# 2021 대한재활의학회 추계학술대회 런천 심포지움

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이 시 욱

# NABOTA® inj.

## (Prabotulinumtoxin A)

# NABOTA® overview

美 FDA 승인
NABOTA® inj.
Prabotulinumtoxin A

| | |
|---|---|
| NABOTA® | **Prabotulinumtoxin A**  |
| 카테고리 | New botulinum toxin type A(Hall A), , 50/100/150/200unit<br>**150U 뇌졸중 후 상지근육 경직 급여 165,738원** |
| 효능 및 효과 | 임상 3상을 통해 앨러간 보톡스와의 동일한 역가 입증. 1:1 Conversion ratio |
| 적응증 | **미간주름** (한국 /미국/ 유럽/캐나다 등 국가에서 적응증 획득)<br>**뇌졸중 후 상지근육경직** (한국 적응증 획득)<br>**눈가주름** (한국 적응증 획득)<br>**안검경련** (본태성 눈꺼풀 경련) (한국 적응증 획득) |
| 특장점 | - **미국 FDA, 유럽 EMA, 캐나다 Health Canada의 승인을 받은 아시아 최초의 보툴리눔 톡신**<br>- **특허 받은 공정으로 제조된 고순도 제품 (High Purity Toxin)**<br>- **대규모 임상을 통해 Onabotulinumtoxin A와의 비열등성 입증 및 우월한 경향성 확인** |
| 특허 | **HI-pure technology**, NABOTA®'s manufacturing process, patented |


Ref) 1. Prabotulinumtoxin A : Registered as NABOTATM in Korea and Asia, JEUVEAUTM in the US, and NUCEIVATM in Canada and EU. 2. Evolus Press Release, Feb/01/2019
3. Evolus Press Release, Oct/01/2019 4. Kenneth R. Beer et al. Dermatol Surg. 2019;45(11):1381-1393
5. The United States Patent and Trade Mark Office; Registration no. 9,512,418 6. Rzany BJ et al. Aesthet Surg J. 2019; 40(4):413-429

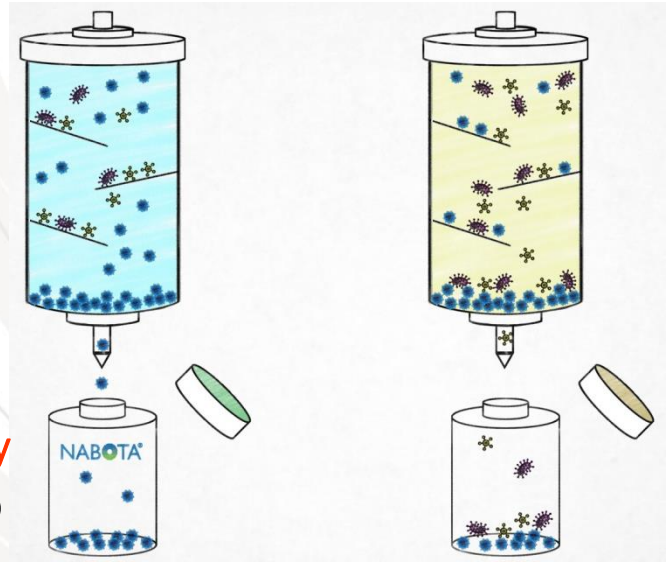
# Patented process (HI-PURE™ technology)

"나보타는.."

✓ 특허공정을 적용한 고순도 보툴리눔 톡신 제품
(>98% of 900kDa toxin complex[1])

균주 배양 → 독소 분리/ 정제 → 감압 건조

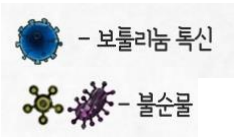
HI-pure™ technology
(특허 제 10-1339349호)




