertical distances between LH and the temporalis muscle were 55.02±8.25 mm, 74.99±9.90 mm, 73.97±10.12 mm, 55.24±13.25 mm, and 47.56±11.41 mm (Table 1).

Table 1. The vertical distance of the temporalis tendon and mucle from LH

Points	The vertical length of the tendon	The vertical length of the muscle
L0	29.7±6.8	55.0±8.3
L1	45.1±8.8	75.0±10.0
L2	37.8±11.2	74.0±10.1
L3	42.5±7.6	55.2±13.3
L4	32.1±0.5	47.6±11.4

Values are expressed in millimeters (mm).

3. Intramuscular nerve distribution of the temporalis muscle

The temporalis is a masticatory muscle that can be divided into anterior, middle, and posterior regions. Sihler's staining showed that the anterior branch of the deep temporal nerve runs through the anterior fibers of the temporalis muscle, which provides upward elevation of the mandible. The posterior branch of the deep temporal nerve runs through the posterior fibers of the temporalis muscle, which provides backward elevation of the mandible. The middle branch of the deep temporal nerve runs through the middle fibers of the temporalis muscle (Fig. 5).

Fig. 5. The temporalis muscle and temporalis tendon could be clearly distinguished after Sihler's staining. The temporalis tendon appeared as a fan beginning at the point where it inserted into the temporalis muscle. The temporalis muscle occupied the remaining area. The nerve trunk of the deep temporal nerve traversed the temporalis tendon. The nerve endings of the deep temporal nerve mainly dispersed in the temporalis muscle.

Ⅳ. DISCUSSION

Migraine treatments can be divided largely into pharmacotherapy and physiotherapy. Pharmacotherapy can be further classified into the oral administration of amitriptyline and topiramate or the injection of BoNT-A and lidocaine. Physiotherapy involves exercise, positional release therapy, and massage therapy (Fernández-de-Las-Peñas et al., 2006; Bendtsen, 2009; Weatherall, 2015). However, the oral administration of drugs for extended periods poses the risk of significant side effects for those with cardiovascular disease, cerebrovascular disease, peripheral vascular disease, liver disease, and pregnancy. Furthermore, there is currently insufficient scientific evidence for the physiological benefits of physiotherapy (Levin, 2010; Chen, 2012).

The mechanism by which BoNT-A relieves migraines is not yet clear. There is empirical evidence suggesting that BoNT-A has minimal side effects, and a single treatment lasts up to 4 months. The FDA has approved 31 sites at which BoNT-A can be injected for treating migraines. However, since these sites were chosen based on observations of the trigger point of migraines, it is unclear whether these are the most anatomically effective sites for injection-based treatments. In order to find the most anatomically effective injection sites, an extensive study of the nerve endings in the temporalis muscle is necessary.

Sihler's staining was used in this study to observe the neural distribution in the temporalis region. The tendon and muscle regions could be clearly distinguished after applying Sihler's staining, which was bolder in the tendon region. The anterior, middle, and posterior branches of the deep temporal nerve traverse the temporalis tendon into the intramuscular layer. A notable characteristic of the deep temporal nerve was that all of its branches traverse

without dispersion in the temporalis tendon—only when the nerve branches reached the muscle region did the nerve endings disperse.

There is anatomical evidence supporting the clinical practice of injecting BoNT-A into the temporalis muscle while avoiding the temporalis tendon, including because (1) there is pharmaceutical evidence that BoNT-A acts in the muscle region (Durham and Cady, 2011) and (2) the neural distribution of the temporalis muscle indicates that its nerve endings are densely located in the muscle region. This anatomical evidence can be used to produce a guideline for injection sites on the temporalis muscle. Since the temporalis region can be morphologically divided into the tendon and muscle regions, a guideline on the anatomical surfaces in which BoNT-A should be injected can be suggested. Based on the results of this study, we suggest that the temporalis tendon is horizontally located approximately 45 mm from LH, and any location more than 45 mm vertically above LH can be considered the muscle region.

The jugale is a part of the zygomatic bone that horizontally follows the superior margin of the zygomatic arch. Horizontal line LH, which passes the jugale, coincides with the superior margin of the zygomatic arch. It can therefore be clinically applied as the superior margin of the zygomatic arch. We conclude that the temporalis tendon stretches 45 mm from the superior margin of the zygomatic arch.

