J. Biomedical Science and Engineering, 2014, 7, 446-452
Published Online June 2014 in SciRes. http://www.scirp.org/journal/jbise
http://dx.doi.org/10.4236/jbise.2014.78047

Scientific Research

Comparison of Botox® or Prosigne® and Facial Nerve Blockade as Adjuvant in Chronic Migraine

Gabriela R. Lauretti[1*], Christiane P. Rosa[2], Antônio Kitayama[1], Bruno C. P. Lopes[1]

[1]School of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil
[2]Sirio Libanes Hospital, São Paulo, Brazil
Email: [*]grlauret@fmrp.usp.br, chris.pellegrinorosa@mac.com, akitayama@hotmail.com, brunocapolo@yahoo.com.br

Received 10 April 2014; revised 23 May 2014; accepted 5 June 2014

Copyright © 2014 by authors and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY).
http://creativecommons.org/licenses/by/4.0/
Open Access

Abstract

Background: The treatments suggested for chronic migraine (CM) include: 1) intramuscular (im) botulinum toxin (BTX) every 12 weeks, and 2) blockade of peripheral nerves of the head. The present study evaluated the efficacy of facial nerve blockade in combination with a single administration of different low BTX. Methods: Forty patients with CM submitted to unilateral facial nerve blockade (supraorbital, supratrochlear and auriculotemporal) were divided into 4 randomized groups in a double-blind manner in order to receiveim, after 7 days: 25 IU Botox® (Botox group), 25 IU Prosigne® (25-Pro group), 33.3 IU Prosigne® (33-Pro group) or saline (control group), with the dose divided for application to 10 sites in the frontal and bilateral temporal regions. Analgesia and adverse effects were evaluated: 1) before blockade of the facial nerves and 2) 4 weeks, 3) 8 weeks and 4) 12 weeks after BTX-A or saline application (HC clinical trial no. 12465). Results: Botox® (25 IU) or Prosigne® (33.3 IU) resulted in at least seven-day intervals between headache attacks associated with 70% reduction in frequency and intensity of crises over 12 weeks ($P < 0.05$), while the 25 IU dose of Prosigne® resulted in 8 weeks of analgesia. The conversion factor between Botox® and Prosigne® was 1:1.3. Conclusions: Im application of Botox® (25 IU) or Prosigne® (33.3 IU) one week after nerve blockade on the painful side was equally effective for 12 weeks in patients with chronic daily headache, with the conversion factor between Botox® and Prosigne® being 1:1.3.

Keywords

Botox, Prosigne, Chinese Toxin Botulin, Chronic Migraine, Peripheral Blocks

[*]Corresponding author.

How to cite this paper: Lauretti, G.R., *et al.* (2014) Comparison of Botox® or Prosigne® and Facial Nerve Blockade as Adjuvant in Chronic Migraine. *J. Biomedical Science and Engineering*, **7**, 446-452. http://dx.doi.org/10.4236/jbise.2014.78047

1. Background

The application of onabotulinumtoxin-A (Botox®) represents a prophylactic therapy for patients with chronic migraine (CM) [1] which was approved in 2010 for this indication by the Food and Drug Administration. Migraine is the most common subtype of chronic daily headache (44%), followed by the tension headache subtype (28%) [2]. The recommended treatment is applied every 12 weeks with injections of botulinum toxin (BTX) at multiple head and necksites, with a total dose of 155 to 195 IU [3] [4], and with a total of 5 cycles being suggested for an effective result [5]. However, blockade of peripheral facial nerves such as the auriculotemporal, supraorbital and supratrochlear nerves, among others, represents a target for the control of migraine [6]. Patients with migraine submitted to blockade of the supraorbital and infraorbital nerves with 1% lidocaine in 3 cycles at 3 day intervals showed an effective reduction of crises during 6 months of evaluation [7].

The present study evaluated the efficacy of peripheral blockade of the trigeminal branches (supraorbital, supratrochlear and auriculotemporal) in combination with a single administration of low doses of different BTXs to the frontal and temporal regions of patients with CM, *i.e.*, Botox® and Prosigne® (Chinese BTX).

