



## BÖLÜM 26

### BAŞ AĞRISI TEDAVİSİNDE BOTULİNUM TOKSİN UYGULAMALARI

Muharrem Anıl GÜRKAN<sup>1</sup>

## GİRİŞ

Kronik baş ağrıları, hastaların yaşam kalitesini bozarak günlük aktivitelerini engellemekte ve aynı zamanda ciddi iş gücü kaybı ve ekonomik kayıplara yol açmaktadır. Uzun aylar ve yıllar boyunca devam eden baş ağrıları hastalarda ek olarak depresyon gibi psikiyatrik bulguları da ortaya çıkarmaktadır. Baş ağrısı tedavisinde medikal tedaviler ve yaşam tarzi düzenlemeleri fayda sağlamakla birlikte tedavi seçeneklerinden yarar görmeyen hastalar dirençli grubu oluşturmaktadır. Kronik ve dirençli migren baş ağrılarında son yıllarda Onabotulinum toksin serotip-A (BoNT-A) enjeksiyonu ruhsatlı bir tedavi yöntemi olarak öne çıkmaktadır. Migren dışında diğer kronik ve dirençli ağrı tedavisinde yapılan çalışmalarda da BoNT-A tedavi etkililiği açısından olumlu sonuçlar olduğu bildirilmiştir.

## BOTULİNUM TOKSİN TARİHÇESİ

Botulinum Toksini (BoNT) sinir-kas kavşağında presinaptik veziküllerden asetil kolin salımını inhibe ederek doza bağımlı ve geri dönüşümlü müsküler paraliziye yol açan bir nörotoksindir. Gram pozitif anaerob bir bakteri olan *Clostridium botulinum*'un otolizi esnasında ortama salınır.(1) Botulizm

<sup>1</sup> Uzm Dr., Serbest nöroloji hekimi, İzmir, Türkiye. e-posta: manilgurkan@gmail.com



## SONUÇ

Özetle migren önleyici tedavilere yanıt vermeyen, ağrı sıklığı ve ağrı şiddeti nedeniyle yaşam kalitesi bozulan kronik migrenli hastalarda BoNT-A enjeksiyon tedavisi, uygun aralıklarla ve uygun dozlarda uygulandığında ağrının yarattığı yaşam kalitesindeki azalmanın önüne geçmektedir. Bunun yanı sıra santral desensitizasyonu artırarak uzun dönemde ağrı kontrolünde de etkili olmaktadır. Nevralljik ağrıarda ve gerilim tipi baş ağrılarında BoNT-A tedavisi henüz ruhsat almamakla birlikte, yapılan çalışmalarda bu çeşit ağrıları olan hastalarda da ağrı kontrolünde etkililiği olduğu gösterilmiştir. Aşırı ilaç kullanım Baş Ağrısı ile birlikte görülen kronik migrenli hastalarda ise analjezik ilaçların kesilmesini beklemeden başlanan BoNT-A tedavisi, bu hastalarda Baş Ağrısı tedavisinde hızlı bir yanıt ortaya çıkardığı için avantajlı olduğu saptanmıştır.

## KAYNAKLAR

1. Jankovic J, Brin MF. Botulinum toxin: historical perspective and potential new indications. *Muscle & nerve Supplement*. 1997;6:S129-45.
2. Erbguth FJ. From poison to remedy: the chequered history of botulinum toxin. *Journal of neural transmission (Vienna, Austria : 1996)*. 2008;115(4):559-565. doi:10.1007/s00702-007-0728-2
3. Lew MF. Review of the FDA-approved uses of botulinum toxins, including data suggesting efficacy in pain reduction. *The Clinical journal of pain*. 18(6 Suppl):S142-6. doi:10.1097/00002508-200211001-00005
4. Scott AB, Magoon EH, McNeer KW, Stager DR. Botulinum treatment of strabismus in children. *Transactions of the American Ophthalmological Society*. 1989;87:174-180; discussion 180-4.
5. Evidente VGH, Pappert EJ. Botulinum toxin therapy for cervical dystonia: the science of dosing. *Tremor and other hyperkinetic movements (New York, NY)*. 2014;4:273. doi:10.7916/D84X56BF
6. Binder WJ, Blitzer A, Brin MF. Treatment of hyperfunctional lines of the face with botulinum toxin A. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 1998;24(11):1198-1205. doi:10.1111/j.1524-4725.1998.tb04098.x
7. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalgia : an international journal of headache*. 2010;30(7):793-803. doi:10.1177/0333102410364676
8. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalgia : an international journal of headache*. 2010;30(7):804-814. doi:10.1177/0333102410364677
9. Choudhury S, Baker MR, Chatterjee S, Kumar H. Botulinum Toxin: An Update on Phar-



