

# Botulinum Toxin Type A for Treatment of Chronic Migraine



이 미 지

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## Mechanism of action

## Action of BTA

- Preferentially acts on **cholinergic** neurons (**motor and sympathetic nerve terminals**)
- Non-cholinergic actions
  - BTA blocks the  $\text{Ca}^{2+}$ -evoked neuroexocytosis of neurotransmitters other than Ach
  - Potential indications for hypersecretory diseases, myofascial pain syndrome, trigeminal neuralgia, and chronic migraine
    - Sympathetic sudomotor C nerve fiber terminals – co-localization of Ach and CGRP
    - CGRP = enhancing cholinergic sweating
    - BTA → reduction of focal hyperhidrosis

## Proposed Mechanism of Action for the antinociceptive action

- Preclinical findings
  - **Inhibit substance P release** in dorsal root ganglion neurons
  - **Reduce stimulated release of CGRP** from trigeminal ganglia neurons
  - In the experimental pain model, BTA inhibits activation of primary sensory neurons (glutamate release; Fos expression in the spinal cord, and activation of wide dynamic range (WDR) neurons in the dorsal horn)
- Healthy volunteers
  - Did not show anti-nociceptive effects

NeuroToxicology 26 (2005) 785–793

### Proposed Mechanism of Action for the Headache disorders

- Hypothesis = deactivation of sensory neuron (1st- and maybe 2nd-order neuron)
- Direct effect on peripheral sensitization
  - BTA Inhibits evoked release of CGRP in TG
  - BTA influences the release of SP in DRG
  - BTA inhibits mechanical nociception in peripheral trigeminovascular neurons
- Indirect effect on central sensitization
  - BTA-truncated SNAP-25 in the medullary dorsal horn

Toxins 2015, 7, 3818-3844; doi:10.3390/toxins7093818

### Proposed Mechanism of Action for the Headache disorders

- Extracranial injection → modulates intracranial meningeal nociception
- Actions on nociceptive C fiber
- No influence on non-nociceptive mechanoreception or activity of Aδ fiber
- Suture injection > suture + muscle injection

Zhang et al. Cephalalgia 2016, 36(9) 875-886.  
Burststein et al. Cephalalgia 2014, 34(11) 853-869.

### Trial Results

### PREEMPT trial

- The Phase III REsearch Evaluating Migraine Prophylaxis Therapy 1,2 (PREEMPT 1,2)

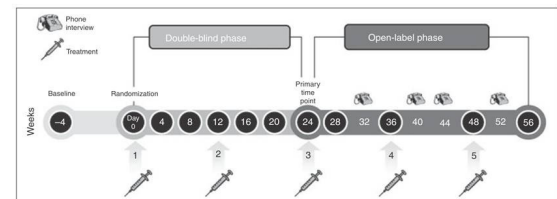
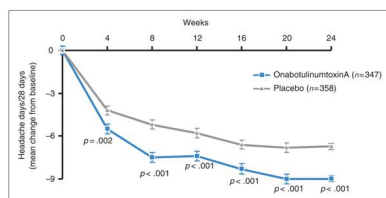


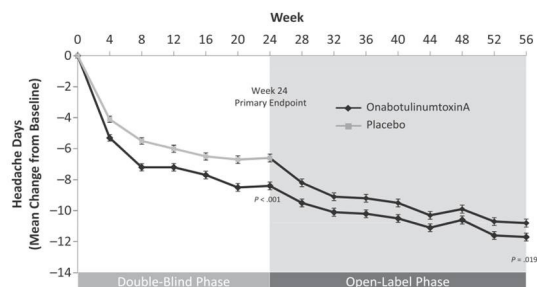
Figure 1. PREEMPT study design.

Aurora et al. Cephalalgia 30.7 (2010): 790-803.

- PREEMPT-1
  - Primary outcome: headache frequency (NEGATIVE)
  - Secondary outcome: headache days / migraine days / moderate-severe headache days ... (ALL POSITIVE) migraine frequency (NEGATIVE)
- PREEMPT-2
  - Primary outcome: headache days (POSITIVE)
  - Secondary outcome: migraine days / moderate-severe headache days / Total headache hours (ALL POSITIVE) headache frequency (POSITIVE)



Diener et al. Cephalalgia 30.7 (2010): 804-814.