<나보타 정제공정>



<기존 정제공정>

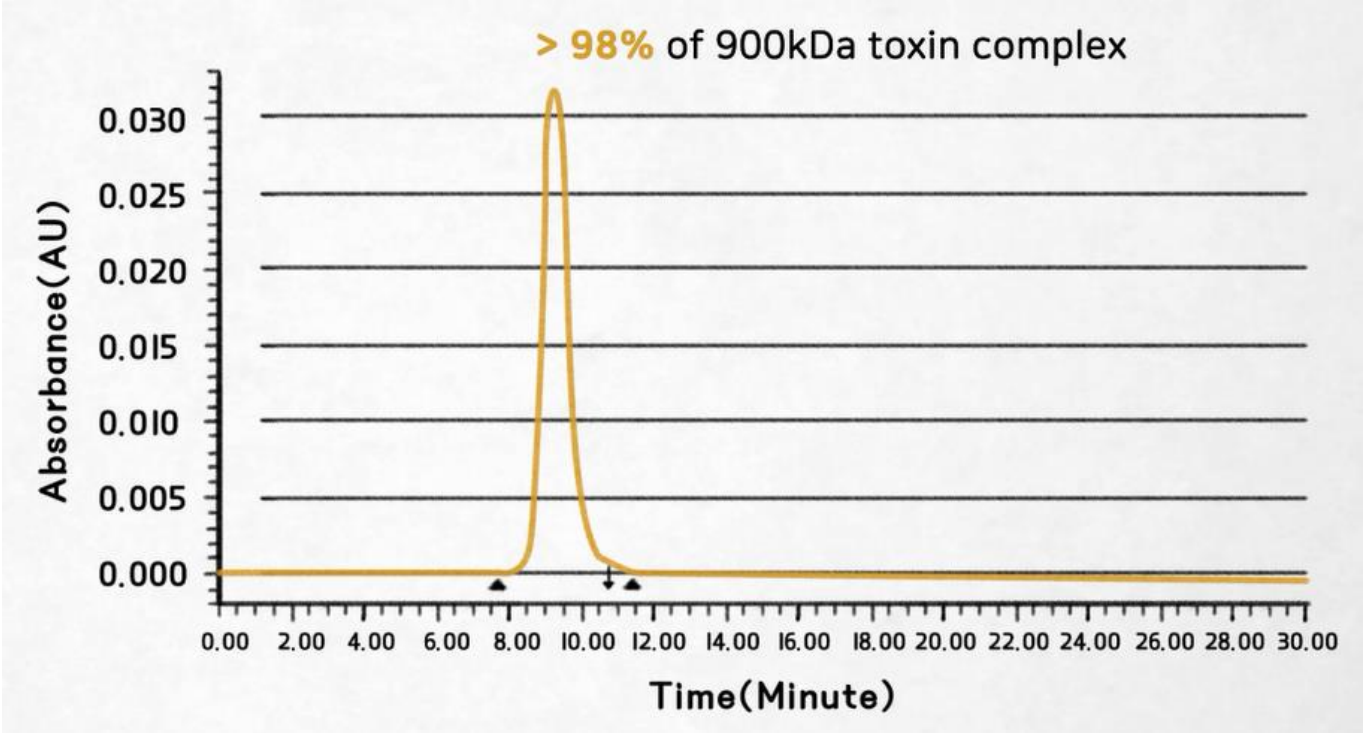



Ref. 1) Won CH et al. *Int J Dermatol*. 2015;54(2):p227-234

# Reduced Impurity

美 FDA 승인
NABOTA® inj.
Prabotulinumtoxin A

## Purity Test Result (SEC-HPLC)




✓ 나보타는 고순도 보툴리눔 톡신을 생산할 수 있는 제조시설에서 생산된 제품입니다

Ref.> Won CH, et al. *Int J Dermatol.* 2015;54(2):p227-234.

# Product profile


| 제품명 | 나보타®주 | | | |
|---|---|---|---|---|
| 성분 | Botulinum toxin type A | | | |
| 용량 | 50 Units | 100 Units | 150 Units | 200 Units |
| 급여 여부 | 비급여 | 비급여 | 뇌졸중 후 상지근육 경직 급여 | 비급여 |

