Neurotoxins and headache: A review of the evidence

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Disclosures

• Allergan: Trainer 2010 – present
• Glaxo Smith Kline: Speaker 1992 – present
• Merck: Speaker – inactive
• Defense and Veterans Brain Injury Center/contractor for Henry Jackson Foundation
Publication of toxin trials in headache
1989: orphan drug botulinum toxin batch 79-11 (“Oculinum”)

• Within 5 years, the first paper appeared on the use of botulinum toxin in headache
  – temporomandibular dysfunction (TMD)
  – myofascial face pain
  – and bruxism

• The evidence for treating myofascial pain of and outside of the face with BT was not forthcoming
  – TMD pain relief correlated with weakening muscles
  – “appears both safe and efficacious in ...chronic facial pain associated with masticatory hyperactivity”
  • one “RCT... is not enough to establish firm evidence”

Analgesic/Focal Primary Headache?

- Unsuccessful in
  - trigeminal neuralgia
  - occipital neuralgia
- No RCTs
  - cluster headache
  - other trigeminal autonomic cephalalgias
  - Hemicrania Continua
Secondary Headaches

- 2 papers with level 1 evidence
  - 30/38 were Level 4
  - Recommendations:
    - Grace A or B: none
    - Grade C:
      - Chronic headache attributed to whiplash injury
      - Cephalagic alopecia areata
      - Headache and facial pain in blepharospasm
      - Trigeminal Neuralgia
      - Occipital Neuralgia
      - Nummular headache

Hagen & Stovner, Acta Neurol Scand 2011
Tension type Headache

- 3 class I studies – ineffective
  - one class II study - modest reduction in headache frequency
    - cervical myofascial trigger points were injected
- blinded class II study
  - shoulders and cervical myofascial points
    - “follow the pain”
    - fewer headache days and lesser headache severity.

Tension Type Headache

• N = 6
  – prior positive response to ONB = 0
  – One side of the head was injected with 30 – 40 units and the other side was used as a control.
  – The authors concluded that muscles do not cause TTH, and that BT was not an effective treatment.

Hyperfunctioning Facial Lines

- Improvement in headache noted
- Open label study (n=77) of 77 patients who they classified as “true migraine subjects”.
  - Complete response: 51% (95% confidence interval, 39% to 62%)
  - Mean (SD) response duration of 4.1 (2.6) months
  - Partial Response: 38% response duration of 2.7 (1.2) months
  - Overall improvement was independent of baseline headache characteristics.
  - 75% (95% confidence interval, 35% to 93%) of n=10 reported complete response with improvement 1 to 2 hours after treatment.
  - No adverse effects were reported.

TENSION TYPE HEADACHE

• 9 of 134 patients treated for glabellar and forehead wrinkles reported improvement in their TTH
• RCT from Europe in 2000, showed no benefit for BT in TTH
• Goben published an evidence based review confirming no benefit

Tension Type Headache

• Silberstein et al (2006)
  – “insured” (authors’ words)
    • a stable headache frequency,
    • that patients did not have migraine or they could distinguish TTH from migraine and
    • that prescribed areas were suggested for injection
    • a total dose
  – Did not inject the area of the glabellar (procerus/corrugator) or frontal wrinkle sites (frontalis)

Chronic TTHA

• lower doses of 100 u in 5 muscles or 86 units in 3 muscles were best.

• They formed a sponsored group called the BOTOX CTTH Study Group including Allergan Inc.

• They showed no benefit c/w placebo in TTH

Silberstein et al., Cephalalgia. 2006 Jul; 26 (7) :790-800.
BOTOX CDH STUDY GROUP

• BOTOX CDH Study Group, took all comers who screened in with more than 15 days of headache in a 30 day baseline period. Using a double blind placebo controlled design in which placebo responders were separated from placebo non-responder they devised analyses done at 30 day increments. About 200 units of ONA were injected in a modification of the “follow-the-pain” technique, as outlined by Blumenfeld.

