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A STUDY OF THE EFFECTIVENESS AND SAFETY OF BOTULINUM TOXIN A AND CLINICAL EVIDENCE ON CHRONIC MIGRAINE

Sahil V. Bhoir*, Swati D. Yeole, Harshal L. Tare

TSPM'S Trimurti Institute of Pharmacy, Jalgaon, Maharashtra, India.

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For Correspondence:

Sahil V. Bhoir

TSPM'S Trimurti Institute of Pharmacy, Jalgaon, Maharashtra, India

E-mail:

sahilbhoir547@gmail.com

ABSTRACT

Botulinum Toxin A (BTA) is widely used as treatment of chronic migraine. Efficacy in studies, however, was only modest and likely influenced by unbinding due to BTA- induced removal of forehead wrinkles. Moreover, most study participants were overusing acute headache medications and might have benefited from withdrawal. We assessed in a double blind, placebo-controlled, randomized clinical trials whether add- on therapy with BTA enhances efficacy of acute withdrawal. Participants were enrolled between December 2012 and February 2015, with follow-up to January 2016, in a single academic hospital in the Netherlands. A total of 179 participants, male and female, aged 18-65, diagnosed with chronic migraine and overuse of acute headache medication were included. All participants were instructed to withdraw acutely from all medications for a 12- week period, in an outpatients setting. In addition, they were randomly assigned (1:1) to 31 injections with BTA (155 units) or placebo (saline); to prevent unbinding, placebo- treated participants received low doses of BTA (17.5 units in total) in the forehead, along with saline injections outside the forehead region. Primary endpoints was percentage change in monthly headache days from baseline to the last 4 weeks of double-blind treatment (weeks 9-12). Among 179 randomized patients, 90 received BTA and 89 received placebo, and 175(98%) completed the double phase. All 179 patients were included in the intention-to-treat analyses. Thus in patients with chronic migraine and medication overuse, BTA does not afford any additional benefit over acute withdrawal alone. Acute withdrawal should be tried first before initiating more expensive treatment with BTA.

INTRODUCTION

A 'Migraine' is not just a headache ,it is a neurological condition of a brain, which is very distressing and disabling. This type of headache is ubiquitous, prevailing and essentially treatable, but still under-estimated and under treated[1].

Not all headaches represent migraines, that mean migraine is not only condition that cause severe and disabling pain. The cause of migraine is a common neurological disorder that is caused by the stimulation of a mechanism in the brain that leads to release of pain producing inflammatory substances around the nerves and blood vessels of the head[2]

Migraine has throbbing quality, of moderate to severe intensity, generally unilateral, and has associated symptoms including photophobia, phonophobia and gastrointestinal distress. Episodic migraines occur less than 15 days per month, while chronic migraines occur more or equal to 15 days per month. Treatment of migraine consists of abortive and preventive therapy as well different effective drugs[3]

Effectiveness of Botulinum toxin Type A drug to treat migraine

Botulinum toxin (BTX) is a neurotoxic protein produced by the Bacterium Clostridium Botulinum and related species. Clostridium Botulinum is the bacterial source of the toxin[4].

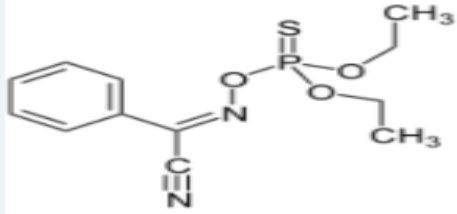


Figure 1: Chemical structure

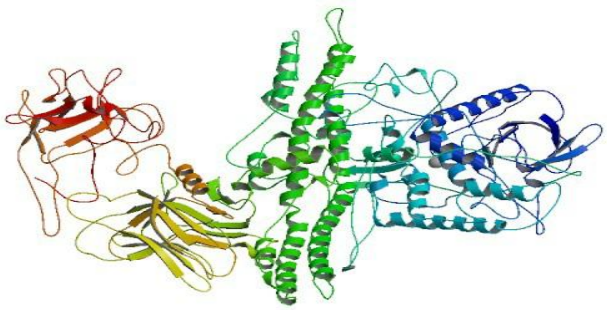


Figure 2: 3D Structure

Botulinum toxin is the form of NSAIDs and thus NSAIDs are often used for the management of mild attacks. The intravenous NSAIDs is recommended for severe episodes[5]. The other related derivative of Botulinum toxin type A drug is Botulinum toxin type B which is use for the treatment of patients with cervical dystonia to reduce severity of abormal head[6].