2. Methods

The study was approved by the Research Ethics Committee of the institution (HC clinical trial no. 12465) and all patients studied gave written informed consent to participate. We selected 40 patients attending the Center for Pain Treatment of the Teaching Hospital, School of Medicine of Ribeirão Preto, University of São Paulo, aged 21 to 60 years with chronic daily unilateral headache characterized as CM of more than 12 months duration and not responding to standard treatment with antidepressants, nonsteroidal anti-inflammatory agents or anticonvulsants or beta-blockers [8]. The patients were divided into 4 groups (n = 10) and prospectively evaluated in a randomized double-blind study. Exclusion criteria were: presence of an infectious process at the site of application, associated immunological diseases, a previous history of allergy to BTX-A, application of BTX-A during the last year, diabetes mellitus or refusal to participate in the study.

All patients were first submitted to three facial nerve blockades on the affected side (supraorbital, supratrochlear and temporomandibular blockade) while lying in dorsal decubitus. The final solution volume of 9 ml was equally divided among the three blockades performed in each patient. Each of the three facial blockades was performed by administering a solution containing 1) 10 μg clonidine, 2) 6.6 mg depot dexamethasone, and 3) 20 mg lidocaine without a vasoconstrictor (3 ml volume). Seven days after the facial nerve blockades, the patients randomly received anintramuscular (im)injection of 25 IU Botox® (Botox group), 25 IUProsigne® (Pro-25 group), 33.3 IUProsigne® (Pro-33 group), or only 0.9% physiological saline (Control group). The patients were coded for random assignment to the various groups with the aid of a computer.

Flasks containing 100 IUBTX-A (Botox® or Prosigne®) were stored under refrigeration at –4˚C. Each flask was diluted with 0.9% physiological saline at room temperature immediately before application. BTX-A coded for each patient was diluted to a final volume of 5 ml with 0.9% physiological saline by one of the authors. Another author administered 0.5 ml per application site in the bilateral frontal and temporal muscular regions. The final dose of zero, 25 or 33.3 IU was administered by the intramuscular route in the frontal region of the patientin equal doses at 8 different sites in the frontal region and 2 sites in the temporal region (1 site on each side) by the second author, who was unaware of the content of the previously prepared syringe (zero, 2.5 or 3.3 IU per site of application). The 8 frontal sites were defined starting from two horizontal midlines (one of them 1 cm above the eyebrow line and the other dividing the forehead in the middle) and these lines were crossed by two other vertical lines on each side equidistant from one another. Each site located at the intersection of the lines was infiltrated with a volume of 0.5 ml, for a total of 8 sites in the frontal region. One site on each side of the temporal musculature was equally infiltrated with 0.5 ml of the solution, for a total of 10 sites per patient.

The administration was performed with the patient comfortably sitting in a chair. After discharge from the hospital, the patient was instructed not to apply pressure to the frontal region, to remain with the head in the vertical position and without lowering it for a period of 4 hours. Data regarding pain and adverse effects were evaluated by a third author at each of the following time points according to the daily report of the patients: 1) before the blockade of facial nerves; 2) 4 weeks; 3) 8 weeks and 4) 12 weeks after application of BTX-A or of 0.9% physiological saline.

The frequency of occurrence of headache attacks and their intensity were recorded using a visual numeric scale of 10 cm (VNS-10-cm), where the zero end corresponded to “absence of pain”, and the 10-cm end to the

"worst possible pain". The time from their intake to at least 50% pain relief were recorded. Diclofenac (50 mg) was prescribed at 6 hour intervals for pain relief as a rescue analgesic and all patients took 25 mg amitriptyline before bedtime.