• Twenty-four percent received masseter injections.

• “all patients may actually have deserved a diagnosis of migraine even though this diagnosis was not indicated by the investigator for all patients”.

Mathew et al, BOTOX CDH Study Group. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache. 2005 Apr; 45 (4) :293-307
CDH

• Prophylactics: 35.8%
• MOH: 47.3%
  – Present in placebo responders.
• Results
  – Significant drop in the “number of headaches” (not clearly defined in the methods)
  – *post-hoc* analysis well defined “headache free days” showed at least a 50% decrease from baseline.
• Non-significant decreases in acute medication use were reported and it appeared safe with the authors concluding:
The authors stated

• “a number of factors should be considered
  – choice of the primary outcome measure
  – confounding factors of placebo response
  – prophylactic and acute treatments
  – patient population
  – the fundamental design
  – and the results of additional analyses

• ....However a statistically significant treatment effect was demonstrated for these severely affected patients

• .... (and) a majority of patient with CDH have a primary diagnosis of migraine, as did the majority of patients evaluated in this study”
What was going on in episodic migraine during all this?

- Cortical spreading depression and trigeminal activation
- Peripheral sensitization
  - a target for acute treatment.
  - Improving the efficacy of triptans
  - testing them against
    - timing
    - severity
**IMPLODING VERSUS EXPLODING: Outside versus Inside**

- **Episodic migraine**
  - non-responders: 92% described a buildup of pressure inside their head (*exploding headache*).
  - Responders: 74% perceived their head to be crushed, clamped or stubbed by external forces (*imploding headache*).

- **Conclusion**
  - “exploding headache was impervious to extracranial BTX-A injections is consistent with the prevailing view that migraine pain is mediated by *intracranial* innervations”.

Exploding Headache

- Allodynia during acute migraine attacks
- 100 units
- 21 sites
  - frontal, occipital, temporal sites and the trapezius, semispinalis, and splenius capitis muscles
- No placebo arm
  - “we were only interested in finding a marker that would distinguish responders from non-responders, rather than evaluating the efficacy of BTX-A”

- Results (pooled retrospective and prospective cohorts)
- 95% drop in migraine days per month for responders
  - Imploders: reduction to “0.8 ± 0.3” migraine days in the 29 (74%)
- non-responders
  - pre-treatment baseline: of 11 days In his editorial, reviewing this paper, Goadsby stated:
Episodic migraine

- N = 102 subjects
- 31 units
- glabellar, temporal and frontal areas
- less than 8 migraines per month (83%)
  - “true migraine” 86% have 8 or less migraines per month
  - They concluded that “subjects with low baseline frequency were more likely to
    report complete response (my emphasis)”. 

BOTOX Migraine Clinical Research Group

- RCT
- 25 or 75 units
- corrugator and procerus muscles.
- Average 5 migraines per month
  - mean duration of about a day and a half
- Conclusion “significantly more subjects reported fewer migraines of any severity at month” in the lower dose treated group compared to vehicle.
  - treated migraine days
  - severity of attacks
  - and vomiting
- Questions raised
  - Tension type study did not use glabellar sites
  - The migraine RCT did not use posterior sites
  - Why did lower doses work better?

• status migranosis in Thailand
• reporting intractable headaches after injections
• Advice for the “viselike-headache patient”
• Acupuncture toxin
• Single site and surgery

traditional acupuncture sites

• N = 10 subjects
• 37 units.
  – “trapezius”
  – vertex of the head
  – suboccipital areas
  – temporal points
  – midline parasagital
  – midline frontal sites
• The authors concluded that “acupuncture-based sites are useful...”