- macology and Newer Products in Development. *Toxins.* 2021;13(1). doi:10.3390/toxins13010058
- 10. Fusco BM, Barzoi G, Agrò F. Repeated intranasal capsaicin applications to treat chronic migraine. *British journal of anaesthesia.* 2003;90(6):812. doi:10.1093/bja/aeg572
  - 11. Edelmayer RM, Le LN, Yan J, et al. Activation of TRPA1 on dural afferents: a potential mechanism of headache pain. *Pain.* 2012;153(9):1949-1958. doi:10.1016/j.pain.2012.06.012
  - 12. Whitcup SM, Turkell CC, DeGryse RE, Brin MF. Development of onabotulinumtoxinA for chronic migraine. *Annals of the New York Academy of Sciences.* 2014;1329:67-80. doi:10.1111/nyas.12488
  - 13. Matak I, Riederer P, Lacković Z. Botulinum toxin's axonal transport from periphery to the spinal cord. *Neurochemistry international.* 2012;61(2):236-239. doi:10.1016/j.neuint.2012.05.001
  - 14. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. *The Cochrane database of systematic reviews.* 2018;6:CD011616. doi:10.1002/14651858.CD011616.pub2
  - 15. Ahmed F, Gaul C, García-Moncó JC, Sommer K, Martelletti P, REPOSE Principal Investigators. An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study. *The journal of headache and pain.* 2019;20(1):26. doi:10.1186/s10194-019-0976-1
  - 16. Blumenfeld AM, Tepper SJ, Robbins LD, et al. Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety. *Journal of neurology, neurosurgery, and psychiatry.* 2019;90(3):353-360. doi:10.1136/jnnp-2018-319290
  - 17. Demiryurek BE, Ertem DH, Tekin A, Ceylan M, Aras YG, Gungen BD. Effects of onabotulinumtoxinA treatment on efficacy, depression, anxiety, and disability in Turkish patients with chronic migraine. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* 2016;37(11):1779-1784. doi:10.1007/s10072-016-2665-z
  - 18. Aydinlar EI, Dikmen PY, Kosak S, Kocaman AS. OnabotulinumtoxinA effectiveness on chronic migraine, negative emotional states and sleep quality: a single-center prospective cohort study. *The journal of headache and pain.* 2017;18(1):23. doi:10.1186/s10194-017-0723-4
  - 19. Maasumi K, Thompson NR, Kriegler JS, Tepper SJ. Effect of OnabotulinumtoxinA Injection on Depression in Chronic Migraine. *Headache.* 2015;55(9):1218-1224. doi:10.1111/head.12657
  - 20. Chen TY, Garza I, Dodick DW, Robertson CE. The Effect of OnabotulinumtoxinA on Aura Frequency and Severity in Patients With Hemiplegic Migraine: Case Series of 11 Patients. *Headache.* 2018;58(7):973-985. doi:10.1111/head.13317
  - 21. Relja M, Poole AC, Schoenen J, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNT-A) for the prophylaxis of episodic migraine headaches. *Cephalgia : an international journal of headache.* 2007;27(6):492-503. doi:10.1111/j.1468-2982.2007.01315.x
  - 22. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2016;86(19):1818-1826. doi:10.1212/WNL.0000000000002560