The Triptanes, Beta-blockers, Topiramate, Amitryptyline are the other forms of drug ued in the treatment of migraine. The Botulinum toxin A has been used to treat variety of disorders including involuntary muscle contraction, blepharospasm, strabismus, cervical dystonia, analgesic effect, leading investigation for painful conditions such as migraine. Botulinum toxin type A has been used off label since 2000 for the treatment of mgraine headache[7]

Since, then multiple small trials report the effectiveness of Botulinum toxin A for migraine headache prevention. However, the phase3 research evaluating migraine prophylaxis therapy (PREEMPT) 1 and 2 trials the class1 A evidence was concluded that Botulinum toxin A treatment reduces chronic migraine headache impact and improves headache related quality of life[8]

The Botulinum toxin was discover by Dr. Burgen's ASV group in 1949. The FDA approval of Botulinum toxin A drug to treat migraine was granted on 15 October 2010[9].

MOA

After intramuscular or subcutaneous injection BoNT is internalized into peripheral motor neurons via SV2 binding protein. Once translocated into the cytosol BoNT.

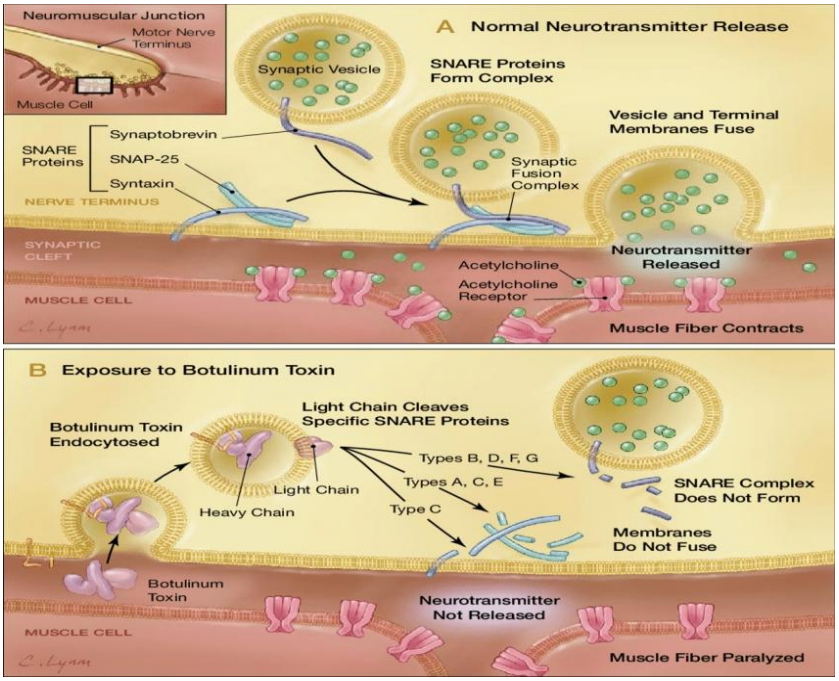


Figure 3: MOA of drug

Enzymatically cleaves the 25 kDa synaptosomal –associated protein (SNAP-25), a protein, which mediates the fusion of neurotransmitter containing vesicles with the cell membrane[10].

The Botulinum toxin A inhibits the release of CGRP from peripheral trigeminal neurons and consequently, reduces the CGRP- mediated trigeminal sensitization in migraine[11] This effect has been studied for the suppression of acetylcholine release at the neuromuscular junction.

