

만성편두통에서 보툴리눔독소 치료



문 희 수

성균관의대, 강북삼성병원 신경과

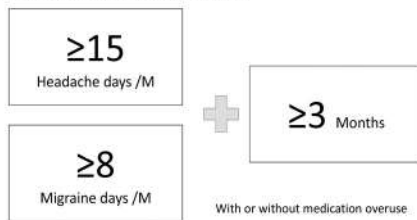
Botulinum Toxin for Chronic Migraine

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Identifying BOTOX® candidates: Diagnosis of Chronic migraine

- Practical clinical criteria for Chronic Migraine diagnosis



PREEMPT Paradigm overview The basis of the Botox® treatment protocol for chronic migraine

PROVEN DOSE	PROVEN SITES	PROVEN SCHEDULE
155 UNITS	31 SITES	12 WEEKS
MUSCLE AREA	NUMBER OF SITES	RECOMMENDED DOSE
Corrugator	2	10
Procerus	1	5
Frontalis	4	20
Temporalis	8	40
Occipitalis	6	30
Cervical paraspinal	4	20
Trapezius	6	30

A Fixed-Site, Fixed-Dose Injection paradigm

Injection points & distribution: Fixed-Site Fixed-Dose

- The anatomic injection sites follow distributions and areas innervated by the trigeminal - cervical nerve complex



5 U/mL = 15 Units
Bennett et al. Presented at AAN 2010.

5u x 31 sites=155u

Additional Injection Points: Follow-the-pain approach



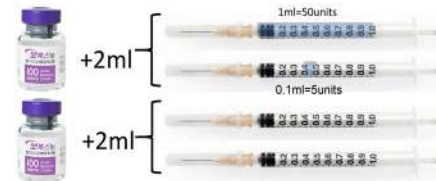
8 additional injection * 5 units =Extra Max 40u
Total 155u- 195 u

The Preparations



Dilution Overview

	Dilution	
	Saline added (0.9% sodium chloride injection)	Resulting BOTOX® dose (Units per 0.1 ml)
100 U vial	2.0 ml (=2.1ml)	5.0 Units



What to consider each injection

Look at the muscle

- Inspect
- Activate
- Palpate

Consider

- Anatomical landmark
- Injection site
- Depth
- Angle

Inject with the bevel up

hold the hub of the needle with 1 hand

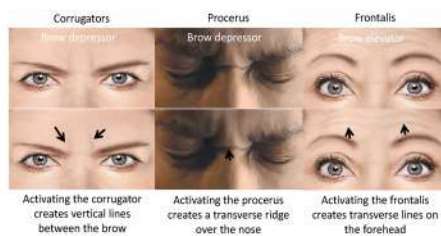
Aspirate

0.1ml (=5Units) / injection

Practical Injection Method for individual muscles

Anterior injections

Functional Anatomy of each anterior injection site



Corrugator



Tips: 눈썹안쪽 끝과 1cm 위를 핀치 한 후 중간 지점을 90도 각도로 주사한다. 너무 위쪽(Frontalis medial part) 또는 너무 아래쪽 (orbicularis oculi)로 잘못 타겟팅되지 않도록 주의!!

- Anatomical landmark**
Medial inferior edge of the superior orbital rim
- Injection site:** About 1 finger breadth (1.5 cm) above the medial inferior edge of the superior orbital rim (bony landmark)
- Furrow the brow (Activate/Palpate)
 - Pinch the corrugator (Isolate)
 - Inject 5 u at 90° angle (Not 45°)
 - Not too deep (above periosteum)

Procerus

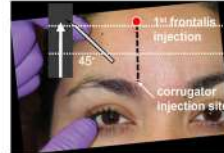


Tips: 양측 Corrugator 주사부위
중간 지점을 90도 각도로 주사한다.

