Subcutaneous histamine versus botulinum toxin type A in migraine prophylaxis: a randomized, double-blind study

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Objectives: To compare the efficacy and tolerability of the subcutaneous administration of histamine and botulinum toxin type A (BoNTA) in migraine prophylaxis. *Background:* Histamine has a selective affinity for H3 receptors and it may specifically inhibit the neurogenic edema response involved in migraine pathophysiology. *Methods:* One hundred patients with migraine were selected in a 12-week double-blind controlled clinical trial to evaluate the efficacy of subcutaneous administration of histamine (1–10 ng twice a week) $n = 50$, compared with administration of 50 U of BoNTA (one injection cycle) $n = 50$. *Results:* The data collected during the 4th week of treatment revealed a significant decrease in all parameters studied, in histamine and BoNTA ($P < 0.001$). After 4 weeks of treatment, but one injection cycle of 50 U BoNTA had only a 40-day period of efficacy. *Conclusions:* This randomized study demonstrated that both histamine and BoNTA are similarly effective and well tolerated in reducing or eliminating headache in migraine prophylaxis. Low doses of histamine applied subcutaneously may represent a novel and effective therapeutic alternative in migraine patients and lay the clinical and pharmacological groundwork for the use of H3 agonist in migraine prophylaxis.

Introduction

Migraine affects nearly 12% of the adult population in occidental countries, imposing considerable economic and social losses [1,2]. Despite the diversity of drugs used in migraine prophylaxis [3], there is a 10–30% therapeutic failure rate with high drug consumption [4,5]. As yet, few of the drugs employed in migraine prophylaxis act on specific mechanisms related to migraine pathophysiology [6–8]. And despite the fact that the cause and pathophysiology of migraine are not well understood, migraine is considered a neurovascular headache disorder; with activation of meningeal nociceptors releasing neuropeptides, including calcitonin gene-related peptide (CGRP), substance P.7, serotonin, histamine, bradykinin, PGs, neurokinin A and endothelin-3 ET-3. They end ending in neurogenic-vasogenic inflammation, an important component in migraine that is perhaps genetically determined [9]. In 1991, we carried out an initial study [10] that provided evidence for the beneficial effects of histamine (1–10 μg) in migraine prophylaxis; these findings can be explained by histamine's control of mast cells, acting on H3-receptors which engage the nerves containing neuropeptides and probably reflects a local feedback circuit between C-fiber nerve endings and mast cells, which control neurogenic inflammation [11–13]. Botulinum toxin type A (BoNTA) has been reported as a possible contributer to migraine prophylaxis; pre-clinical *in vitro* and *in vivo* evidence demonstrates that BoNTA inhibits the release of nociceptive mediators such as glutamate, substance P, and CGRP from nociceptive fibers, suggesting that BoNTA may have direct antinociceptive action distinct from its neuromuscular activity [14–17]. The objective of this study is to evaluate the therapeutic potential of the subcutaneous administration of histamine in migraine prophylaxis, compared with BoNTA by undertaking a clinical trial.

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Methods

This was a 12-week randomized, controlled, double-blind study in 100 diagnosed migrainous patients under