However, more recent studies show the BoNT also modifies the release of neurotransmitters, which are relevant in transduction of pain such as substance calcitonine gene related peptide CGRP[12]

Thus it is supposed that the inhibition of peripheral sensitization leads to an indirect inhibition of central sensitization and thus is a possible mechanism for the efficacy of BoNT in chronic pain[13]

On the contrary, animal model stuidies support the view, that there is site for BoNT in the central nervous system, although the mechanism off a central antinociceptive action of BoNT remain unclear14]

Simply Botulinum toxin exerts its effect by cleaving key proteins required for nerve activation. First, the toxin binds specifically to nerves which use the neurotransmitter acetylcholine. Once bound to the nerve terminal,the neuron takes up the toxin into a vesicle moves farther into the cell, it acidifies, activating a portion of a toxin which triggers it to push across the vesicle membrane and in to the cell cytoplasm[15]

Once inside the cytoplasm, the toxins cleaves SNARE proteins (proteins that mediated vesicle fusion, with their target membrane bound compartments) meaning that the acetylcholine vesicles can't bind to the intracellular cell membrane, preventing the cell from releasing vesicles of neurotransmitters. This stops nerve signaling, leading to paralysis[16].

The toxin itself is released from the bacterium as a single chain, then becomes activated when cleaved by its own proteases[17].

The active form consists of a two- chain protein composed of a 100-KDa heavy chain polypeptide joined via disulfide bond to a 50-KDa light chain polypetide[18].

The heavy chian contains domains with several functions: it has the domain responsible for binding specifically to presynaptic nerve terminals, as well as domain responsible for mediating translocation of the light chain into the cell cytoplasm as the vacuole acidifies.

The light chain is azinc metalloprotease and is the active part of the toxin. It is translocated into the host cell cytoplasm where it cleaves the host protein SNAP-25, a member of a SPARE protein family which is responsible for fusion. The cleaved SNAP-25 is unable to mediate fusion of vesicles with the host cell membrane, thus preventing the release of the neurotransmitter acetylcholine from axon endings.

The seven toxin (A-G) have different tertiary structures and sequence differences[19].