Injection site: 양측 Corrugator 주사부위 중간지점

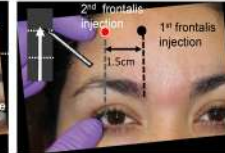
- Find the halfway point between the 2 corrugator injections
- Inject 5 u at 90° angle
- Not too Deep (above periosteum)
- Not too high

Frontalis



Tip: Corrugator 주사부위에서 수직으로
올려서 hair line과 만나는 지점 또는 약간
아래 지점 (frontalis 상방 1/3)

Anatomical landmark:
Corrugator injection site
Injection site:
About 2 FB (3cm) up above the corrugator
injection sites



Tip: Cornea 외측경계면에서 수직으로
올려서 hair line과 만나는 지점 또는 약간
아래 지점 (frontalis 상방 1/3)

Anatomical landmark:
The lateral limbus of the cornea
Injection site:
move about 1 FB (1.5cm) laterally from the
medial injection site

In the upper 1/3 of the forehead

Inject 5 u at 45° angle superiorly

Not too Deep, Not too low

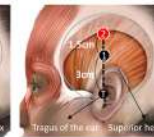
Temporalis injections

Temporalis

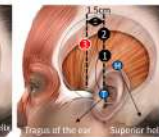
Anatomical landmark: Tragus of the ear



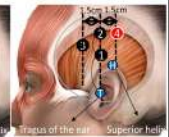
Tragus에서 3cm 수직상방
포인트에 45도 각도,
바늘이 후방을 향하게