23. Shen B, Wang L. Impact of the botulinum-A toxin on prevention of adult migraine disorders. *Journal of integrative neuroscience*. 2020;19(1):201-208. doi:10.31083/j.jin.2020.01.1240
24. Bruloy E, Sinna R, Grolleau JL, Bout-Roumazeilles A, Berard E, Chaput B. Botulinum Toxin versus Placebo: A Meta-Analysis of Prophylactic Treatment for Migraine. *Plastic and reconstructive surgery*. 2019;143(1):239-250. doi:10.1097/PRS.0000000000005111
25. de Goffau MJ, Klaver ARE, Willemsen MG, Bindels PJE, Verhagen AP. The Effectiveness of Treatments for Patients With Medication Overuse Headache: A Systematic Review and Meta-Analysis. *The journal of pain*. 2017;18(6):615-627. doi:10.1016/j.jpain.2016.12.005
26. Butera C, Colombo B, Bianchi F, et al. Refractory chronic migraine: is drug withdrawal necessary before starting a therapy with onabotulinum toxin type A? *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2016;37(10):1701-1706. doi:10.1007/s10072-016-2662-2
27. Andreou AP, Trimboli M, Al-Kaisy A, et al. Prospective real-world analysis of OnabotulinumtoxinA in chronic migraine post-National Institute for Health and Care Excellence UK technology appraisal. *European journal of neurology*. 2018;25(8):1069-e83. doi:10.1111/ene.13657
28. Bendtsen L, Sacco S, Ashina M, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. *The journal of headache and pain*. 2018;19(1):91. doi:10.1186/s10194-018-0921-8
29. Silberstein SD, Göbel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. *Cephalgia : an international journal of headache*. 2006;26(7):790-800. doi:10.1111/j.1468-2982.2006.01114.x
30. Shehata HS, El-Tamawy MS, Shalaby NM, Ramzy G. Botulinum toxin-type A: could it be an effective treatment option in intractable trigeminal neuralgia? *The journal of headache and pain*. 2013;14:92. doi:10.1186/1129-2377-14-92
31. Türk Börü Ü, Duman A, Böyük C, Coşkun Duman S, Taşdemir M. Botulinum toxin in the treatment of trigeminal neuralgia: 6-Month follow-up. *Medicine*. 2017;96(39):e8133. doi:10.1097/MD.0000000000008133
32. Bendtsen L, Zakrzewska JM, Abbott J, et al. European Academy of Neurology guideline on trigeminal neuralgia. *European journal of neurology*. 2019;26(6):831-849. doi:10.1111/ene.13950
33. Sostak P, Krause P, Förderreuther S, Reinisch V, Straube A. Botulinum toxin type-A therapy in cluster headache: an open study. *The journal of headache and pain*. 2007;8(4):236-241. doi:10.1007/s10194-007-0400-0
34. Bratbak DF, Nordgård S, Stovner LJ, et al. Pilot study of sphenopalatine injection of onabotulinumtoxinA for the treatment of intractable chronic cluster headache. *Cephalgia : an international journal of headache*. 2016;36(6):503-509. doi:10.1177/0333102415597891
35. Lampl C, Rudolph M, Bräutigam E. OnabotulinumtoxinA in the treatment of refractory chronic cluster headache. *The journal of headache and pain*. 2018;19(1):45. doi:10.1186/s10194-018-0874-y
36. Zabalza RJ. Sustained response to botulinum toxin in SUNCT syndrome. *Cephalgia : an international journal of headache*. 2012;32(11):869-872. doi:10.1177/0333102412452045
37. Kapural L, Stillman M, Kapural M, McIntyre P, Guirgius M, Mekhail N. Botulinum Toxin Occipital Nerve Block for the Treatment of Severe Occipital Neuralgia: A Case Series. *Pain Practice*. 2007;7(4):337-340. doi:10.1111/j.1533-2500.2007.00150.x