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criteria established by the International Headache Society [18], who were unresponsive to available abortive (acetaminophen, ergotamine, dexamethasone, sumatriptan) and/or prophylactic agents (beta blocker, amitriptyline, divalproex sodium, topiramate) without sustained pain-free response, with an attack frequency of 4–6 per month, a severity of 2–3, and overuse of acute pharmacotherapy. Patients came from multiple physicians and neurologists and their diagnoses were independently confirmed by a second member of the research team [18,19]. All participants signed a letter of consent in accordance with the Helsinki statement. The patients were male or female adults between the ages of 18 and 65 years, all having a history of migraine for several years. Pregnant women, patients suffering daily headaches, and patients whose radiological tests revealed any pathology, including computer-assisted tomography, were excluded from the study. Selected patients underwent a one-month period of prophylactic agent washout, during which headache was monitored. They were then divided into two groups for treatment in randomized blocks of three [20], double-blind fashion: the histamine study group ($n = 50$) and BoNTA (BOTOX®, Allergan Inc., Irvine, CA, USA) control group ($n = 50$). This randomization was carried out by a research collaborator who throughout the duration of the study had no contact with the patients and prepared vials containing either 10 μg/ml subcutaneous histamine or subcutaneous placebo (Evan's solution = phenol 0.4%, isotonic sodium chloride); and 50 U of BoNTA (one injection cycle) or subcutaneous placebo (Evan's solution = phenol 0.4%, isotonic sodium chloride). The vials were numbered and identical in appearance, which allowed the blinding to be effective as neither the patients nor the physicians were able to identify the vehicle or active drug. In the Histamine Study Group, the treatment consisted of subcutaneous (back region of the upper arm) administration of histamine (10 μg/ml in Evan′s solution) 1–10 μg. Twice a week; the regimen began with the administration of 0.1 ml volume of either subcutaneous histamine, which was consecutively increased (by 0.1 ml) until reaching 1.0 ml., continuous repetition of this protocol (beginning again with 0.1 ml volume administration) or placebo one injection cycle (Evan's solution = phenol 0.4%, isotonic sodium chloride 2cc) divided into 10 injections sites across pericranial and neck muscles. In the BoNTA control group a total of 50 units of BoNTA (one injection cycle) was injected in 10-fixed sites of the muscles including procerus, corrugator, frontalis, temporalis and occipitalis [21], or subcutaneous placebo in the back region of the upper arm (Evan's solution = phenol 0.4%, isotonic sodium chloride, this was done twice a week for a period of 12 weeks). To avoid medication overuse that contributes to the transformation of episodic migraine, during treatment, patients were allowed to take 500 mg acetaminophen tablets if they had moderate or severe headache with an intensity value of 2 on a scale of 1–3, and lasting for more than 8 h. The variables used for the evaluation of efficacy [22] were: (i) headache frequency, measured by numbers of attacks per month; (ii) intensity of pain (scale from 1–3); (iii) duration of pain, measured by hours of headache per attack; (iv) intake of rescue analgesics, measured by the number of acetaminophen tablets (500 mg) taken per month; and (v) migraine disability assessment (MIDAS) score [23]. The MIDAS questionnaire developed to assess headache-related disability with the aim of improving migraine care. Headache sufferers answer five questions, scoring the number of days, in the past 3 months, of activity limitations because of migraine. Values for the parameters studied were collected over a period of 4 weeks before initiation of treatment (baseline), and efficacy and safety assessments were carried out every 30 days for a period of 12 weeks. Patients were instructed to keep a daily record of events. The relationship between an adverse event and study treatment was assessed by the investigator as none, possible, probable, or definite. Patients who abandoned the study were still taken into account in the final analysis. All patients were evaluated by a neurologist experienced in headache medicine and blinded to the results of randomization. Statistical analysis: average descriptive statistics and standard deviations were applied to data obtained. Two-tailed student's t-test was used to compare means and the evaluation of statistical significance for differences found between values for both groups, was performed using a Mann–Whitney U-rank-sum test. In order to analyze the temporal course of each treatment (for each variable studied), a Friedman repeated measures ANOVA on ranks test was used to evaluate the statistical significance of differences between basal values and values found for the 4th and 12th weeks of treatment. With an alpha level of 0.05, the trial was designed to have a statistical power of 80 percent, $P < 0.05$ was considered significant [24]. Data statistical analysis was carried out using the Statistical Package for Social Sciences program (SPSS 10.0; SPSS Inc., Chicago, IL, USA.)The study was approved by the Ethical and Scientific Committee of our hospital.

Results

From the total of 100 patients enrolled and randomized into the two groups (histamine $n = 50$; BoNTA $n = 50$), 40 patients in the histamine group and 45 patients in the BoNTA group completed the study. A

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total of 92% of the patients was female and mean age was 33 years ± 10.4 (range 18–60). Length of time presenting with headache was 15 ± 11.3 years and frequency of migraine attacks was 4.12 (95% CI 1.23–1.89) per month, with or without aura. The treatment groups were similar at baseline based on demographic and clinical characteristics (Table 1) for all variables studied. The statistical analysis of data collected showed no significant differences between the baseline values obtained for the histamine and the BoNTA treatment groups ($P > 0.05$). We compared the response of one group with its baseline and the differential response of one group with the other. Analysis of the temporal course of events showed that by the beginning of the 4th week, there was a significant decrease (with respect to basal values) in the magnitude of all parameters studied, as a result of the schema followed for the administration of histamine ($P < 0.001$) and BoNTA ($P < 0.001$). Comparison between both groups (Table 2) revealed a significant reduction on duration of migraine attacks: The rate of response to histamine was 62 percent (31 of 50 patients), reported a 72% reduction in duration of migraine attacks $P < 0.001$ (mean, 46.08 95% CI 12.5 to 6.4 h of headache per attack before treatment vs. 18.10 95% CI 9.6–9.2 h of headache per attack after treatment) (NNT 71); and the rate of response to BoNTA was 68 percent (34 of 50 patients), reported a 71% reduction $P < 0.001$ (mean 43.08 95% CI 11.1–6.5 h of headache per attack before treatment vs. 17.87 95% CI 8.2–9.4 h of headache per attack after treatment (NNT 71). In relation to rescue medication: 52% of patients receiving histamine reported a 63% reduction in the number of tablets ingested $P < 0.001$ (mean, 17 95% CI 12.1–7.2 acetaminophen tablets per month before treatment vs. 9.98 95% CI 3.2–10.1 acetaminophen tablets per month after treatment) (NNT 9.5), whereas 64% of patients receiving BoNTA reported a 57% reduction ($P < 0.001$) (mean 19.64 95% CI 7.5–4.5 acetaminophen tablets per month before treatment vs. 10.47 95% CI 5.2–4 acetaminophen tablets per month after treatment) (NNT 10.5). For pain intensity: 46 percent (23 of 50 patients) receiving BoNTA reported a 59% reduction in headache intensity ($P < 0.001$) (mean, 2.9 95% CI 1.2–0.2 before treatment vs. 1.96 95% CI 0.5–0.2 after treatment), whereas 50 percent (25 of 50 patients) receiving histamine reported a 62% reduction in intensity of pain ($P < 0.001$) (mean 2.96 95% CI 1.8–