1st 포인트에서 1.5cm
수직상방 포인트



1st, 2nd 포인트 중간지점에서
얼굴쪽으로 1.5cm 수평이동
Hairline 안쪽에 위치하도록

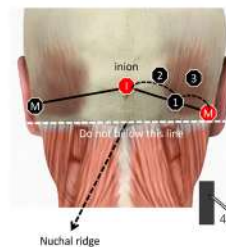


2nd 포인트에서 윗통수쪽으로
1.5cm 수평이동

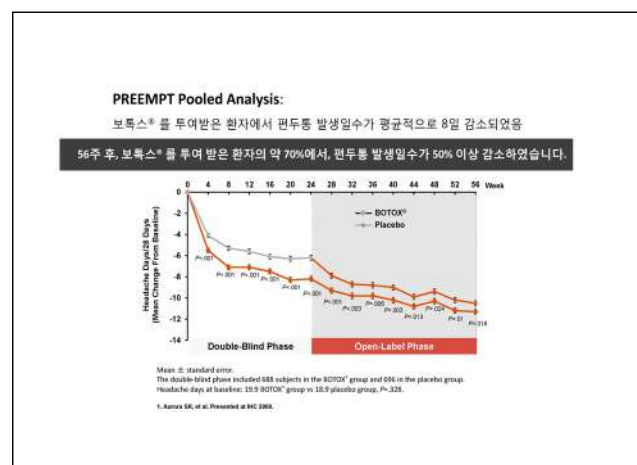
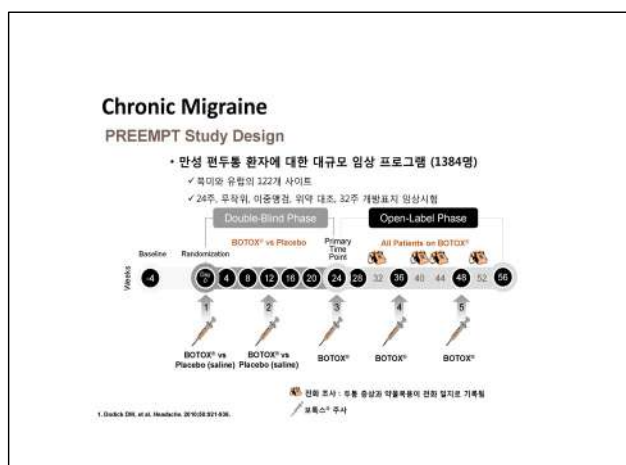
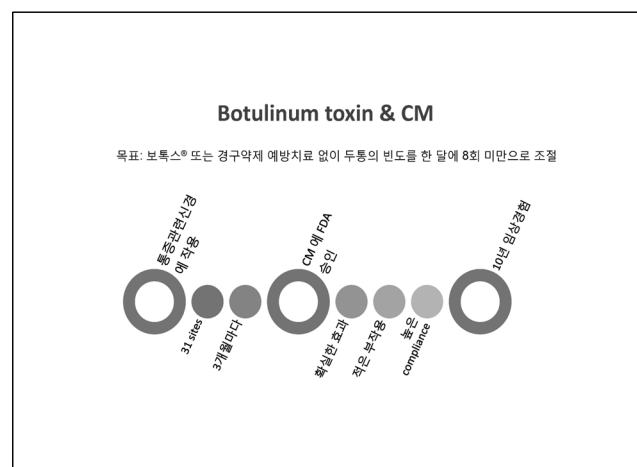
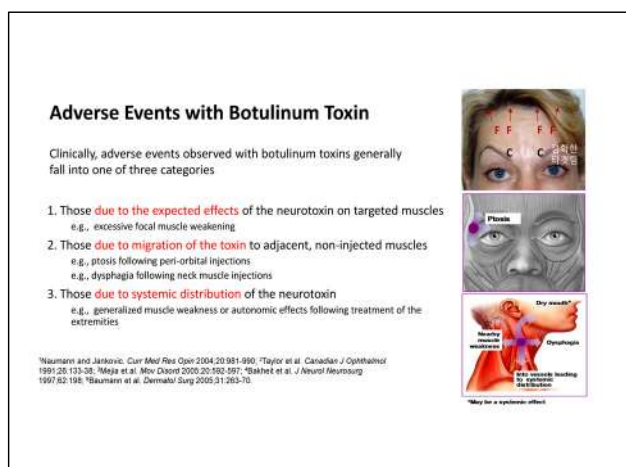
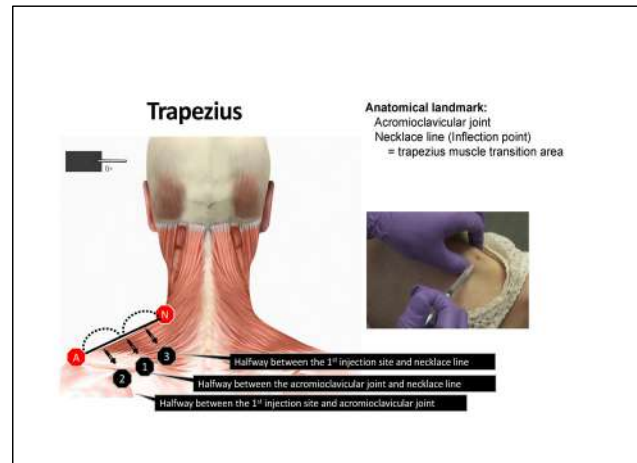
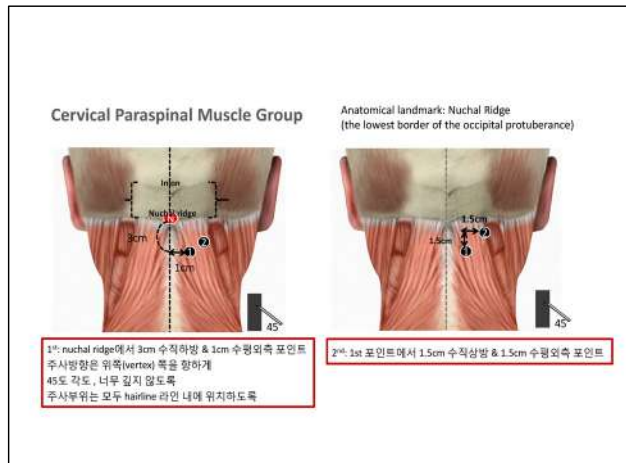
Posterior injections

Occipitalis

Anatomical landmarks:
1. Inion (bony prominence in the mid-portion of occipital protuberance)
2. Mastoid process



1st: Inion과 mastoid process 연결하는 가상선의 중간포인트
2nd: 1st포인트에서 10시방향으로 1.5cm 사선상방
3rd: 1st포인트에서 2시방향으로 1.5cm 사선상방
주사방향은 위쪽(vertex) 쪽을 향하게
45도 각도
주사부위는 모두 Nuchal ridge 라인 위에 위치하도록



Response Rate



Botulinum Toxin A for Chronic Migraineurs: A single center experience

- Total N= 58 patients: 4-6 weeks FU
- Thirty-two patients (55.1%) were 50% responder that: at least a 50% decrease from baseline in the headache frequency.
- No difference were observed in a reduction in headache days/month and total HIT-6 score between patients with MOH and without MOH ($p=0.647$ and $p=0.999$).