Headache 2011;51:1358-1373

## Discussion with Patients

## How should we expect the effect?

### • pooled analyses of PREEMPT 1&2 trials

- 50% responder rate = 47.1% at 24 weeks (2 cycles)
- 50% responder rate = 68.8% at 56 weeks (5 cycles)
- 75% responder rate = 22.8% at 24 weeks (2 cycles)

### • Real-world data of 254 patients

- Headache days: 27 days → 18 days (-7 days)
- Migraine days: 15 days → 7 days (-6 days)
- Crystal clear days: 3 days → 12 days (+7 days)

- It's important to set a **realistic goal** before treatment

Aurora et al. Headache 2011;51:1358-1373  
Khalil et al. The Journal of Headache and Pain 2014;15:54

## How many cycles are needed?

- No absolute number of cycles
- Single injection may lead to a long-term remission

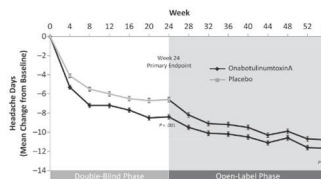
But...

- PREEMPT trial consisted of 2 cycles
- Responder rate may rise after repeated injection
- 50% responder rate
  - ~50% at 24 week (2 cycles)
  - ~70% at 56 week (5 cycles)
- Plan **at least two regular injections** with patients prior to the first injection regardless of the initial response (*Personal opinion*)

Headache 2011;51:1358-1373

## Is it mandatory to repeat the injection every 3 months?

- Not mandatory but...
- At least half of patients show aggravation when BTA effects are diminished
- You can discuss with regular injection every 4 months or as needed
- Better outcome of early treatment (5 cycles) than later treatment (3 cycles)



Cephalalgia 2015, Vol. 35(10) 864-868

## Some patients are non-responders

- Definition of responder
  - 30% reduction of HA days (30% responder)
  - 50% reduction of HA days (50% responder)
- Maximal effect = 3 weeks
- **Less than 50%** of patients respond to the first injection
- Non-responder at 1st cycle
  - **additional 10%** respond at 2nd cycle
  - **additional 10%** respond at 3rd cycle

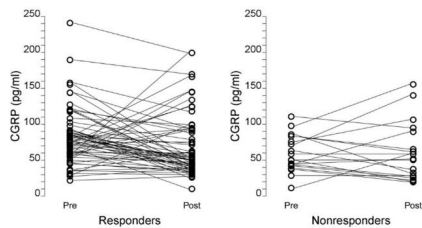
J Neurol Neurosurg Psychiatry 2015;86:996-1001.

## Can I predict non-responder prior to the injection?

- Predictor of responder
  - **Shorter disease duration** (Eross EJ et al, 2005)
  - "Imploding" headache nature (Jakubowski M et al, 2006)
  - **Unilateral location, scalp allodynia and pericranial muscle tenderness** (Mathew Nt et al, 2008)
  - **Ocular-type headache** (Kuan-Hsiang Lin et al, 2014)
  - **Increased interictal calcitonin gene-related peptide (CGRP)** and vasoactive intestinal peptide (VIP) in responders (Cernuda-Morollon E et al, 2014)
  - **Shorter disease duration** and higher **pretreatment MCA/ICA index** on TCD (Lee et al, 2016)

### Isn't the BTA just a placebo?

- High placebo effect in trials for treatment of headache disorders
- Spontaneous conversion (CM ↔ EM)
- BTA decreases plasma CGRP levels in patients with CM

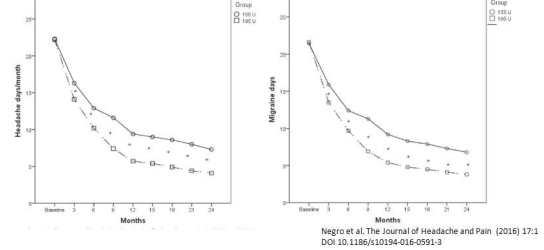


Cernuda-Morillon E et al, 2014 Neurology

### 155 IU vs 195 IU

Higher dosage might be better

Fixed-dose fixed-site + Follow-the-pain > Fixed-dose fixed-site



Negro et al. The Journal of Headache and Pain (2016) 17:1  
DOI 10.1186/s10194-016-0591-3