3. Statistical Analysis

The number of patients per group and the BTX-A doses used were based on a previous pilot study. It was suggested that the application of BTX-A would reduce the frequency of pain crises and their intensity by at least 50% compared to Control. With a test power of 80% and $\alpha = 0.05$, at least 8 patients per group would be necessary. Demographic data were analyzed by the chi-square test (physical status and sex) or by one-tailed ANOVA (remaining data). One-tailed ANOVA was used to compare the time of headache, the frequency of headache attacks and the time for pain relief among the various groups. Analysis of the different times within the same group was performed using the Friedman test. The incidence of adverse effects and the use of adjuvant drugs were compared by the chi-square test corrected for multiple tests. VNS values and the consumption of analgesics were compared by two-tailed ANOVA for repeated measures or by the Kruskal-Wallis test. The level of significance was set at $p < 0.05$. p values were later corrected by the post-hoc Tukey honestly significant difference test.

4. Results

The four study groups were statistically similar regarding ASA status, sex, age, body weight, height, and duration of the history of CM in years (**Table 1**). All patients classified their CM as severe as possible (VNS = 10 cm, data not shown, $p > 0.05$). One patient from each of the groups Control, 25-Pro and Botox were excluded due to incomplete data.

Table 2 presents the values of pain intensity during the headache attacks based on the VNS scale (0 - 10 cm), immediately before the administration of BTX-A (VNS-0) and in the 4th (VNS-4), 8th (VNS-8) and 12th week (VNS-12).

Before facial nerve blockade, the four groups were similar to one another related to pain intensity (VNS-0; **Table 2**) and frequency of migraine crises (cycles) (**Table 3**; $p > 0.05$).

Table 1. Demographic data.

	ASA I/II	Gender (M/F)	Age (years)	Weight (kg)	Height (cm)	History time of CM (years)
Botox Group	0/9	3/6	46 ± 13	64 ± 10	163 ± 9	17 ± 7
25-Pro Group	0/9	3/6	45 ± 16	64 ± 11	166 ± 7	17 ± 10
33-Pro Group	0/10	3/7	43 ± 14	66 ± 10	166 ± 8	15 ± 7
ControlGroup	0/9	2/7	49 ± 14	68 ± 14	165 ± 8	16 ± 9

Groups were demographically similar ($p > 0.05$). CM—chronic migraine; ASA—American Society of Anesthesiology-II-classified as past history of CM. F—female; M—male. Data expressed as mean ± STD; 25-Pro—25 UI of Prosigne®; 33-Pro—33 UI of Prosigne®.

Table 2. Numerical values (VNS 0 - 10 cm) during the migraine rises immediately before BTX-A application (VNS-0), at the 4th week after BTX-A application (VNS-4), at the 8th week application (VNS-8) and at the 12th week application (VNS-12).

	VNS-0	VNS-4	VNS-8	VNS-12
Botox Group	9.4 ± 0.7	4.3 ± 0.9	4.4 ± 1.3	5.2 ± 1.3
25-Pro Group	9.3 ± 0.9	4.5 ± 1.2	5.9 ± 1.2	9.0 ± 1.4
33-Pro Group	9.4 ± 0.8	4.3 ± 0.9	4.6 ± 1.3	5.4 ± 1.3
ControlGroup	9.5 ± 0.5	6.4 ± 0.8	9.2 ± 0.7	9.2 ± 0.7

Data expressed as mean ± STD; 25—Pro—25 UI of Prosigne®; 33—Pro—33 UI of Prosigne®. **Amongdifferent groups:** (significant reatment ncluded Botox and 33 Pro for 12 weeks, while 25 Prowasin—signicantatthe 12th weekevaluation). VNS—0 and VNS—4: All groups were similar ($p > 0.05$); VNS-: 25-Pro = 33-Pro = Botox < Control ($p < 0.05$); VNS-12: Botox = 33-Pro < 25-Pro = Control ($p < 0.05$). **Between the same group:** (significant treatment was maintained for 12 weeks for Botos and 33 Pro, while only for 8 weeks for the 25 Pro G). Botox: VNS-0 > VNS-4 = VNS-8 = VNS12 ($p < 0.02$); 25-Pro: VNS-0 = VNS-12 > VNS-4 = VNS-8 ($p < 0.05$); 33-Pro: VNS-0 > VNS-4 = VNS-8 = VNS12 ($p < 0.02$); Control: VNS-0 = VNS-8 = VNS-1 > VNS-4 ($p < 0.05$).