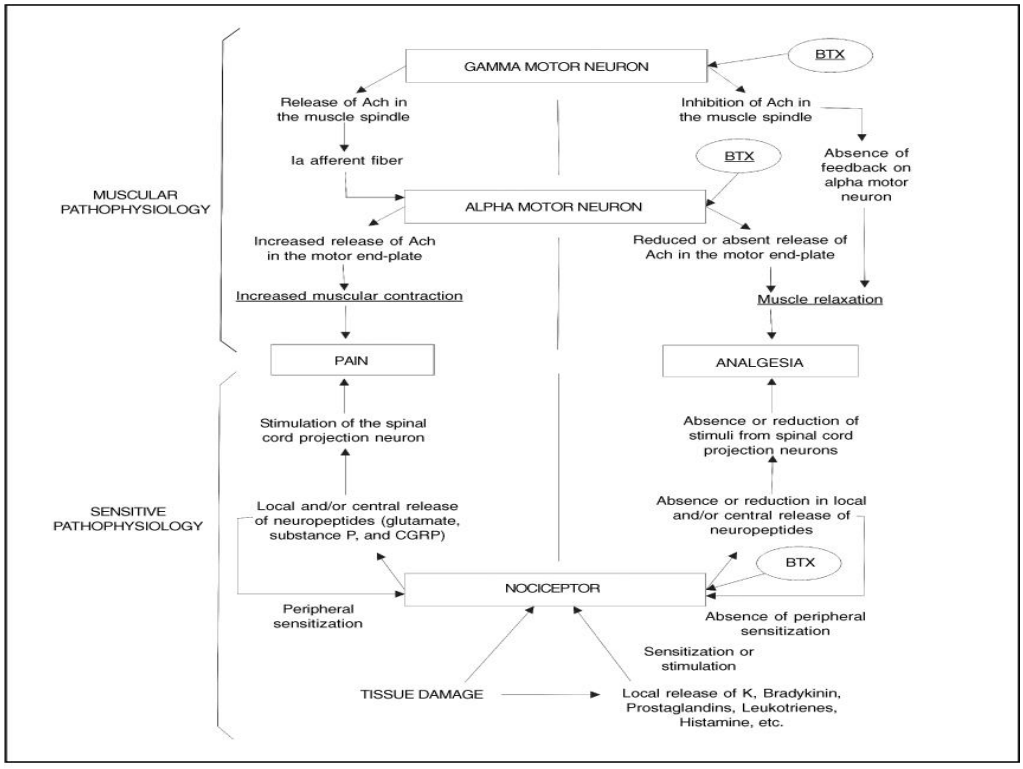


Figure 1 - Analgesic Actions of Botulinum Toxin. On the left, the muscular and sensorial pathophysiology that triggers pain. On the right, the analgesic effects of botulinum toxin on those pathophysiological mechanisms. Ach - acetylcholine; CGRP – calcitonin gene-related peptide; BTX – botulinum toxin.

Figure 4: Analgesic action of Botulinum toxin A

CLINICAL EVIDENCE

Materials and methods use in clinical evidence:

This was a randomized, double blind, placebo-controlled, clinical trials done at leiden University Medical Centre Headache Clinic: the Chronification and reversibility of migraine study (CHARM; www.trialregister.nl #3440).

We enrolled consecutive patients with chronic migraine and medication overuse (Headache Classification Committee of the International Headache Society,2013).

The study was performed in accordance with the declaration of Helsinki and Good Clinical Practices and approved by the local ethics committee[20].

Procedures

Participants starred with a 4- week baseline- assessment period, followed by a 12- week randomized, double- blind, placebo-controlled phase with BTA injections immediately prior to medication withdrawn. After this double blind phase, participants who had withdrawn from medications but remained to have chronic migraine were offered open- label BTA injections (155 units, one treatment cycle) in addition to standard care regarding acute headache medications (open- label phase). Participants who were not eligible for BTA open label treatment received standard care with acute headache medication and, if needed, prophylactic treatment.

Study follow-up visits were planned at weeks 12, 24, and 48, with additional clinical visits according to medical need. Participants kept 4-weeks paper diaries with daily registration of headache characteristics, accompanying symptoms, and use of acute headache medication during the baseline observation period and post treatment weeks 9-12, 21-24, 33-36, and 45-48. The diaries had to be sent in every week to ensure an accurate status. Cross checking of data (entry) was performed both manually in a random manner and electronically with fixed algorithms. Determinations of migraine and non-migraine headache on any given calendar day was calculated by an algorithm based on the International Classification of Headache Disorders criteria[21].

Treatment and masking

In accordance to our national guidelines and other withdrawal studies participants were instructed to withdraw abruptly from all acute headache medications and caffeine in an outpatient setting for 12 weeks. Prophylactic treatment was tapered off and rescue medications to treat headache of any kind was not allowed. Participants were explained what to expect after withdrawal symptoms, and were informed about the possible practical, social and professional consequences.

BTA was administered at 31 predefined injection sites (5 units per injection; 155 units in total), in accordance with published protocols. Placebo was administered at the same 31 injection sites. However, while the 24 injections outside the forehead region contained saline, the seven injection in the forehead contained saline, the seven injections in the forehead contained low dose BTA (2.5 units per injection site; 17.5 units in total). Participants were explained that change in facial expression was not indicative of any particular treatment. Active and placebo treatment were indistinguishable. Participants and investigators were blinded for treatments[22].