### Any caution after the injection?

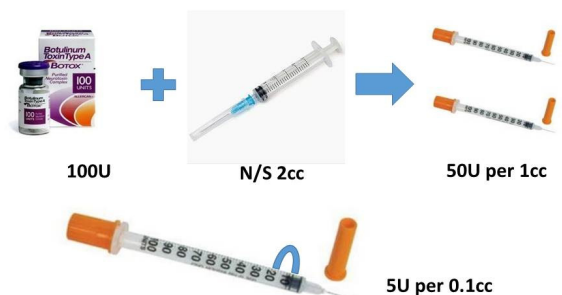
- Side effect: Injection site pain, headache, ptosis, reduced facial expression, shoulder/neck weakness...
- **Do not rub the injection site**, especially the **forehead**, on the day of injection  
→ may lead a diffusion of BTA to functional muscles
- Can wash gently the face on the day of injection
- **Do not shampoo** the hairs on the day of injection

### Injection Details

### Preparation



### Reconstitution and Dilution



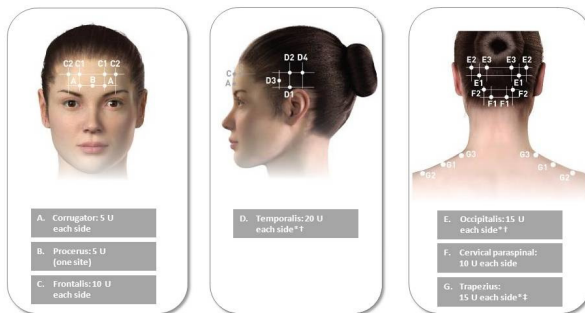
- For each injection site the injection volume will be 0.1 mL = (5 U/site)
- Administered IM using a sterile 30-gauge, 0.5-inch needle

### General Instructions

- 155 IU PREEMPT protocol
  - Fixed-dose fixed-site (FDFS) strategy
  - Additional follow-the-pain strategy
- Depth of the needle
  - Not too superficially (to prevent injection into the dermis)
  - Not too deep (to prevent injection directly on the periosteum)
- Direction of the needle
  - 45-degree angle (\*exceptions: forehead, trapezius injections)
  - With the bevel up
  - Not toward the muscles of frequent side-effects
- Injection
  - Ensure no blood regurgitation before the injection
  - Hold the hub of the needle

### PREEMPT protocol

### Overview of the Injection Sites

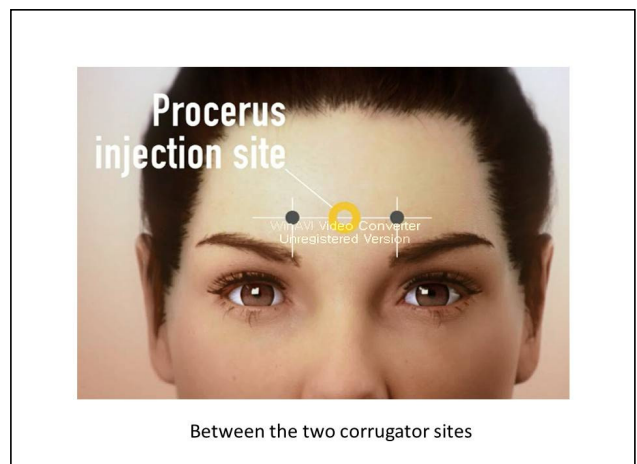
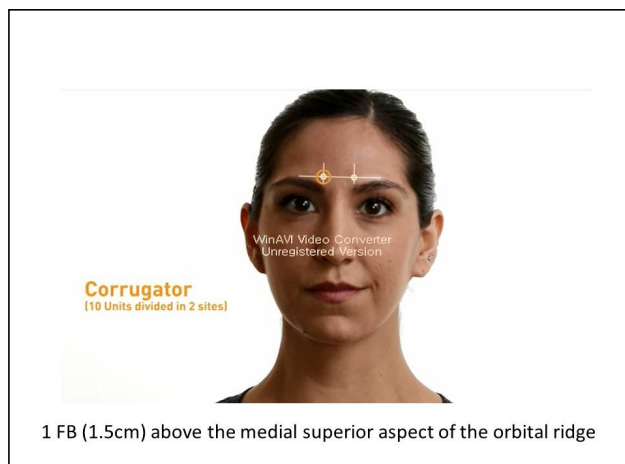
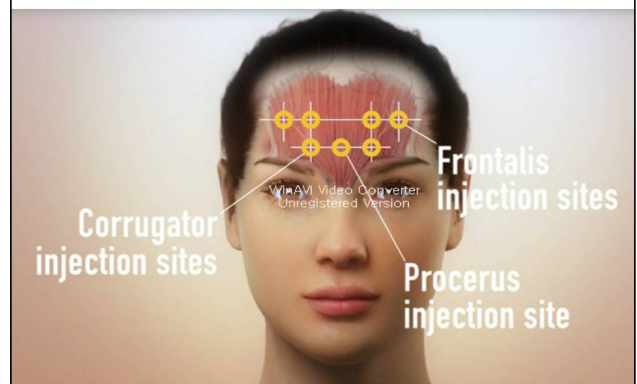