Table 3. Frequency of migraine crises during the past 4 weeks.

	Day 1	4th week	8th week	12th week
Botox Group	12 ± 9	2 ± 2	2 ± 3	5 ± 3
25-Pro Group	13 ± 8	3 ± 2	4 ± 3	10 ± 3
33-Pro Group	13 ± 7	3 ± 1	3 ± 2	5 ± 2
ControlGroup	14 ± 6	5 ± 4	13 ± 7	13 ± 7

Data expressed as mean ± STD; 25-Pro—25 UI of Prosigne®; 33-Pro—33 UI of Prosigne®. **Amongdifferent groups:** (decrease of CM crises in time was significant only for Botox and 33 Pro during 12 weeks evaluation, while 25 Pro was in-significant at this time). Day 1 and 4th week: All groups were similar ($p > 0.05$); 8th week: Botox = 25-Pro = 33-Pro < Control ($p < 0.05$); 12th week: Botox = 33-Pro < 25-Pro = Control ($p < 0.05$). **Between the same group:** Botox: VNS-0 > VNS-4 = VNS-8 = VNS12 ($p < 0.05$); 25-Pro: VNS-0 = VNS-12 > VNS-4 = VNS-8 ($p < 0.05$); 33-Pro: VNS-0 > VNS-4 = VNS-8 = VNS12 ($p < 0.05$); Control: VNS-0 = VNS-4 = VNS-8 > VNS-4 ($p < 0.05$).

In the 4th week of evaluation, within group comparison revealed that all patients showed improvement of pain intensity (**Table 2**) and migraine crises frequency (**Table 3**) compared to their initial week of treatment ($p < 0.05$ for the Control group and 25-Pro group, $p < 0.02$ for the remaining groups). In contrast, among-group comparison revealed that all groups were similar to one another ($p < 0.05$).

In the 8th week of evaluation, the Botox and 33-Pro groups continued to have a reduction of crises of at least 70% (**Table 3**; $p < 0.02$) and a reduction of pain intensity (**Table 2**; $p < 0.05$), with a reduction of the numeric VNS value compared to Control ($p < 0.02$). The 25-Pro group showed less pain intensity (50%) and a lower frequency of headache crises compared to Control (**Table 2** and **Table 3**; $p < 0.05$).

In the 12th week of evaluation, only the Botox and 33-Pro groups continued to have reduced pain intensity ($p < 0.05$) and a lower frequency of crises during the 4 week period compared to the Control and 25-Pro groups ($p < 0.05$). During this period, the 25-Pro and Control groups were similar to one another ($p > 0.05$).

Table 4 describes the time (min) elapsed to get release from pain (at least 50% pain relief) after the migraine crises following the ingestion of oral rescue analgesics. Data revealed that among groups, patients were similar on day-1 and day-28 ($p > 0.05$). However, before im TXB-A application, the elapsed time for pain relief was 6 hours compared to 1 hour 4 weeks after its application ($p < 0.02$; **Table 4**). In overall, until the 4th week, all groups were similar ($p > 0.05$), until the 8th week, the Control group showed no analgesia ($p < 0.05$); and at the 12th week, only the Botox and 33-Pro groups remained with benefits for pain control ($p < 0.05$).

5. Discussion

The present results demonstrate that intramuscular application of 25IU of Botox®or 33.3 IU of Prosigne® resulted in similar analgesia during the 12 week period of evaluation in patients with CM in terms of intensity of headache attacks, time for relief after ingestion of the rescue analgesic diclofenac and frequency of headache attacks in the last weeks evaluated. Both groups experienced at least seven days of interval with no headache attacks and a reduction of at least 70% of the frequency and intensity of attacks, with similar transitory adverse effects among groups during the periods of 4 and 8 weeks. In the 12th week of evaluation, there was a reduction of frequency and intensity of attacks of at least 50%.