Table 1 General and clinical characteristics of patients (before undergoing period washout of prophylactic agents)

Feature	Histamine ($n = 50$)	BoNTA ($n = 50$)
Age (mean years)	35.34 (15.5)	33.56 (10.4)
Male	3	5
Female	47	45
Years of migraine (mean)	12.44 (12.55)	16.72 (11.90)
Migraine type		
with aura	10	9
without aura	40	41
Age at onset, mean years	22.42 (10.64)	17.76 (9.83)
Baseline MIDAS, mean score	70.22 (6.56)	73.20 (4.75)
Frequency of headaches per 30-day periods at baseline, mean score	4.42 (1.28)	4.22 (1.13)
Intensity of headache at baseline[a]	2.96 (0.20)	2.90 (0.42)
Duration of headache (hours) mean score	46.08 (21.46)	43.08 (27.28)
Tablets/mo of rescue mean score	17.0 (11.22)	19.64 (19.68)

[a]Intensity of headache, scale 1–3: (1-minimum), (2-moderate), (3-severe). Mean (SEM); MIDAS, migraine disability assessment; BoNTA, botulinum toxin type A.

Table 2 Efficacy response measures and comparision of treatment groups

	Histamine 1–10 μg ($n = 50$) (%)			BoNTA 50 U ($n = 50$ (%)			ANOVA between groups	
Variable	Pre	4 w CI	Basal-4 w p	Pre	4 W	Basal-4 w p	F df = 1,84	Significance
Number of attacks per month	4.42 (100)	2.80 (60RR) CI.6–0.2	<0.001	4.22 (100)	2.76 (60RR) CI 0.6–0.2	<0.001	1.4	0.52
Headache duration (h)	46.08 (100)	18.10 (72RR) CI 6.3–8.1	<0.001	43.08 (100)	17.87 (71RR) CI 7.2–8.4	<0.001	1.8	0.21
Intensity of attacks (1–3)	2.96 (100)	1.80 (62RR) CI 0.1–0.2	<0.001	2.90 (100)	1.96 (59RR) CI 0.1–0.5	<0.001	1.0	0.32
Tablets ingested per month	17.00 (100)	9.98 (63RR) CI 4.2–5.1	<0.001	19.64 (100) CI 4.5–8.5	10.47 (57RR) CI 4.1–5.2	<0.001	3.4	0.12
MIDAS	70.22 (100)	54.90 (56RR) CI 9.8–11.2	<0.001	73.20 (100)	57.44 (56RR) CI 10.8–11.1	<0.001	3.2	0.12

Values within brackets are in percentages. w, weeks; RR, response rates; CI, confidence interval; MIDAS, migraine disability asessment; BoNTA, botulinum toxin type A.