	Pre-injection	Post-injection	P value
Headache days/Month	22.4 (5.7)	12.2 (7.0)	< 0.001
No. of medication intake/Month	21.4 (5.8)	11.7 (7.1)	< 0.001
Total HIT-6 score	63.9 (10.4)	53.7 (11.7)	< 0.001

HS MOON, Kanbuk Samsung Hospital



N=70 patients, 4-8wks FU
Responder rates(> 50% decreased in Headache days,
acute medication intake frequency or headache intensity):
42 patients (60%)

Table 1
Baseline and post-treatment headache characteristics

	Baseline (N = 70)	Post-treatment (N = 70)	p
Headache days (/m)	25.9 ± 6.0	17.0 ± 11.0	<0.001
Pain intensity score (0-3)	2.8 ± 0.5	2.1 ± 0.9	<0.001
Rescue medication intake (/m)	17.9 ± 10.2	12.0 ± 9.1	<0.001
HIT-5 score	68.2 ± 5.7	62.0 ± 8.4	<0.001

Values are presented as mean \pm SD
HIT-6 = headache impact test-6.

Onabotulinumtoxin-A treatment
patients with chronic migraine

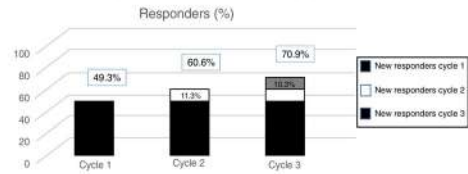
- A total of 119 patients with CM
- Changes from baseline to the period **after its 3rd administration**
- Responder rate : **80.2 %** (24.7 %: 50% responder, 55.6%: 75 % responder)

Vikels et al. The Journal of Headache and Pain (2016) 17:84
is the approved generic name of Quabeh dihydrochloride A in Korea

*Botulinumtoxin Type A is the approved generic name of Onabotulinumtoxin A in Korea

% of First-Time Responders

Percent of First-Time Responders* With $\geq 50\%$ Improvement From Baseline in Treatment Cycles 1–3 for Multiple Headache Symptom Measures

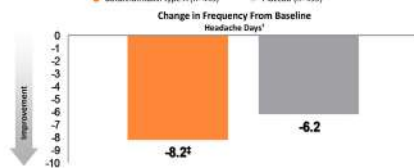


*First-time responders for a given time point are subjects who never responded at any previous time points.

Neurologia 2019; volume 34, issue 6, Pages 438-447

PREEMPT pooled, subgroup analysis: of acute medication overuse

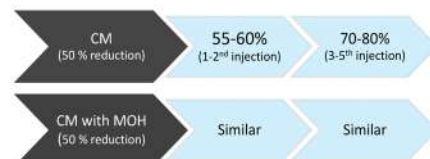
Efficacy of botulinum toxin type A in Medication Overuse Subgroup* at Week 24†



*Of the total pooled FREEMPT population, 64.7% and 65.9% of botulinum toxin type A and placebo groups, respectively, overused acute headache pain medication (simple analgesics, ergotamines/DHE, triptans, opioids, combination of analgesics, or any combination of the preceding classes).^{1,2}

1. Silberstein SO et al. Presented at IAC 2009.
2. Quilley DW et al. *Neurology*. 2010;59:921-926.

Responder Rates



한번 주사 맞아서 효과가 만족스럽지 못하더라도 2번까지는 시도해보고 평가합시다.