The temporalis tendon can be easily found by first aligning the thumb and the first finger in a flat stretched-out state and then placing the second finger on the inferior margin of the zygomatic arch. This will result in the tip of the thumb being located approximately 45 mm from the superior margin of the zygomatic arch (Fig. 6). This method makes it easy to identify the temporalis muscle and therefore also the effective injection site for BoNT-A.

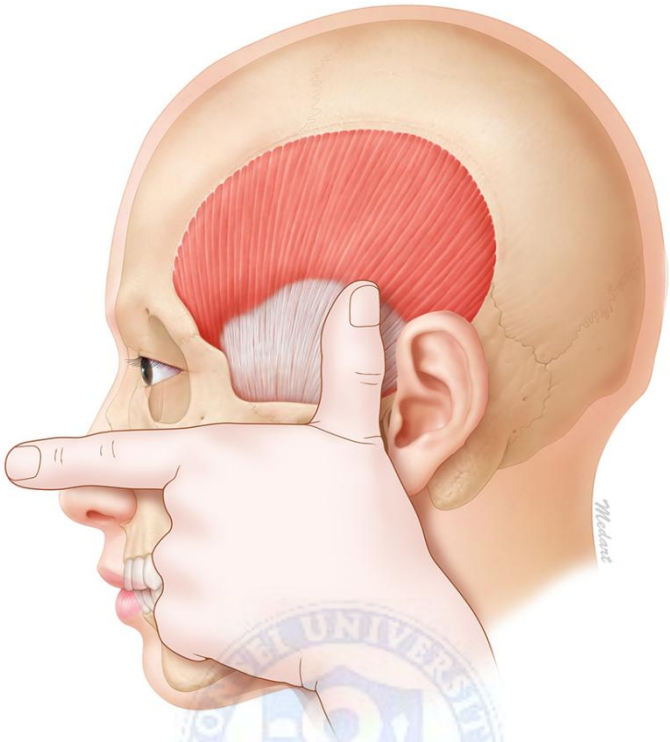

Fig. 6. The position of the temporalis tendon can be easily determined first aligning the thumb and first finger in a flat stretched-out state and then placing the second finger on the inferior margin of the zygomatic arch. The tip of the thumb is then located approximately 45 mm from the superior margin of the zygomatic arch.

Ⅴ. CONCLUSION

An easily identifiable and effective injection site for BoNT-A on the temporalis muscle has been suggested based on the results of this research. BoNT-A should be injected into the temporalis muscle at least 45 mm vertically above the zygomatic arch. This will ensure that the target is the muscle region, which will produce the greatest clinical effect using the minimum concentration of BoNT-A. The main findings of this study can be summarized as follows:

1. The temporalis tendon is shaped like a fan. The most distant point of the tendon region is located 45 mm from the zygomatic arch. Therefore, the site of BoNT-A injection into the temporalis muscle should be at least 45 mm from the zygomatic arch.

2. Sihler's staining shows that the nerve endings that BoNT-A acts on are densely dispersed in the temporalis muscle, which indicates that the muscle region is an effective site for BoNT-A injection.

3. In order to easily identify the temporalis muscle in a clinical setting, the second finger should be placed on the bottom corner of the zygomatic arch. The tip of the thumb will then be located 45 mm from the zygomatic arch.

Clinicians with a comprehensive understanding of the results reported in this paper will be easily able to determine an effective BoNT-A injection site for migraine treatment.

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Abstract (in korean)

편두통 치료를 위한 관자근의 보툴리눔독소 주사점에 대한 연구

<지도교수 허 경 석>

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두통은 일상생활에서 우리가 흔하게 겪는 증상으로, 일반적으로 편두통과 긴장성두통이 가장 빈번하게 발생한다. 두통의 치료방법 중 보툴리눔독소 주사법은 주로 관자부위에 주사를 하게 되는데, 비침습적이고, 부작용이 적으며, 치료 효과가 탁월하여 일반적으로 널리 이용되지만, 관자근의 해부학적 정보를 기반으로한 정확하고 효과적인 보툴리눔독소 주사점에 대한 연구는 부족한 실정이다. 이에 본 연구에서는 관자근에 대한 표면해부학적 분석을 시행하여 보툴리눔독소 주사 시 임상에서 쉽게 적용가능한 주사점을 제시하는데 그 목적이 있다.