Single sites and surgeons

• N = 29 subjects
• 25 units of BTA
  – bilateral corrugator supercilii muscles
  – 28/29 < 8 headaches per month (mean 5.9)
• Results
  – Improved: 83%
  – Complete resolution: 16/29 (55%)
  – Average duration: 8 weeks
    • “discernible muscle function recovery was noted 3 to 4 weeks after recurrence of migraine.”
• Caveats:
  – # of headache days not stated
  – no comment about the difference between headache frequency and headache days
  – Uncontrolled
  – Unblinded
  – Not reproduced

The surgeons ascribe success to:

• “Guided by the most prevalent site from which the migraine pain started and settled consistently and a positive response (i.e., at least 50 percent decrease in the migraine headache intensity, duration, frequency, and the migraine index, all four being considered the endpoint) to the injection of 25 units of botulinum toxin type A (Botox; Allergan, Inc., Irvine, Calif.) at the site....”

1.5.1 Chronic migraine

New entrant to classification

A. Headache fulfilling criteria C and D for
   1.1 Migraine without aura on ≥15 d/mo for >3 mo

B. Not attributed to another disorder
Chronic Migraine

- The goal of migraine prevention: recognize and reduce the burden of disease
- Historically, researchers defined migraine as an episodic disorder with “countable” headache frequency
  - Run in periods allowed study designers to insure that preventive treatments reduced the number of days that a person had migraine
    - Methodologies
      - Diaries
      - PDA
      - daily calls from subjects detailing the presence or absence of headache (a headache day) and also the number of hours per day
  - Calculation of burden
    - assumes that a successfully treated headache or a spontaneous remission to headache freedom (<4 hours) improved the overall quality of the day
Back to the Future: CDH

• Mathew et al
  – separated placebo responders from non responders
    • Total dose: 190
    • 24% got masseters
  – did not meet the primary endpoint of more “headache free days”
    • reduction in the “number of headache episodes”
    • “responder rate” of those with a “50% reduction in headache days” was significant (secondary endpoint).

• Dodick et al
  – Not taking a prophylactic at the time of the study
    • more likely to meet the secondary endpoints
    • used less acute headache medication

• post hoc analyses suggested
  – Headache duration > 4 hours
    • were reduced at most evaluated time points to 180
    • headache episode reduction in patients overusing medication

Botox and Chronic Migraine

• Chronic Daily Headaches are mostly migraines
  – Headache days differ from migraine day

• primary endpoints
  – Not reduction in headache episodes
  – But migraine days
    • headaches lasting more than 4 hours

• Caveats
  – fixed sites and fixed doses
  – not using prophylactic migraine medications
  – with or without medication overuse
OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial

• largest RCT in the history of CM: PREEMPT® I & II.
  – 24-week, double-blind, placebo-controlled phase, followed by a 32-week, open-label phase. Subjects were randomized (1:1) to injections of onabotulinumtoxinA (155U–195U; n = 347) or placebo (n =358) every 12 weeks for two cycles.

• The primary efficacy endpoint was mean change in headache days per 28 days from baseline to weeks 21–24 post-treatment.

• Fixed sites and doses
  – procerus, corrugator, frontalis, temporalis, occipitalis, cervical paraspinal muscles and trapezius)
  – 5 units per site for a total of 155 units
  – headache day > more than 4 hours of headache
  – participants would call in daily and report the details of their headaches.
Botox and Chronic Migraine

• PREEMPT® I
  – did not show a difference in headache episodes (primary endpoint)
  – did show a significant difference in total number of headache days

• PREEMPT II
  – headaches lasting more than 4 hours
  – mean difference between OBA and placebo of 42.4 hours \{132.4 vs. 90\} (p value <.001) in 30 days
  – side effects were frequent in both groups
    • onabotulinumtoxinA group 65.1% vs. placebo group 56.4%
    • only neck pain (7.5%) and muscular weakness (5.2%) as well as eyelid ptosis, myalgia and musculoskeletal stiffness were considered significant events.
Other toxin headache trials


Implications for treating patients

• Botox has Class 1 evidence for efficacy and safety
  – in a patient with a specific profile
  – in a setting of expert administration

• NO:
  – follow the pain
  – single site injections
  – acupuncture points
  – myofascial complications
  – Masseters
  – TTH
  – difference if MOH is present