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0.5 before treatment vs. 1.80 95% CI 0.4–0.3 after treatment). Also Comparison between both groups revealed a significant reduction between headache frequency and MIDAS. The rate of response to histamine was 52 percent (26 of 50 patients) reported a 60% reduction in headache frequency ($P < 0.001$) (mean, 4.42 95% CI 1.2–6.8 attacks per month before treatment vs. 2.8 95% CI 1–1.2 attacks per month after treatment), and the rate of response to BoNTA was 54 percent (27 of 50 patients), reported a 60% reduction ($P < 0.001$) (mean 4.22 95% CI 0.6–1.6 attacks per month before treatment vs. 2.76 95% CI 0.6–1.1 attacks per month after treatment). Mean MIDAS score decreased significantly 1 month after injection, 62 percent (31 of 50 patients) receiving histamine reported a 56% reduction ($P < 0.001$) (mean, 70.22 95% CI 0.7–5.82 before treatment vs. 54.90 95% CI 1.2–6.8 after treatment), and 68% of patients receiving BoNTA reported a 58% reduction ($P < 0.001$) (mean 73.20 95% CI 9.2–8.6 before treatment vs. 57.44 95% CI 10.1–9.8 after treatment). After 12 weeks of treatment, the effects of histamine remained identical to the values found at the 4th week. But one injection cycle of 50 U BoNTA had only a 40-day period of efficacy and showed no significant differences with respect to basal values (Fig. 1).

No serious adverse events were reported in any of the patients in either of the groups during the study. Ten percent (5/50) of the study patients in the BoNTA group, withdrew early from the trial after the first 3 weeks because they were not satisfied with the results (No improvement of intensity nor duration of pain). The most common adverse effect the BoNTA group experienced was intense transient pain at the injection site. Twenty percent (10/50) of patients in the histamine group withdrew without adverse events, because they were not satisfied with the speed of the results even though they did not present any side effects; some transitory burning and itching at the injection site was reported, but it was not significant enough to impede the blinding of the assay or the planned order of events. There were no modifications in arterial tension or cardiac frequency in either group for the duration of the study, nor were there any alterations in the laboratory analyses performed at the beginning and end of the study.

Discussion

This randomized study demonstrated that both histamine and BoNTA applied subcutaneously are similarly effective and well tolerated in reducing or eliminating headache in migraine prophylaxis and this was evident within the first month of treatment. However one injection cycle of 50 U BoNTA was effective for only 40 days. The use of botulinum toxin type A continues to be investigated by the US FDA for potential use in the treatment of headache. We chose 50-U BTX-A because of its cost-effectiveness and to reduce the incidence of adverse events such as weakness, neck pain, blepharoptosis and cost. Research has shown pericranial injection of 50-U BTX-A to be efficacious and well-tolerated as a prophylactic agent [25] and various studies have had similar results for BoNT-A as a stand-alone prophylaxis agent for headache in patients with a history of migraine or probable migraine headache [26]. However, in other studies, the efficacy of BoNT-A in preventing migraine headache attacks remains controversial. A consistent or dose-dependent response to BT-A treatment has not been seen, rendering the underlying scientific rationale debatable [27–29]. In this study, safety and tolerability were similar between the groups, but there was a great difference between BoNTA and histamine regarding cost and pain during administration. A cross-over study was not carried out, because of the fact that the use of drugs having a prolonged therapeutic effect does not lend itself well to such a study.

The results obtained in this and in previous placebo-controlled studies [10] show that histamine is a safe drug with therapeutic potential in migraine prophylaxis, exercising specific mechanisms on pathophysiological processes involved in this disease. Antidromic stimulation of trigeminal nerve endings induces the release of substance P and other neuromodulatory peptides, which in turn stimulate the release of histamine from mast cells. In meningeal blood vessels, activation of H1-receptors (H1-R) by histamine, results in vasodilatation and plasma protein extravasation, causing vasogenic-neurogenic inflammation [9]. However, degranulation of mast cells and neuropeptide release from C fiber endings are inhibited by the histamine interaction with H3-receptors (H3-R), representing a local feedback circuit between C-fiber nerve endings and mast cells, controlling neurogenic inflammation [6,8,11]. Histamine H3 receptors (H3Rs) are autoreceptors that negatively regulate the release of histamine and other neurotransmitters and are believed to play a variety of physiological roles, including the regulation of feeding, arousal, cognition, pain, and endocrine systems [12,13,30]. Histamine has become a therapeutic alternative in our medical consultations in patients presenting recurrent migraine who do not respond to β-adrenergic or calcium channel blockers. It is our treatment of choice in migraine patients over 60 years of age who have hypotension or cardiac rhythm alterations, and in whom the usual drugs are contraindicative, or in patients having developed secondary gastritis and cannot tolerate further oral drug therapy. Twice-weekly,