\*Additional Units of BOTOX® can be administered per physician's discretion.

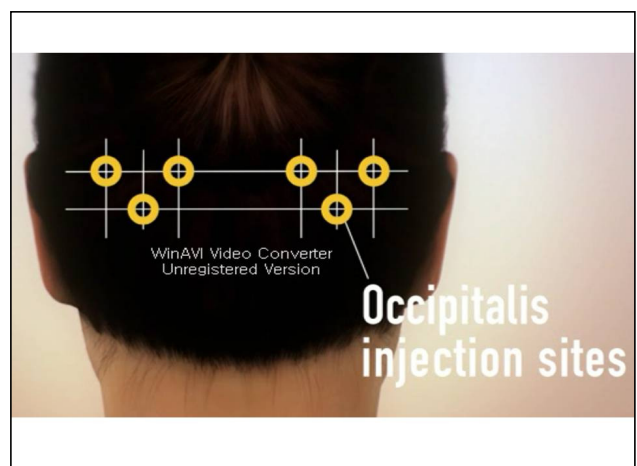
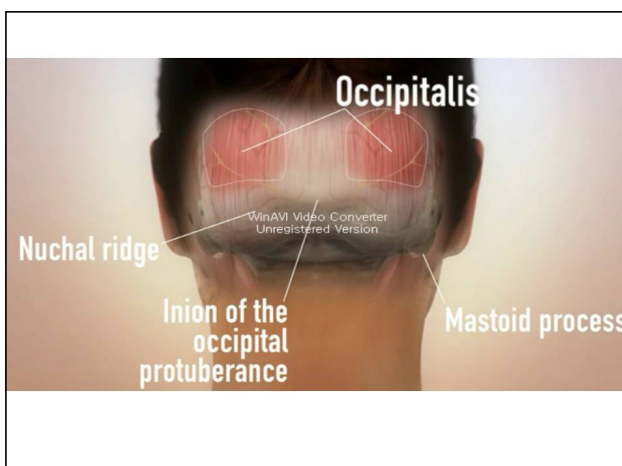
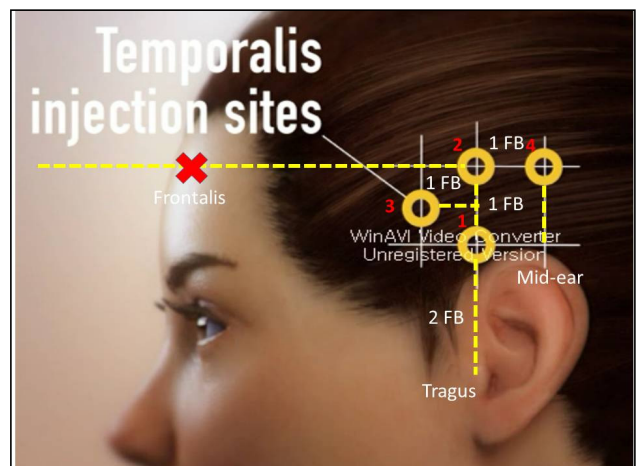