The Prosigne® dose of 25 IUinduced a 70% reduction of the frequency and intensity of headache attacks, an effect that lasted until the 8th week for the 25-Pro group and until the 4th week for the Control group. The data obtained in a double-blind manner defined the conversion factor between Botox® and Prosigne® as 1:1.3, in agreement with previous non-blind studies on patients with dystonia and muscle spasm [9] [10]. In contrast, two other studies concluded that the relation between Botox an Prosigne was 1:1 regarding the evaluation of spasticity (12 weeks) [11] and dystonia (11 weeks) [12] where as Prosigne® was similar to Botox®for the mitigation of facial wrinkles over a period of 8 weeks, in agreement with the present study [13].

BTX-A has been used as a prophylactic agent against migraine [5] [13]. The final analgesic effect of BTX-A (Botox® or Prosigne®) may probably be due to a combination of its peripheral and central actions. Classically, BTX-Aacts on the peripheral synaptic endings by blocking the release of the neurotransmitter acetylcholine by binding to its receptor on the neuronal membrane, being then transported into the cell and stored in an endosomal compartment through pH-dependent translocation [14]. Once inside the cytoplasm, serotype-A cleaves the protein SNAP-25, one of the proteins necessary for the function of the endosomal vesicle. SNAP-25 proteolysis is exacerbated by depolarization of the secondary membrane to K^+ in the presence of Ca^{++} [14]. Locally, there

Table 4. Time (min) elapsed to get release from pain (at least 50% pain relief) after the migraine crises following the ingestion of oral rescue analgesics.

	Time-day 1(min)	Time-day 28 (min)	Time-day 56 (min)	Time-day 84 (min)
Botox Group	245 ± 69	59 ± 28	57 ± 13	70 ± 22
25-Pro Group	246 ± 95	57 ± 32	84 ± 16	176 ± 56
33-Pro Group	252 ± 69	59 ± 28	65 ± 13	68 ± 34
ControlGroup	246 ± 80	65 ± 42	228 ± 74	240 ± 77

Data expressed as mean ± STD; 25-Pro—25 UI of Prosigne®; 33-Pro—33 UI of Prosigne®. **Among different groups:** Day-1 and day-28: All groups were similar ($p > 0.05$); Day 56: Botox = 25-Pro = 33-Pro < Control ($p < 0.02$); Day 84: Botox = 33-Pro < 25-Pro = Control ($p < 0.05$). **Between the same group:** Botox: day-1 > day-28 = day-56 = day-84 ($p < 0.05$); 25-Pro: day-1 = day-84 > day-28 = day-56 ($p < 0.05$); 33-Pro: day-1 > day-28 = day-56 = day-84 ($p < 0.05$); Control: day-1 = day-56 = day-84 > day-28 ($p < 0.05$).

may be reduced excitability of gamma motoneuron endings and possible migration to muscles surrounding the application site or remotely located [15]. The application of BTX has been shown to reduce the local production of nociceptor sensitizers such as substance P [16] [17], and to block local autonomic pathways, with a resulting analgesic effect through a peripheral action, or through an action on muscle tonus [18]. Despite the analgesic effect observed in different models of analgesia, BTX-A does not seem to act as an analgesic in the presence of an inflammatory process or of primary or secondary hyperalgesia [19], a fact that would justify its use for the prophylaxis of chronic headache and not as an analgesic drug with an abortive effect on headache attacks.

There is evidence suggesting that, in addition to acting locally and peripherally, the botulinum toxin acts on the central nervous system. After peripheral application, the toxin appears to reach the anterior horn of the spinal cord by retrograde axonal transport [15], acting there on central synapses that inhibit Renshaw cells, thus exacerbating the effect of peripheral muscle relaxation of the gamma motoneuron [15]. The inhibition of the release of the central neurotransmitter glutamate and the prevention of the production of Fos, an immediate product of the c-Fos gene, may result in reduced central sensitization [20].