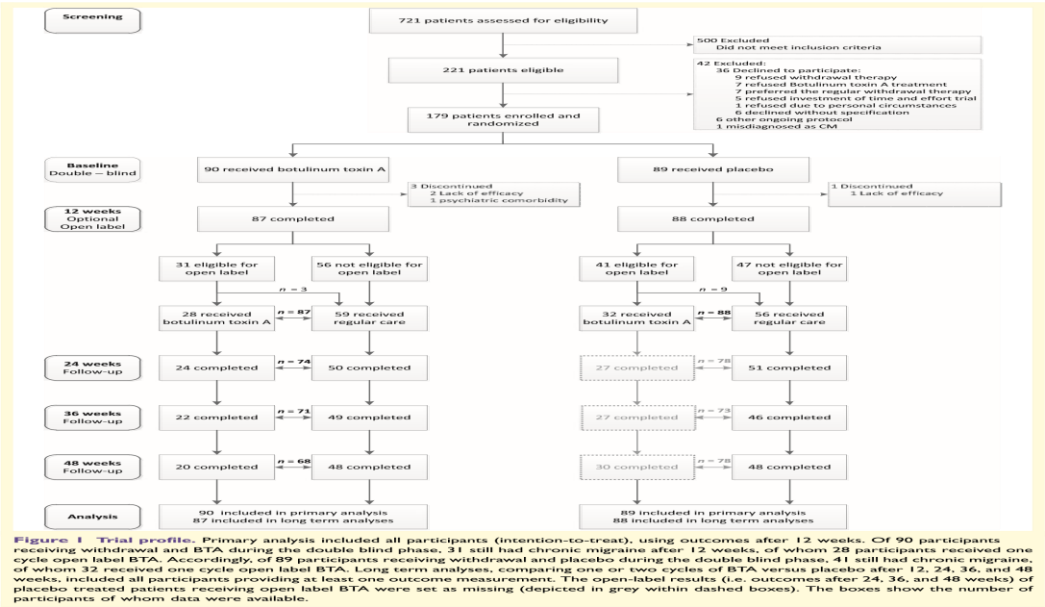


Figure 1 Trial profile. Primary analysis included all participants (intention-to-treat), using outcomes after 12 weeks. Of 90 participants receiving withdrawal and BTA during the double blind phase, 31 still had chronic migraine after 12 weeks, of whom 28 participants received one cycle open label BTA. Accordingly, of 89 participants receiving withdrawal and placebo during the double blind phase, 41 still had chronic migraine, of whom 32 received one cycle open label BTA. Long term analyses, comparing one or two cycles of BTA versus placebo after 12, 24, 36, and 48 weeks, included all participants providing at least one outcome measurement. The open-label results (i.e. outcomes after 24, 36, and 48 weeks) of placebo treated patients receiving open label BTA were set as missing (depicted in grey within dashed boxes). The boxes show the number of participants of whom data were available.

Figure 5: Evidence chart

Outcomes

There is no universally agreed primary endpoint for trials in chronic migraine. The differences, however, between the various recommended are in fact only marginal. We choose primary outcome the percentage change in 4- weekly headache days from baseline to the last 4 weeks of double blind treatment (Weeks 9-12). As patients with chronic migraine have a headache frequency at baseline, percentage change in headache days is considered a more meaningful end-point than absolute change.

Percentage number of baseline headache days. A headache day was any calendar day on which a migraine or non-migraine headache of any duration was reported. We did not include a minimal duration of 4 h (as used in some trials), as most of our participants would usually use medications within 4 h after headache onset. For the same reason we decided not to specify that headache had to have a moderate or severe peak intensity.

Secondary outcomes were assessed 12,24,36 and 48 weeks after therapy onset. The main secondary outcome was change in quality of life (SF-36). Additional secondary outcome were change from baseline in number of (1) headache days; (2) migraine days (days with headache fulfilling migraine criteria or treated with acute migraine medication); (3) moderate or severe headache days; (4) hours with headache (cumulative); and (5) days with use of acute headache medication[23].