- Patients should be administered at least 2 treatment cycles
- Over 47% of botulinum toxin type A-treated patients had $\geq 50\%$ reduction in multiple headache symptoms measures at Week 24
- Most patients continued to receive treatment benefit after 5 treatment cycles
- Nearly 70% of patients treated with botulinum toxin type A throughout the study had $\geq 50\%$ reduction in multiple headache symptom measures at Week 56

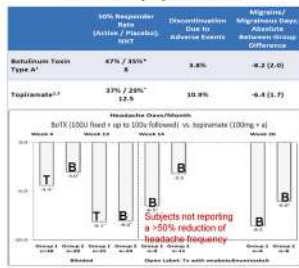
1. Dodick DW et al. Headache. 2010;50:921-936.
2. Data on file, Allergan.
3. Aurora SK et al. Presented at IAC 2009.

Preventative therapy: evidence for use in CM

FDA	Treatment	Evidence for Use in Chronic Migraine
•	Botulinum toxin type A	• Two double-blind placebo-controlled trials in CM ¹
	Anticonvulsants	
	Topiramate	• Two double-blind, placebo-controlled trials in CM ^{2,3}
	Valproate	• Small double-blind, placebo-controlled trials in CM ^{4,5}
	Gabapentin	• One double-blind, placebo-controlled trial in CDH ⁶
	Antidepressants	
	Amitriptyline	• Small open-label trial in TM ⁷
	Fluoxetine	• Small double-blind, placebo-controlled trial in CDH ⁸
	Tizanidine	• Small double-blind, placebo-controlled trial in CDH ⁹
•	CGRP monoclonal Ab	

1. Aurora et al. Headache. 2011;51(9):1358-7.
2. Dodick DW et al. Cephalalgia. 2007;27:824-825.
3. Silberstein SD et al. Headache. 2007;47:170-180.
4. Yarnitzky VA et al. Headache Pain. 2008;9:17-41.
5. Bartolotti M et al. Clin Neuropharmacol. 2005;28:277-279.
6. Spina FS, Benesi RS. Neurology. 2003;61:1753-1756.
7. Kynchaitzovskiy AY et al. Headache. 2002;42:530-534.
8. Saper JB et al. Headache. 1996;36:407-422.
9. Saper JB et al. Headache. 2002;42:407-422.

Botox® and Topiramate for the Prophylaxis of CM



Common side effects of Topiramate (5%)

Topiramate Side Effects List (% incidence)	Dosage (mg/day)
	50mg 100mg
Pain and needles	35 51
Taste perversion	15 9
Fatigue	14 15
Upper respiratory tract infection	13 14
Sinusitis	10 6
Anorexia	9 15
Nausea	9 13
Diarrhea	9 11
Injury	9 6
Dizziness	8 9
Sleepiness or drowsiness	8 7
Difficulty with memory	7 7
Language problems	7 6
Joint pain	7 3
Weight loss	6 7
Hyposthesia	6 7
Insomnia	6 7
Abdominal pain	6 6
Pharyngitis	5 6

1. Dodick DW et al. Headache. 2010;50:921-936.
2. Silberstein SD et al. Headache. 2008;48:1153-1162.
3. Silberstein SD et al. Headache. 2007;47:170-180. Roger K. Cady et al. Headache 2011;51:21-32

경구예방치료제에 만족하십니까?

Oral	Propranolol	Valproate	Topiramate	Amitriptyline
Dropout rate due to AEs	20%	8%	22%	12%

Agent	Schedule	Adverse effects
Propranolol	20mg hs → increase 20mg/wk	Depression, asthma, Raynaud phenomenon
Topiramate	25mg/d → increase 25mg/wk	Paresthesia, Weight loss, memory problem
Lisinopril	5mg hs → 10mg hs	Dizziness, cough, chest pain

Weak points of Oral Preventives

- Titration Schedule
- Gradual dose escalation
- The late emerging onset of action
- Limited efficacy
- Many Side effects
- Contraindications
- Lack of target specificity
- Drug interaction
- Daily multiple dosing schedule
- Low drug adherence

Refractory chronic migraine: is drug withdrawal necessary before starting a therapy with onabotulinum toxin type A?

Colagrosso Roberto¹, Bruno Colagrosso², Francesca Bianchi³, Marco Cusi⁴, Roberto Mestivo⁵, Stefano Attardo⁶, Roberto Garziera⁷, Giuseppe Cusi⁸, Ubaldo Di Caro⁹

Adverse events were reported in 13 treatments (5.04%) by 6 patients during the whole follow-up period and included: palpitations, pruritus, cervical pain, dizziness, blurred vision. These adverse events lasted from three to 30 days, were considered mild or moderate, and no patient asked for stopping BT-A treatment.