As part of the protocol, all patients with CM were submitted to blockade of facial nerves with the administration of dexamethasone, clonidine and lidocaine. Several studies have reported the use of blockade with lidocaine and steroids, with a uniform observation of analgesia that exceeds the time of action based on the mechanism of action of the local anesthetic lidocaine and of the steroidal anti-inflammatory agent [21]-[23].

Control patients showed analgesia similar to that of group 25-Pro on the 28th day, suggesting that the initial and transitory analgesic action in the different groups was due in part to the administration of dexamethasone, lidocaine and clonidine. The use of steroids for chronic headache can have an abortive action on the attacks, but these drugs cannot be used as prophylactic agents, indicating their limited use [24]. In the current study, dexamethasone was used as an adjuvant abortive agent for the control of headache attacks, as clinically observed on the basis of the reduced frequency and intensity of headache attacks in Control patients. Steroids have been shown to interact with glucocorticoid receptors located peripherally and in the spinal cord, modulating the action of spinal N-methyl-D-aspartate receptors [25], contributing to the effect of BTX-A on the central nervous system [20]. Although the α-2 agonist clonidine is not apparently effective for the prophylaxis of migraine [26], this drug has a local anesthetic action that potentiates lidocaine [27]. Recent studies have suggested that clonidine administered close to the nerve endings reduces the signals of axonal conduction and reduces the levels of proinflammatory cytokines and of prostaglandins produced during Wallerian degeneration, a fact leading to central sensitization and hyperexcitability [28]. These data may justify the use of clonidine as an abortive coadjuvant in headache attacks, together with dexamethasone, both administered locally. Locally administered lidocaine supported the analgesic effect of dexamethasone and clonidine [29] and was sufficient, of itself, to result in 6 months of analgesia [9].

6. Conclusion

In conclusion, double-blind evaluation of BTX-A as a prophylactic agent revealed a conversion factor of 1:1.3 between Botox® and Prosigne® in patients with CM submitted to blockade of facial nerves with clonidine, dexamethasone and lidocaine for an abortive action against headache attacks. This study relied on self-reported CM frequency and intensity which were subject to bias and under-reporting. In addition, medication use costs and

indirect costs (which might be higher than directcosts for migraine) were not assessed.

References

[1] Frampton, J.E. (2012) OnabotulinumtoxinA (BOTOX®): A Review of Its Use in the Prophylaxis of Headaches in Adults with Chronic Migraine. *Drugs*, **72**, 825-845. http://dx.doi.org/10.2165/11208880-000000000-00000

[2] SeyedSaadat, S.M., Hosseininezhad, M., Bakhshayesh, B., Hoseini, M. and Naghipour, M. (2013) Epidemiology and Clinical Characteristics of Chronic Daily Headache in a Clinic-Based Cohort of Iranian Population. *Neurological Sciences* [Epub Ahead of Print]

[3] Ashkenazi, A. and Blumenfeld, A. (2013) Onabotulinumtoxin-A for the Treatment of Headache. *Headache*, **53**, 54-61. http://dx.doi.org/10.1111/head.12185

[4] Silberstein, S.D., Blumenfeld, A.M., Cady, R.K., Turner, I.M., Lipton, R.B., Diener, H.C., Aurora, S.K., Sirimanne, M., DeGryse, R.E., Turkel, C.C. and Dodick, D.W. (2013) Onabotulinumtoxin-A for Treatment of Chronic Migraine: PREEMPT 24-Week Pooled Subgroup Analysis of Patients Who Had Acute Headache Medication Overuse at Baseline. *Journal of the Neurological Sciences*, **331**, 48-56. http://dx.doi.org/10.1016/j.jns.2013.05.003