Results

Between December 2012 and February 2015,721 patients with frequent migraine were screened, of whom 221 were eligible and 179 included and randomly assigned to either BTA (n=90) or placebo (n=89). The treatment groups were well balanced for age, gender, headache and migraine frequency, and psychiatric comorbidity. Four participants discontinued the study in the double-blind phase, one in the placebo group because of lack of efficacy and three in the BTA group, because of lack of efficacy (n=1) or exacerbation of pre-existing depress (n=1). All 179 participants were included in the intention-to-treat analysis. Follow-up ended in January 2016. Discontinuation of participants until the end of follow-up is depicted.

Figure 6: Drug effect as placebo.

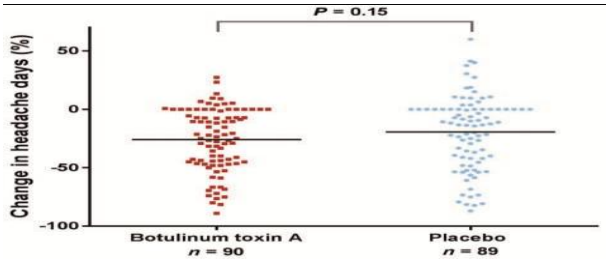
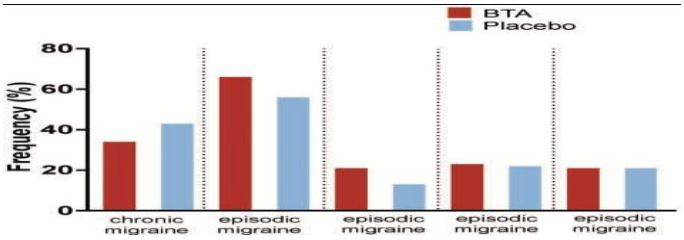


Fig. 7 Drugs by Graphical method



The primary outcome, mean percentage change in 4-weekly headache days from baseline to weeks 9-12 after therapy onset, did not differ between withdrawal plus BTA (-26.9%; 95% CI: -13.5 to -27.6). The adjusted treatment differences was 6.4% (95% CI: -2.4 to 15.2; p=0.15;).

Likewise, there were no treatment differences after 12 weeks for any of the secondary outcome measures, including headache days or hours, migraine days,50% and 25% responder rates, and measure of quality of life. The change in headache days was -5.6 for BTA versus -4.4 for placebo (mean differences -1.3; 95% CI: -3.1 to 0.6) and in migraine days was -6.2 for BTA versus -7.0 for placebo (mean differences 0.8; 95% CI: -1.0 to 2.7. Approximately 60% of participants had reverted back to episode migraine, without any treatment differences. BTA did also not increase the proportion of participants who managed to preserve with withdrawal. In both groups, 90% of participants withdrew successfully, definedas <=2 medication days, and the proportions of participants still meeting the criteria for medication overuse at week 12 were negligible (2.3%).

We also assessed the long term effects of withdrawal plus one or two BTA treatments versus withdrawal without BTA. There were no differences after 12,24,36, or 48 weeks for any of the outcomes measures: days with any headache or migraine, days with moderate or severe headache, cumulative numbers of hours with headache, or days with medication use (adjusted data not shown). These results were supported by comparison for initial double-blind and subsequent open-label treatment, which did not show any relevant differences.

Blinding appears successful. Assumptions about received (participants) or given (investigators) treatment were equally distributed, and neither participants nor investigators guessed the correct treatment significantly more often. At 12 weeks, investigators correctly identified treatment in 54.3% of BTA-treated patients and 55.0% of placebo-treated patients and 55.0% of placebo-treated patients. For participants these proportions were 38.2% and 44.0%[24].

CONCLUSION

The Botulinum toxin A drug substance that has been studied by different clinical evidence proves to be the best for the reduction of headache, migraines and to improve quality of life as well. The Botulinum Toxin A is the most effective and safest substance to treat chronic as well as acute migraines with low side-effects.