재료로는 한국인 성인 시신 머리 21쪽을 사용하였다. 관자근의 힘줄부분이 노출되도록 조심스럽게 해부한 후 얼굴의 표지점을 중심으로 기준점과 기준선을 정하여 관자근에대한 형태학적 분석을 시행하였으며, 그 후 관자근을 적출하여 Sihler 염색을 시행하였다.

관자근의 힘줄부분 형태는 크게 세 가지 형태로 구분되었다. TypeⅠ은 관자근의 힘줄부분이 L2의 앞모서리까지 작게 형성된 형태로 약 5%(1/21)에서 관찰되었으며, TypeⅡ는 관자근의 힘줄부분이 L2와 L3 사이에 위치하는 경우로 약 85%(18/21)에서 관찰되었고, TypeⅢ는 관자근의 힘줄부분이 L3와 L4 사이에 위치하는 경우로 약 10%%(2/21)에서 관찰되었다. 관자근의 힘줄부분은 광대활의 L0, L1, L2 지점에서 각각 29.7mm, 45.0mm, 37.7mm 떨어진 곳까지 존재하였으며, 관자근의 힘살부분은 광대활의 L0, L1, L2, L3, L4 지점에서 각각 55.0mm, 74.9mm,

73.9mm, 55.2mm, 47.5mm 떨어진 곳까지 위치하였다.

Sihler 염색 결과, 관자근에는 깊은관자신경의 앞가지와 뒤가지가 관자근 전체에 분포하는 것을 관찰할 수 있었으며, 특히 관자근의 힘줄부분 깊숙한 곳에서 근육으로 들어온 신경의 줄기가 힘살부분으로 넘어가면서 무수히 많은 신경말단가지를 분지하는 것을 확인하였다.

관자근은 하나의 근육에 힘줄부분과 힘살부분이 동시에 존재하는 근육으로, 이 근육의 힘줄부분에 의해 강력한 힘이 작용한다. 하지만 두통 치료를 위한 주사 시, 보툴리눔독소는 이 근육의 힘살부분에 주입되어야 하며, 힘줄부분에 주입될 경우 그 약리학적 효과를 기대하기 어렵다. 본 연구의 결과 관자근에서 힘줄부분이 위쪽으로 차지하는 영역은, 표면해부학적 지표인 광대활을 기준으로 약 45mm 떨어진 곳까지 존재하였으며, 그 위쪽으로는 모두 힘살의 영역인 것을 확인하였다. 또한 관자근의 힘줄부분이 뒤쪽으로 차지하는 영역은 대부분의 경우에서 귀의 가운데를 지나는 수직선(L3)까지 존재하였다.

또한 Sihler 염색 결과 관자근에 분포하는 깊은관자신경 줄기는 관자근의 힘줄부분 깊은 곳에서부터 이 근육으로 들어와 힘줄부분을 지나 힘살부분에서부터 신경말단가지를 분지하는 것을 관찰하였다. 결론적으로 관자근의 보툴리눔독소 주사는, 실질적으로 보툴리눔독소가 작용하는 신경말단 부위에 주사되어야 하며, 따라서 관자근에서 힘줄부분이 아닌 힘살부분에 주사되어야 한다. 또한 본 연구의 결과 관자근의 힘줄부분은 광대활을 기준으로 약 45mm 떨어진 곳까지 존재하였으며, 이 계측값은 광대활에서부터 엄지손가락 길이만큼 떨어진 곳으로 쉽게 확인이 가능하다.

따라서 본 연구의 결과는 실제 환자의 얼굴 표면에서 광대활을 기준으로 관자근의 힘줄부분이 어느 부분까지 존재하는지 예측할 수 있으며, 이는 보툴리눔독소를 이용한 편두통 치료에서 보다 더 안전하고 효과적인 주사점을 제시할 수 있을 것이라 생각한다.

핵심되는 말 : 편두통, 보툴리눔 독소, 관자근, 주사점, 쉴러 염색법