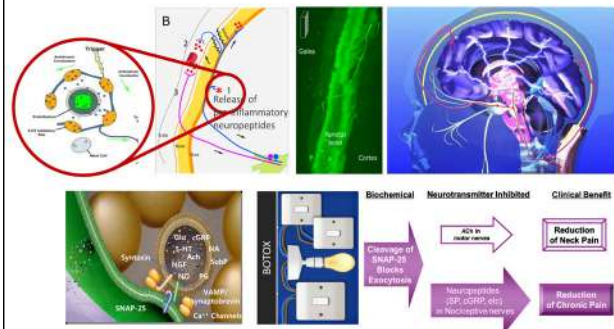
Onabotulinumtoxin-A treatment in Greek patients with chronic migraine

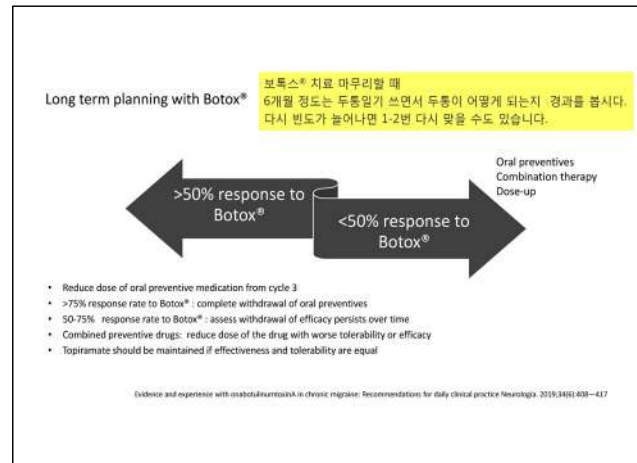
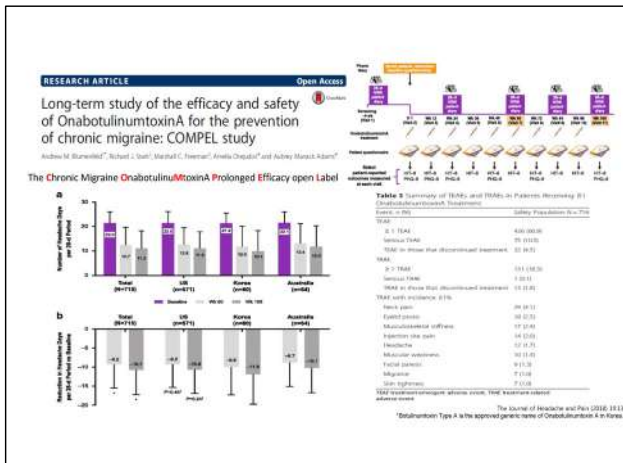
Melani Vassilaki¹, Anthony A. Angelidis², Ioannis V. Steriade³, Anastasios C. Spiliadis⁴, and Demos D. Mavroudis⁵

- Wheals in the injection site (n = 5; 6.2 %)
- Mild ptosis (n = 5; 6.2 %)
- Lateral eyebrow elevation (n = 3; 3.7 %)
- Shoulder and/or neck pain (n = 3; 3.7 %)
- Early withdrawal from intervention (n = 2)



Vassilaki et al. The Journal of Headache and Pain (2016) 17:84
"Botulinum toxin type A is the approved generic name of Onabotulinumtoxin A in Korea."





Take home messages

- 만성편두통환자에게 선택할 수 있는 좋은 치료방법 중 하나
- 환자의 선호도, 경제적 문제, 경구예방약제 투여했을 때의 효과와 부작용 병력 등 고려
- 의사의 숙련도? 기술적인 문제는 어렵지 않음
- 보툴리눔독소치료 설명할 때 강조할 포인트
 - 전문성, 임상 데이터 확보
 - FDA 승인을 받은 만성편두통 치료약제
 - 안전한 치료법