대웅제약

NABOTA®

# A Randomized Controlled Trial to Determine Dose Response Relationship for NABOTA in Finger Spasticity

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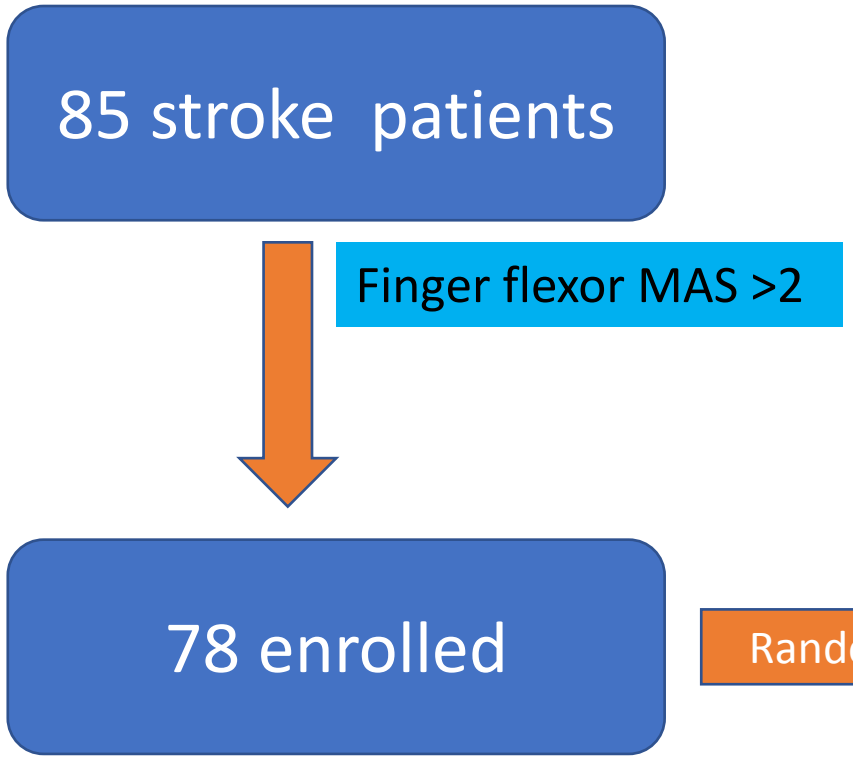
이 시 욱

# Method 1




| Group | Nabota Dose (IU) |
|---|---|
| 1 | 0 |
| 2 | 30 |
| 3 | 60 |
| 4 | 100 |
| 5 | 150 |

# Method 2

- Injection was performed USG guidance
- Injected muscles
  - FDP, FDS : 50% of each assigned dose