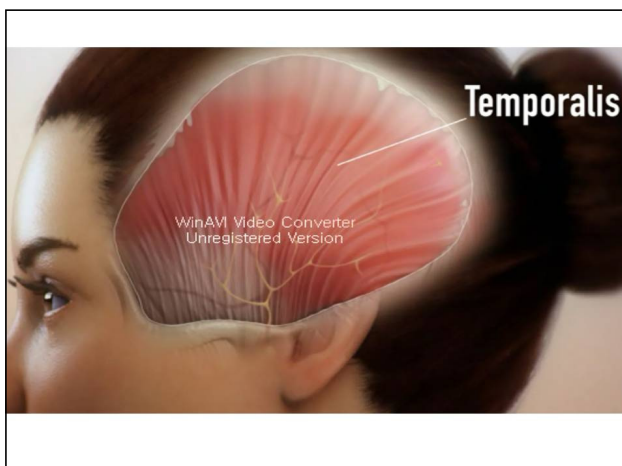
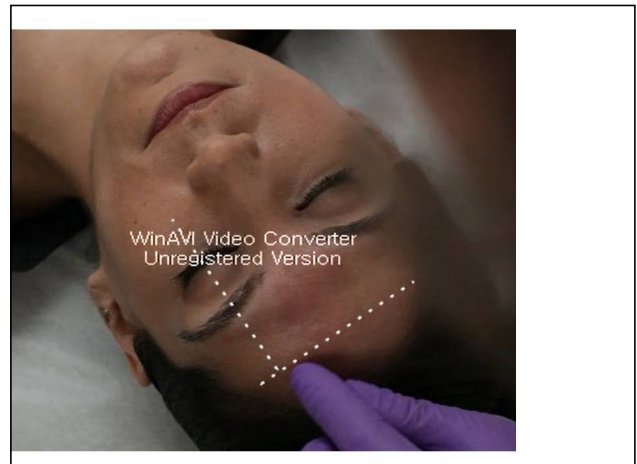
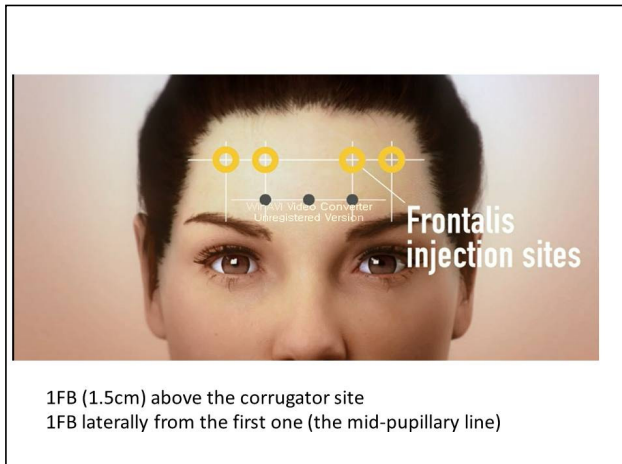
†Up to an additional two doses (2 x 5 Units).