[5] Aurora, S.K., Dodick, D.W., Diener, H.C., Degryse, R.E., Turkel, C.C., Lipton, R.B. and Silberstein, S.D. (2014) Onabotulinumtoxin-A for Chronic Migraine: Efficacy, Safety, and Tolerability in Patients Who Received All Five Treatment Cycles in the PREEMPT Clinical Program. *Acta Neurologica Scandinavica*, **129**, 61-70. http://dx.doi.org/10.1111/ane.12171

[6] Levin, M. (2010) Nerve Blocks in the Treatment of Headache. *Neurotherapeutics*, **7**, 197-203. http://dx.doi.org/10.1016/j.nurt.2010.03.001

[7] Ilhan Alp, S. and Alp, R. (2013) Supraorbital and Infraorbital Nerve Blockade in Migraine Patients: Results of 6-Month Clinical Follow-Up. *European Review for Medical and Pharmacological Sciences*, **17**, 1778-1781.

[8] Schuster, L. (2003) Highlights of the 11th Congress of the International Headache Society, Held September 13-16, 2003, in Rome, Italy. Updating the Headache Classification System. *Drug News & Perspectives*, **16**, 692-697.

[9] Wan, X. and Tang, X. (1998) Comparison of Botox and a Chinese Type A Botulinum Toxin in Cervical Dystonia. *Zhong Hua Yi Xue Za Zhi*, **78**, 131-134.

[10] Tang, X. and Wan, X. (2000) Comparison of Botox with a Chinese Type A Botulinum Toxin. *Chinese Medical Journal* (*England*), **113**, 794-798.

[11] Guarany, F.C., Picon, P.D., Guarany, N.R., dos Santos, A.C., Chiella, B.P., Barone, C.R., Fendt, L.C. and Schestatsky, P. (2013) A Double-Blind, Randomised, Crossover Trial of Two Botulinum Toxin Type a in Patients with Spasticity. *PLoS One*, **8**, Article ID: e56479. http://dx.doi.org/10.1371/journal.pone.0056479

[12] Quagliato, E.M., Carelli, E.F. and Viana, M.A. (2010) A Prospective, Randomized, Double-Blind Study Comparing the Efficacy and Safety of Type a Botulinum Toxins Botox and Prosigne in the Treatment of Cervical Dystonia. *Clinical Neuropharmacology*, **33**, 22-6.

[13] Silberstein, S.D., Stark, S.R., Lucas, S.M., Christie, S.N., Degryse, R.E. and Turkel, C.C. (2005) BoNTA-039 Study Group. Botulinum Toxin Type A for the Prophylactic Treatment of Chronic Daily Headache: A Randomized, Double-Blind, Placebo-Controlled Trial. *Mayo Clinic Proceedings*, **80**, 1126-1137. http://dx.doi.org/10.4065/80.9.1126

[14] Keller, J.E., Cai, F. and Neale, E.A. (2004) Uptake of Botulin Neurotoxin into Cultured Neurons. *Biochemistry*, **43**, 526-532. http://dx.doi.org/10.1021/bi0356698

[15] Gracies, J.M. (2004) Physiological Effects of Botulinum Toxin in Spasticity. *Movement Disorders*, **19**, 120-128. http://dx.doi.org/10.1002/mds.20065

[16] Argoff, C.E. (2002) A Focused Review on the Use of Botulinum Toxins for Neuropathic Pain. *Clinical Journal of Pain*, **18**, 177-181. http://dx.doi.org/10.1097/00002508-200211001-00010

[17] Klein, A.W. (2004) The Therapeutic Potential of Botulinum Toxin. *Dermatologic Surgery*, **30**, 452-455. http://dx.doi.org/10.1111/j.1524-4725.2004.30118.x

[18] Voller, B., Sycha, T., Gustorff, B., Schmetterer, L., Lehr, S., Eichler, H.G., Auff, E. and Schnider, P. (2003) A Randomized, Double-Blind, Placebo Controlled Study on Analgesic Effects of Botulinum Toxin A. *Neurology*, **61**, 940-944. http://dx.doi.org/10.1212/01.WNL.0000086374.92906.6A