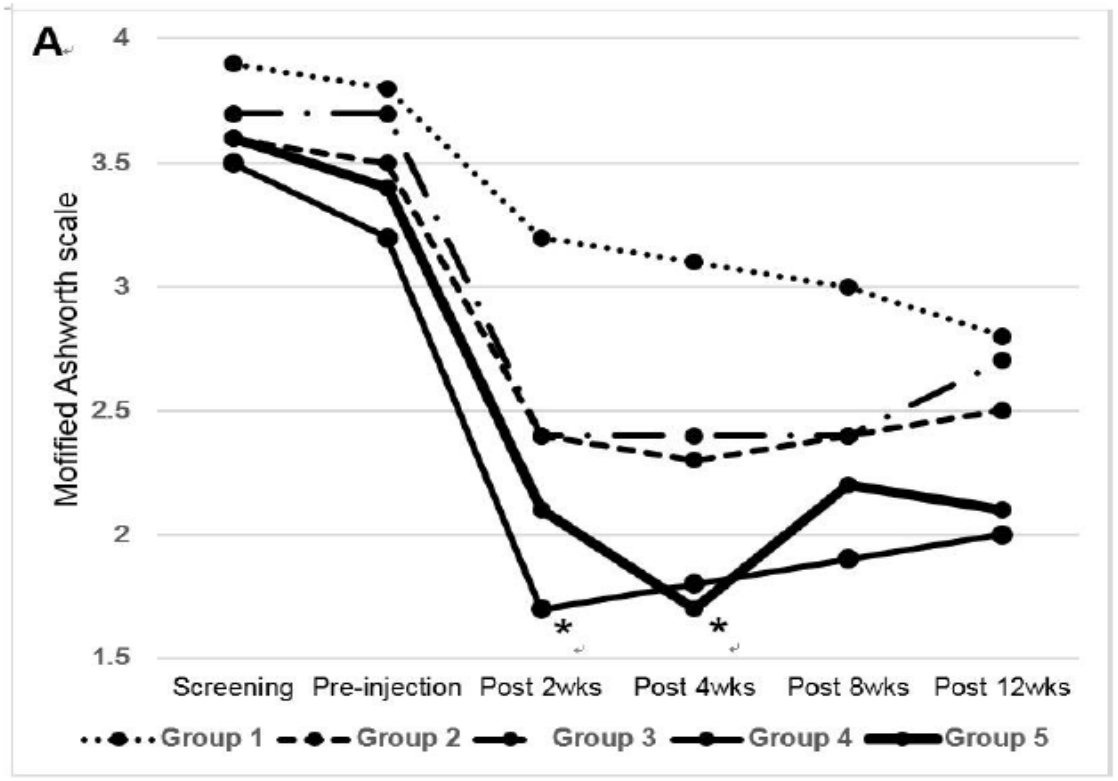
# Outcomes

- Primary outcome: MAS
- Secondary outcome
  - Fugl-Myer assessment
  - Wolf assessment
  - Hand grip strength