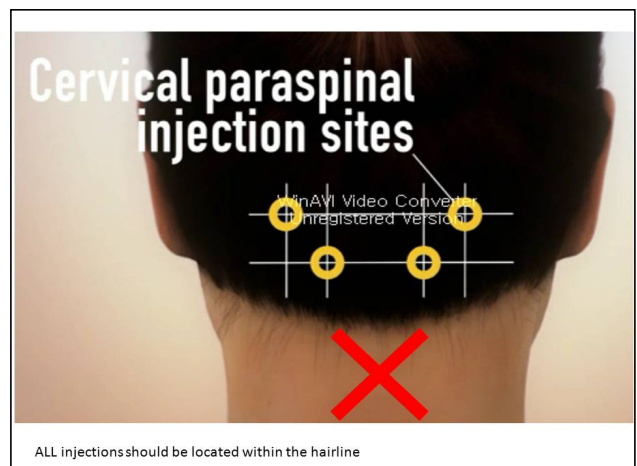
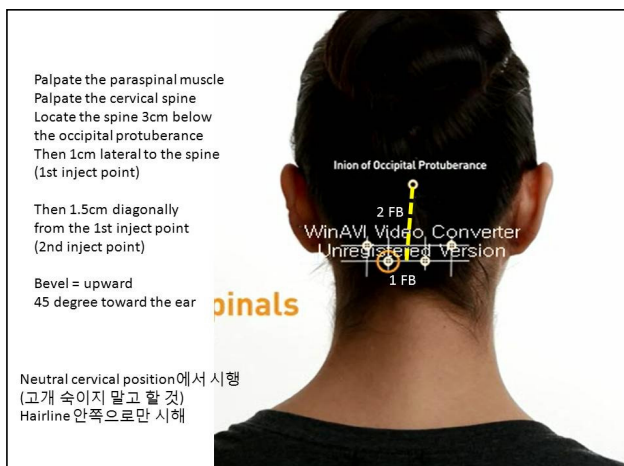
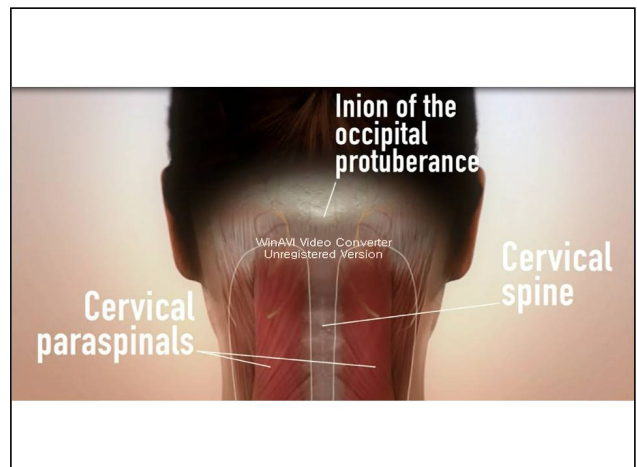
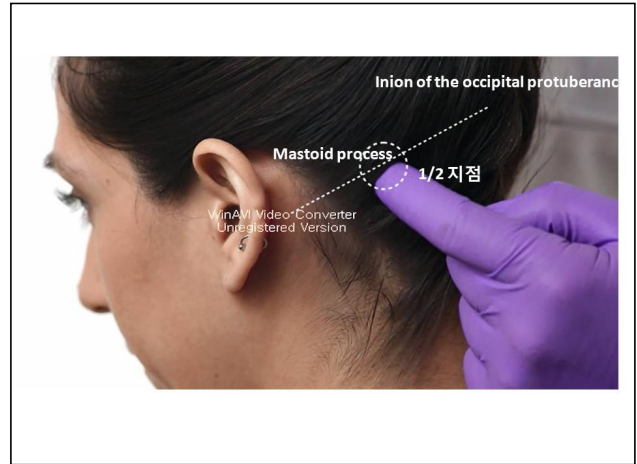
‡Up to an additional 4 doses (4 x 5 Units).