REFERENCES

1. Peter J.et. al, migraine headache disorders. Harison's principle of International medicine edition 2586.
2. Adallah K, Artola A, moncanduit L. Dallul R, Luccarini P. Bilateral descending hypothalamic projections to the spinal trigeminal nucleus Caudalis in rats: plos one 8:e733022, 2013.
3. Lipton RB, stewart WF, Diamond S, Diamond ML, Reed m, at al. Headache. 2001; 41: 646-657. DOI: 10. 1046/j. 1526-4610.2001.041007646.x.

4. En.wikipedia.org/wiki/Botulinum Toxin.
5. Silberstein S, Mathew N, saper J,et. Botulinum Toxin type A as a migraine preventive treatment. Headache .2000; 40: 445-450-DOI: 10.1046/j.1526-4610.2000.00066.x.
6. Hhttps;// www. Drug bank.ca/categories/ DBCAT000183#drugs.
7. Schulte-mattler WJ, Krack P, BoNtTTH study group. Treatment of chronic tension type headache with Botulinum Toxin type A: A randomized, double-blind, placebo-controlled multicenter study.pain. 2004; 109(1-2): 110-114.DOI: 10.1016 j. pain.2004.01.016.
8. Silberstein S,Lipton K, Dodick D, freitage f, Mathew N,et.al Topriamate treatment of chronic migraine. A randomized placebo- controlled trial of quality of life and other efficacy measure headache: 2009:49 (8): 1153-1162, DOI; 10.1111/j.1526-4610. 2009.01508.
9. en.Wikipedia.org/wiki/history/Botulinum Toxin.
10. Matrrhold,S, Rummed,A, Bigalke, H, Davletor, B and Binz, T.(2006) The synaptic veside protein 2C mediate the uptake of Botulinum neurotoxin A into phrenic enerves. FEBS Leu 580: 2011-2014.
11. Cerruda- morollon et al. 2015.
12. Durham,P, Cadyr, and cady, R. and cady, R(2004) Regulation of calcitonine gene-related peptide secretion from trigeminal nerve cells by Botulinum Toxin type A; implications for migraine therapy. Headcahe 35-44.
13. Eros, E, Gladstone, J., Lewis, S, Rogers, R.and Dodica, D.(2005) Duration of migraine is a predictor for response to Botulinum toxin type A. Headache 45: 308-3114.
14. Matak, J and Lackvoic, z (2014) Botulinum Toxin A, brain and pain. Prog neurological 119-120: 39-59.
15. Montecucco. C, molgo J (June 2005). "Botulinal neurotoxins: revival of an old killer", current opinion in pharmacology. 5(3) : 274-79.
16. Dvessler, D, sabrel, Fa;Barbosa, ER (march 2005), "Botulinum Toxin; mechanism of action", Arquivose de Neuro- psiquiatria 63(1): 180-85.
17. Felber ES(October 2006), "Botulinum Toxin in primary care medicine" The journal of the American osteopathic Association, 106(10): 609-14.
18. Li B, peet NP, Buttler mm, Burnett JC, moir DT, Bowlin TL(December 2010).
19. Hill kk, Smith JJ (2013), "Genetic Diversity within clostridium Botulinum serotypes, Botulinum Neurotoxin cone clusters and toxin subtypes". In Rummella Binz T(eds). Botulinum neurotoxins. Current topics in microbiology and immunology 364. Heidelberg. Springer. PP.1-20.
20. Headcache Classification Committee of the International Headache Society, pirazzini et al.,2017.
21. Dodick DW, Turkel CC, Degryse RE, Aurora SK, Silberstein SD, lipton RB,et,et al. onabotulinumtoxin A for treatment of chronic migraine: pooled results from treatment of chronic migrane: pooled results from the double-blind, randomized, placebo controlled phases results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache J Head face pain 2010; 50: 921-36.
22. Rossi P, faroni JV, Nappi G, short- term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication over use headache. Eur J Neuronal 2011;18:396-401.
23. Werkgreep Migraine Ritchtlijin NVN, 2017 and other withdrawal studies [Rossi et al, 2006, 2011; Pijpers et al; 2016, carlsen et al, 2018).