[19] Sycha, T., Samal, D., Chizh, B., Lehr, S., Gustorff, B., Schnider, P. and Auff, E. (2006) A Lack of Antinociceptive or Antiinflamatory Effect of Botulinum Toxin A in an Inflammatory Human Pain Model. *Anesthesia & Analgesia*, **102**, 509-516. http://dx.doi.org/10.1213/01.ane.0000194447.46763.73

[20] Aoki, K.R. (2003) Evidence for Antinociceptive Activity of Botulinum Toxin Type A in Pain Management. *Headache*, **43**, 9-15. http://dx.doi.org/10.1046/j.1526-4610.43.7s.3.x

[21] Afridi, S.K., Shields, K.G., Bhola, R. and Goadsby, P.J. (2006) Greater Occipital Nerve Injection in Primary Headache Syndromes—Prolonged Effects from a Single Injection. *Pain*, **122**, 126-129. http://dx.doi.org/10.1016/j.pain.2006.01.016

[22] Sjaastad, O., Petersen, H.C. and Bakketeig, L.S. (2005) Supraorbital Neuralgia. Vaga Study of Headache Epidemiology. *Cephalalgia*, **25**, 296-304. http://dx.doi.org/10.1111/j.1468-2982.2004.00856.x

[23] Bogduk, N. (2004) Role of Anesthesiologic Blockade in Headache Management. *Current Pain and Headache Reports*, **8**, 399-403. http://dx.doi.org/10.1007/s11916-996-0014-2

[24] Stillman, M. (2006) Steroid Hormones in Cluster Headaches. *Current Pain and Headache Reports*, **10**, 147-152. http://dx.doi.org/10.1007/s11916-006-0027-x

[25] Wang, S., Lim, G., Zeng, Q., Sung, B., Yang, L.L. and Mao, J.R. (2005) Central Glucocorticoid Receptors Modulate the Expression and Function of Spinal NMDA Receptors after Peripheral Nerve Injury. *Journal of Neuroscience*, **25**, 488-495. http://dx.doi.org/10.1523/JNEUROSCI.4127-04.2005

[26] Damen, L., Bruijn, J., Verhagen, A.P., Berger, M.Y., Passchier, J. and Koes, B.W. (2006) Prophylactic Treatment of Migraine in Children. Part 2. A Systematic Review of Pharmacological Trials. *Cephalalgia*, **26**, 497-505. http://dx.doi.org/10.1111/j.1468-2982.2005.01047.x

[27] Kroin, J.S., Buvanendran, A., Beck, D.R., Topic, J.E., Watts, D.E. and Tuman, K.J. (2004) Clonidine Prolongation of Lidocaine Analgesia after Sciatic Nerve Block in Rats Is Mediated via the Hyperpolarization-Activated Cation Current, Not by α-Adrenoreceptors. *Anesthesiology*, **101**, 488-494. http://dx.doi.org/10.1097/00000542-200408000-00031

[28] Liu, B.G. and Eisenach, J.C. (2005) Hyperexcitability of Axotomized and Neighboring Unaxotomized Sensory Neurons Is Reduced Days after Perineural Clonidine at the Site of Injury. *Journal of Neurophysiology*, **94**, 3159-3167. http://dx.doi.org/10.1152/jn.00623.2005

[29] Torelli, P. and Manzoni, G.C. (2004) Cluster Headache: Symptomatic Treatment. *Neurological Sciences*, **25**, 119-122. http://dx.doi.org/10.1007/s10072-004-0267-7

List of Abbreviations

BTX—Botox
CM—Chronic Migraine
HC—Hospital da Clinicas
IU—International Units
Pro—Prosigne
VNS—Visual Numerical Scale
ANOVA—Analysis of Variance
ASA—American Society of Anesthesiology
SNAP—Synaptosomal-Associated Protein

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

Other selected journals from SCIRP are listed as below. Submit your manuscript to us via either submit@scirp.org or Online Submission Portal.