- Evaluated at
  - Baseline
  - 2, 4,8, 12 weeks after injection

# Results (1)

- 72 patients were analyzed per protocol



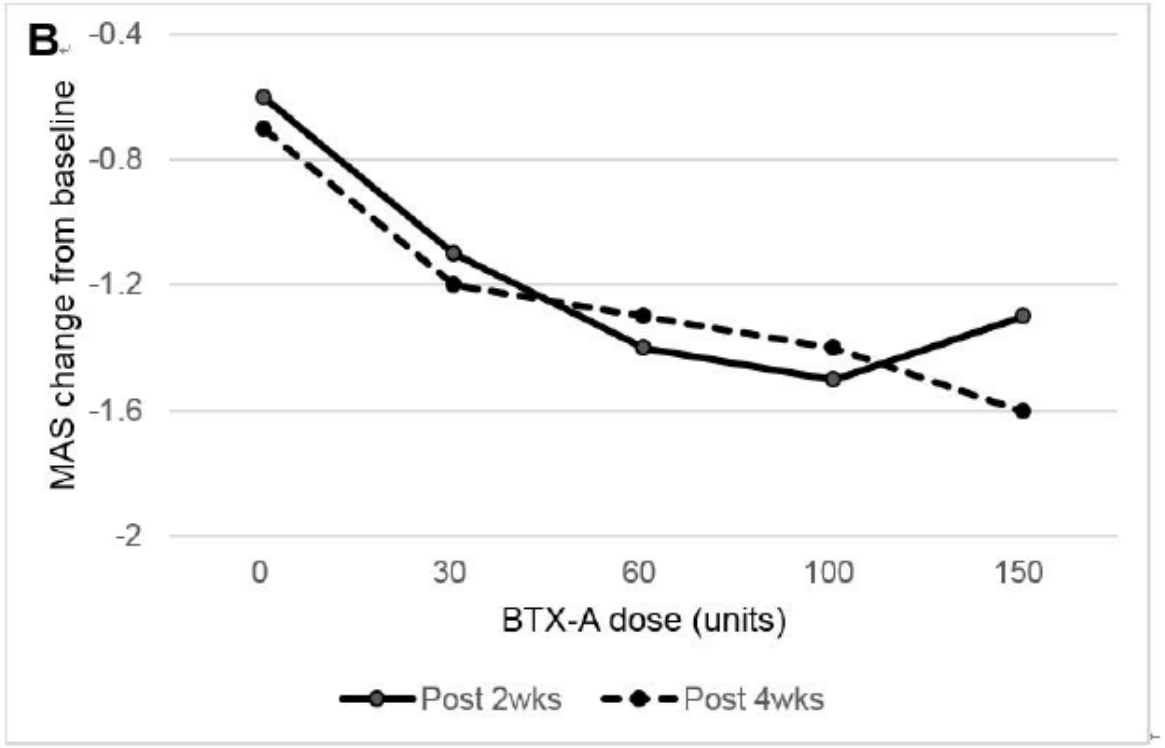
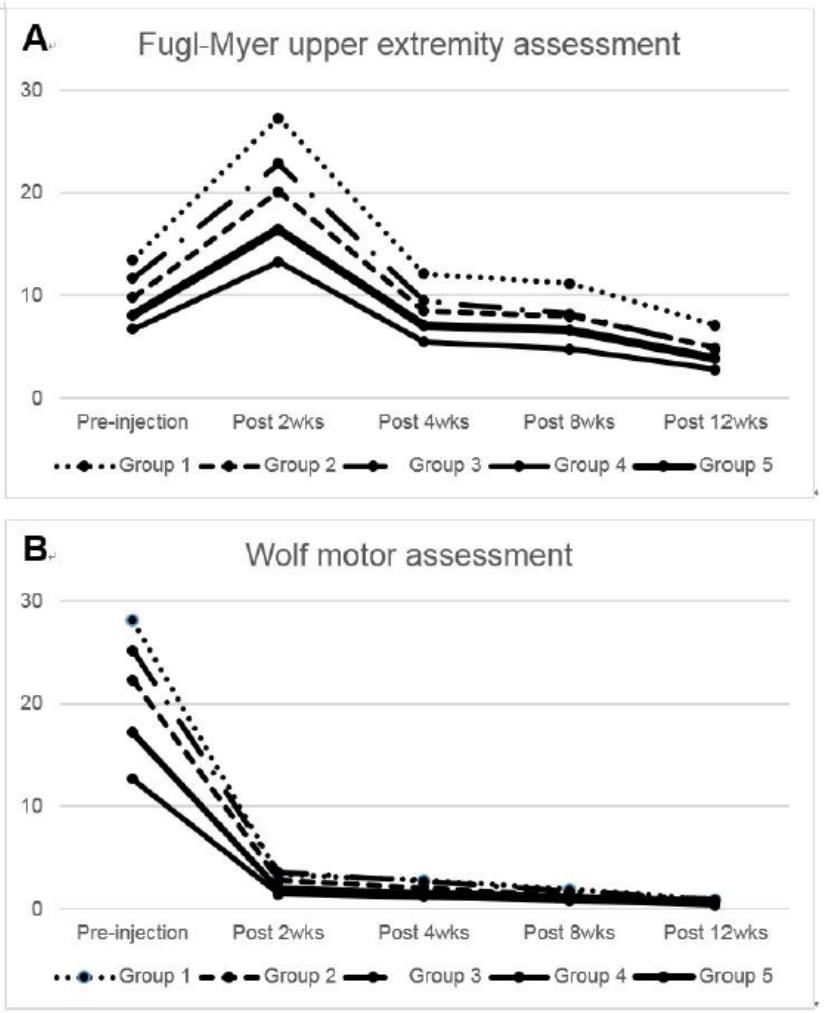




Figure 1. Dose–response analysis of finger flexor spasticity measured by modified Ashworth Scale (MAS): (A) MAS measured at each point, (B) MAS changes from baseline depending on BTX-A dose at 2 and 4 weeks after BTX-A injection. * $P < 0.05$ compared with group 1 at each measure point (by ANOVA test with post-hoc analysis of Tukey HSD)