38. Taylor M, Silva S, Cottrell C. Botulinum Toxin Type-A (BOTOX® ) in the Treatment of Occipital Neuralgia: A Pilot Study. Headache: The Journal of Head and Face Pain. 2008;48(10):1476-1481. doi:10.1111/j.1526-4610.2008.01089.x
39. Allergan Botox® Kısa Ürün Bilgisi (KÜB).
40. Tassorelli C, Diener HC, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia : an international journal of headache.* 2018;38(5):815-832. doi:10.1177/0333102418758283
41. Masters-Israilov A, Robbins MS. OnabotulinumtoxinA Wear-off Phenomenon in the Treatment of Chronic Migraine. *Headache.* 2019;59(10):1753-1761. doi:10.1111/head.13638
42. Quintas S, García-Azorín D, Heredia P, Talavera B, Gago-Veiga AB, Guerrero ÁL. Wearing Off Response to OnabotulinumtoxinA in Chronic Migraine: Analysis in a Series of 193 Patients. *Pain medicine (Malden, Mass).* 2019;20(9):1815-1821. doi:10.1093/pmt/pny282
43. Khan P, Roberto M, Frances JA, et al. The Effectiveness of Botulinum Toxin Type A (BoNT-A) Treatment in Brazilian Patients with Chronic Post-Stroke Spasticity: Results from the Observational, Multicenter, Prospective BCause Study. *Toxins.* 2020;12(12). doi:10.3390/toxins12120770
44. Jakubowski M. Patients with imploding migraine headache respond to botulinum A toxin therapy. *Nature Clinical Practice Neurology.* 2007;3(2):66-66. doi:10.1038/ncpneuro0387
45. Grogan PM, Alvarez MV, Jones L. Headache direction and aura predict migraine responsiveness to rimabotulinumtoxin B. *Headache.* 2013;53(1):126-136. doi:10.1111/j.1526-4610.2012.02288.x
46. Kim CC, Bogart MM, Wee SA, Burstein R, Arndt KA, Dover JS. Predicting Migraine Responsiveness to Botulinum Toxin Type A Injections. *Archives of Dermatology.* 2010;146(2). doi:10.1001/archdermatol.2009.356
47. Burstein R, Dodick D, Silberstein S. Migraine prophylaxis with botulinum toxin A is associated with perception of headache. *Toxicon : official journal of the International Society on Toxinology.* 2009;54(5):624-627. doi:10.1016/j.toxicon.2009.01.009
48. Mathew NT, Kailasam J, Meadors L. Predictors of response to botulinum toxin type A (BoNTA) in chronic daily headache. *Headache.* 2008;48(2):194-200. doi:10.1111/j.1526-4610.2007.00914.x
49. de Tommaso M, Brighina F, Delussi M. Effects of Botulinum Toxin A on Allodynia in Chronic Migraine: An Observational Open-Label Two-Year Study. *European neurology.* 2019;81(1-2):37-46. doi:10.1159/000499764
50. Lovati C, Giani L, Mariotti D Alessandro C, Tabaee Damavandi P, Mariani C, Pantoni L. May migraine attack response to triptans be a predictor of the efficacy of Onabotulinum toxin-A prophylaxis? *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* 2018;39(Suppl 1):153-154. doi:10.1007/s10072-018-3388-0
51. Eren OE, Gaul C, Peikert A, Gendolla A, Ruscheweyh R, Straube A. Triptan efficacy does not predict onabotulinumtoxinA efficacy but improves with onabotulinumtoxinA response in chronic migraine patients. *Scientific reports.* 2020;10(1):11382. doi:10.1038/s41598-020-68149-1
52. Cernuda-Morollón E, Ramón C, Martínez-Camblor P, Serrano-Pertierra E, Larrosa D, Pasqual J. OnabotulinumtoxinA decreases interictal CGRP plasma levels in patients with chronic migraine. *Pain.* 2015;156(5):820-824. doi:10.1097/j.pain.0000000000000119
53. Domínguez C, Pozo-Rosich P, Torres-Ferrús M, et al. OnabotulinumtoxinA in chronic migraine: predictors of response. A prospective multicentre descriptive study. *European jour-*



- nal of neurology. 2018;25(2):411-416. doi:10.1111/ene.13523
54. Domínguez Vivero C, Leira Y, Saavedra Piñeiro M, et al. Iron Deposits in Periaqueductal Gray Matter Are Associated with Poor Response to OnabotulinumtoxinA in Chronic Migraine. Toxins. 2020;12(8). doi:10.3390/toxins12080479
55. Domínguez C, López A, Ramos-Cabrer P, et al. Iron deposition in periaqueductal gray matter as a potential biomarker for chronic migraine. Neurology. 2019;92(10):e1076-e1085. doi:10.1212/WNL.0000000000007047
56. Moreno-Mayordomo R, Ruiz M, Pascual J, et al. CALCA and TRPV1 genes polymorphisms are related to a good outcome in female chronic migraine patients treated with OnabotulinumtoxinA. The journal of headache and pain. 2019;20(1):39. doi:10.1186/s10194-019-0989-9