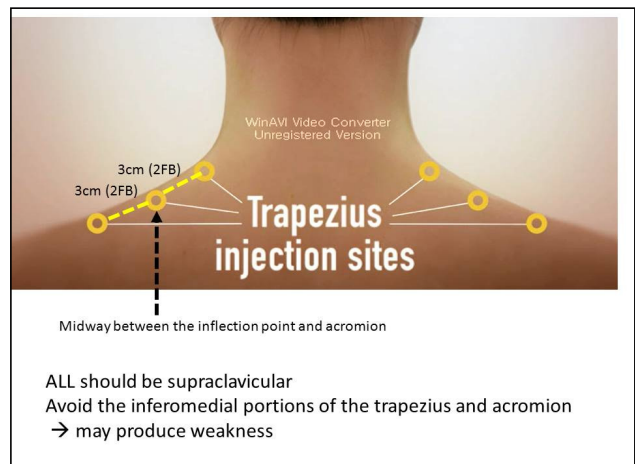
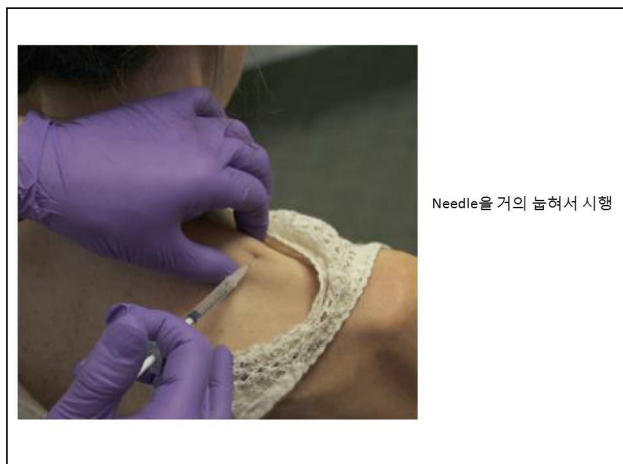
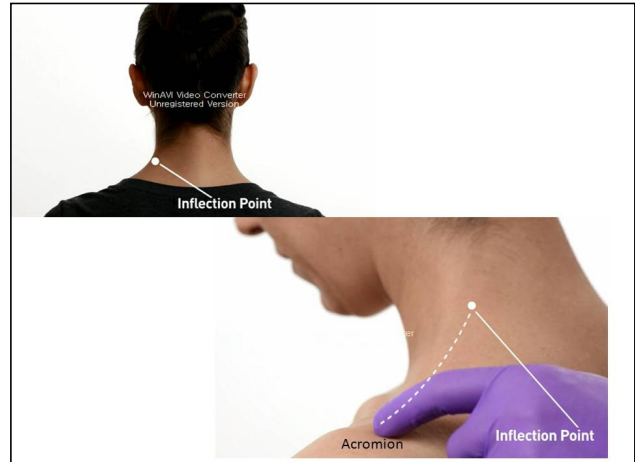
Blumenfeld AM et al. Headache. 2020;50:1408-1418.











References:

1. Blumenfeld A, Silberstein S, Dodick D, et al. Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache*. 2010;50:1406-1418.  
Unregistered Version
2. BOTOX [onabotulinumtoxinA] Prescribing Information]. Irvine, CA: Allergan, Inc.; 2013.

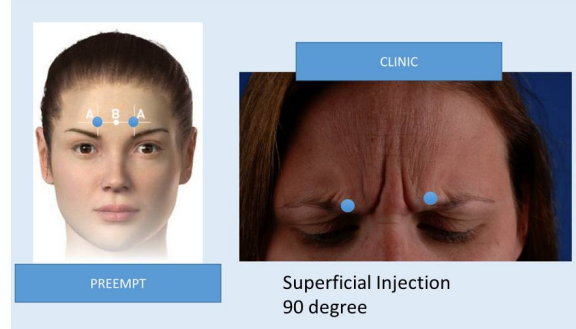
**Modified protocol**



### Procerus Injection (modified)

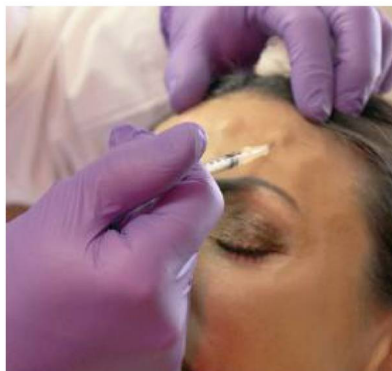
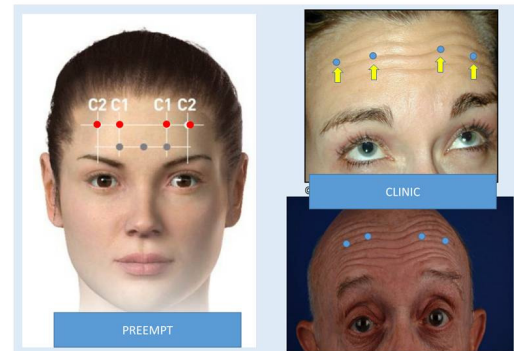


### Corrugator Injection (modified)



90 degree

### Frontalis Injection (modified)



실제 약물이 주입되는 위치가  
Forehead의 upper 1/3 이상이  
되도록

### Forehead Injection (modified)