# Results (2)



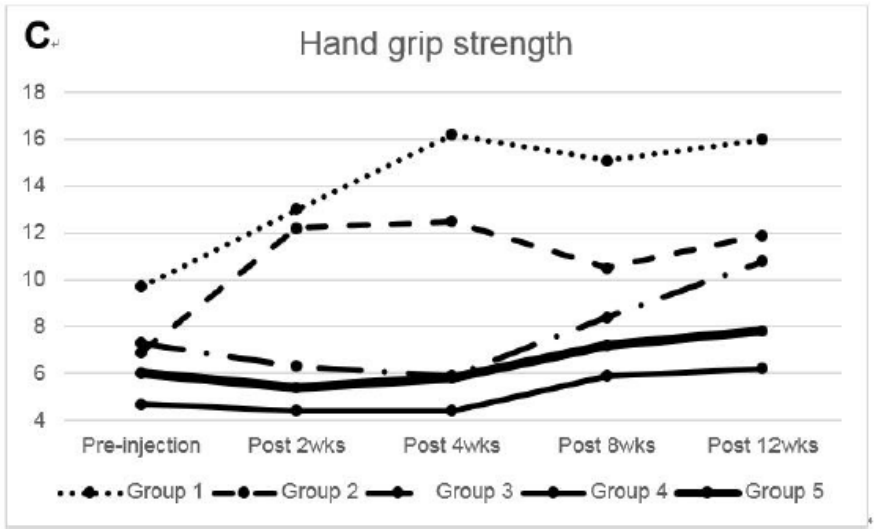




Figure 2. Dose–response analysis of upper extremity functional assessments measured by (A) Fugl-Myer upper extremity assessment, (B) Wolf motor assessment, and (C) Hand grip strength.

# Conclusion

- Botullinum toxin A reduced post-stroke spasticity in a dose-dependent manner in finger flexor.

# Results of Pooled Study

# Table 1. Demographics of the patients. (N=205)

| | | |
|---|---|---|
| **Sex (male)** | | 155 (75.6%) |
| **Age at stroke (year)** | | 52.9 ±12.0 |
| **Disease duration (year)** | | 6.90 ±5.74 |
| **Laterality (right)** | | 106 (51.7%) |
| **Injection dose (IU)** | | 287.0 ±69.13 |
| **Elbow flexor** | Initial MAS | 2.43 ±1.24 |
| | Improved patients | 80 (39.6%) |
| **Wrist volar flexor** | Initial MAS | 2.68 ±1.07 |
| | Improved patients | 111 (54.1%) |
| **Finger flexor** | Initial MAS | 3.00 ±1.12 |
| | Improved patients | 108 (53.2%) |

# Methods

- The muscle groups were categorized into three groups (**elbow flexor, wrist volar flexor, finger flexor**)
- Spasticity was assessed by modified Ashworth Scale (MAS) before and about 1 month after BoNT injection.
- The patients were **dichotomized into groups with and without improvement of MAS ≥ 2**.
- Random walk oversampling was used for balancing the dataset. **Extreme gradient boosting (XGBoost) algorithm,** one of the machine learning algorithm, was used to construct the classifier.
- Performance were evaluated by multiple metrics (**Prediction accuracy, AUROC, F1 score, Matthews correlation coefficient (MCC)**)

# Table 2. Clinical factors associated with improved outcomes (ΔMAS ≥2) after BoNT.

| Muscle groups | Clinical factors | ΔMAS <2 | ΔMAS ≥2 | **p-value** |
|---|---|---|---|---|
| **Elbow flexor** | initial MAS | 2.00 | 3.14 | <.001 |
| | dilution of BoNT | 3.93 | 3.25 | .008 |
| | female | 19.2 % | 32.5 % | .030 |
| **Wrist volar flexor** | initial MAS | 2.04 | 3.22 | <.001 |
| | dilution of BoNT | 3.88 | 3.48 | .009 |
| **Finger flexor** | initial MAS | 2.47 | 3.28 | <.001 |
| | female | 17.7 % | 30.3 % | .037 |

Table 3. Evaluation metrics of the classifier predicting the efficacy of BoNT in each muscle group.

| Classifier of Muscle groups | **Accuracy** | **AUC** | **F1 score** | **MCC** |
|---|---|---|---|---|
| **Elbow flexor** | 0.700 | 0.709 | 0.761 | 0.386 |
| **Wrist volar flexor** | 0.705 | 0.704 | 0.680 | 0.408 |
| **Finger flexor** | 0.764 | 0.757 | 0.714 | 0.514 |

# Conclusion

- The present study showed that **high initial MAS, low ratio of BoNT dilution,** and **female** were associated with markedly improved outcomes of BoNT for post-stroke spasticity.

- **The prediction of markedly improved outcomes of post-stroke spasticity after BoNT in the EF, WVF, and FF** was **feasible based on clinical and BoNT-related factors using a machine learning algorithm.**