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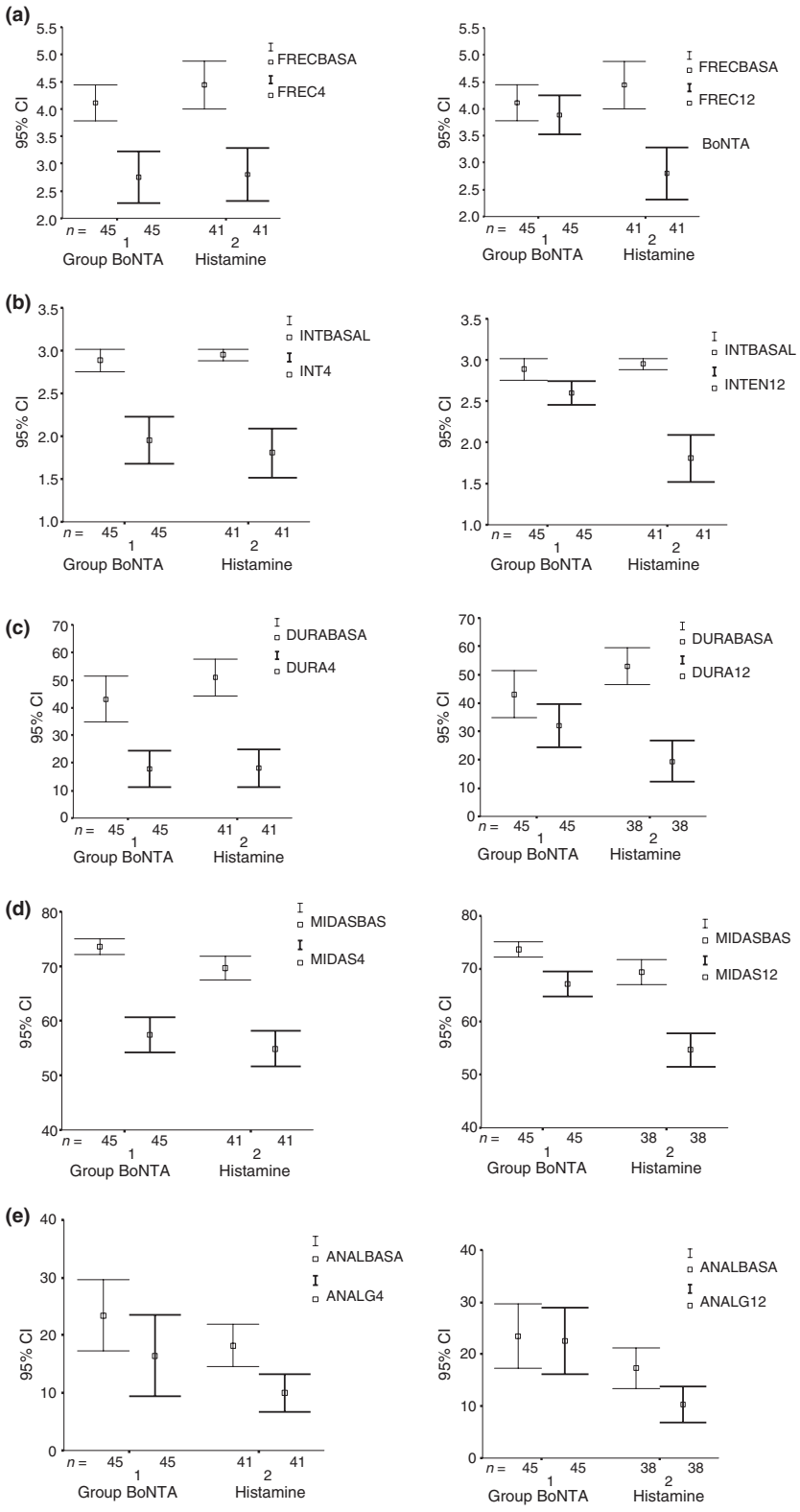

Figure 1 Effects induced (in 100 patients with recurrent migraine) by the subcutaneous administration (twice a week, during 12 weeks) of histamine ($n = 50$) and botulinum toxin type A (BoNTA) ($n = 50$) on frequency of migraine attacks (a), intensity (b), duration (c), migraine disability assessment (d), as well as on the consumption of 500 mg acetaminophen tablets used as rescue medication during headache (e). Data correspond to mean values (plus SEM) obtained prior to initiation of treatment (basal), and 4 weeks of treatment * $P < 0.001$. But BoNTA group has an efficacy of only 40 days period, and showed no significant differences with respect to basal values at the 12th week of treatment.

subcutaneous application of histamine, has been accepted in our practice by patients, who previously had not been satisfied with the daily administration of other medications. A better understanding of migraine pathophysiology along with the discovery of novel molecular targets has led to a growing number of

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upcoming therapeutic proposals. [31–35]. The possibility of better modulating the imbalance between central neurotransmitters that occurs with migraine has created an exciting search for new pharmacologic sites. Neuromodulators for the prevention of multiple mechanisms related to migraine are already available.

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