Title Page

Manuscript Title: Effect of dietary zinc supplementation on botulinum toxin treatments: A modified randomized, double-blind, placebo-controlled, crossover pilot study

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Precis: This study suggests a meaningful role for a combination of zinc and phytase supplementation to increase the efficacy and duration of effect of botulinum toxin treatments for blepharospasm, hemifacial spasm, and facial rhytids.

ABSTRACT

Purpose: To determine whether oral zinc supplementation might affect the efficacy and duration of botulinum toxin treatments for Benign Essential Blepharospasm, hemifacial spasm, and facial rhytids.

Methods: In a modified double-blind, randomized, placebo-controlled, crossover pilot study, we compared the effectiveness of BTX injections (Botox®, Myobloc®, or Dysport®) with either zinc citrate 50 mg plus phytase 3,000 PU, zinc gluconate 10 mg , or placebo supplementation, in individuals being treated for blepharospasm, hemifacial spasm, and facial rhytids. Duration of effect was compared to each participant's established pre-study treatment interval, and efficacy was participant-graded using participants' experience prior to study inclusion as a baseline. Descriptive statistical analysis determined mean duration and effect rating for each supplementation group, and 95% confidence intervals (CI) were calculated to determine statistical significance.

Results: Forty-four participants (33 female) participated in this study. Supplementation with zinc 50 mg and phytase led to a significant increase in both the duration and efficacy of BTX treatments. Duration of effect increased by 23.6% (95% CI +20.3-27%), and rated efficacy increased by 1.6 (95% CI +1.2-1.9). Conversely, all other forms of supplementation had no significant impact. Three participants (6.8%) with blepharospasm suffered treatable exposure keratopathy secondary to excessive BTX action following supplementation with zinc 50 mg and phytase.

Conclusions: This study suggests a meaningful role for zinc and phytase supplementation to increase the efficacy and duration of effect of botulinum toxin treatments for Benign Essential Blepharospasm, hemifacial spasm, and facial rhytids.

INTRODUCTION

Botulinum toxins (BTXs) play a significant and expanding role in the management of many aesthetic and medical conditions, including facial rhytids, Benign Essential Blepharospasm, and hemifacial spasm. In 2009, close to five million cosmetic procedures were performed in the United States using Botox®,[1] with an equal amount of toxin being sold for the treatment of functional medical indications,[2] Although the BTXs are effective for the majority of patients,[3-5] the degree of therapeutic efficacy may vary widely, not only from individual to individual but among different populations as well. For example, up to 30% of patients over the age of 65 years may be poor- or non-responders.[6-9] While some factors have been identified which can affect the efficacy of BTX,[10, 11] much of the variability remains unexplained.

We postulated that one factor responsible for the variability in BTX effect might involve elemental zinc, an essential cofactor for enzymatic BTX function. Although overt zinc deficiency is rare in developed nations, there is a growing awareness that "relative" or "marginal" zinc deficiencies may not only be quite prevalent, but may also have a significant clinical impact on a variety of outcomes.[12-24] The purpose of this study was to investigate whether oral zinc supplementation might affect the efficacy and duration of BTX treatments for Benign Essential Blepharospasm, hemifacial spasm, and facial rhytids.

METHODS AND MATERIALS

Study Design

In this modified double-blind, randomized, placebo-controlled, crossover pilot study, we compared the effectiveness of BTX injections (Botox® (Allergan, Irvine, CA), Myobloc® (Solstice Neurosciences, Malvern, PA), or Dysport® (Tercica, Brisbane, CA)) after four days of

supplementation with either oral zinc citrate 50 mg and phytase 3,000 PU (Z50), zinc gluconate 10 mg (Z10), or lactulose placebo (P).

Study Participants

Patients being treated in the senior author's private practice who were 18 years or older and receiving BTX treatment (Botox®, Myobloc®, or Dysport®) for Benign Essential Blepharospasm, hemifacial spasm, or facial rhytids were approached for participation in this study.

Initially, only "hard to treat" Benign Essential Blepharospasm patients (BH) who met the following criteria were recruited: 1) required greater than 50 units of peri-ocular Botox® or other BTX unit equivalence per treatment session, 2) routinely had patient-reported suboptimal results despite maximized response from a customized injection pattern, and 3) reported a degree of variability in BTX effect from treatment to treatment despite unchanging injection dose and pattern. Patients who were consistent and significant responders or "easy to treat" via an unchanging BTX injection pattern for the treatment of facial rhytids, hemifacial spasm, Benign Essential Blepharospasm (BC), or BH patients being treated with Dysport®, were enrolled later in the study.

Additional inclusion criteria included those who had received at least five prior pattern and dose consistent treatments among the "hard to treat" or three prior treatments among the "easy to treat", and those who were able to attend regularly scheduled visits, understand and provide informed consent, swallow pills, and maintain their usual pre-study diet for the duration of the study period.

Assignment and Treatment

Participants were unequally randomly assigned by a third party to receive supplementation in the form of either: A) Z50, B) P and Z50 (crossover design), C) Z10 and Z50 (crossover design), or D) P, Z10, and Z50 (crossover design). The order of supplementation for individuals involved in groups B, C, and D was randomized. Both investigator and participants were masked from group allocation, and participants were given the assigned supplementation to be taken once a day for four days prior to their BTX injections. The supplements were powder-filled, gelatin capsules (Green Park Pharmacy, Houston, Texas), and lactulose was used for placebo.

For individuals in arms of the study with a crossover design, participants were asked to allow the effects of the previous intervention to wear off completely prior to scheduling their next treatment session. Additional supplementation, if indicated, occured four days prior to the next scheduled intervention. The senior author performed all drug administrations and participant assessments, and administered the BTX injections in accordance with each participant's normal injection pattern and dosing regimen.

Follow-up and Outcome Measures

All study participants with Benign Essential Blepharospasm, in keeping with their usual routine in the senior author's practice, kept a daily log of BTX effect, which documented their ability to keep their eyes open throughout the day. All other participants were asked to keep at least a weekly log of their treatment effect**.** At subsequent office visits, participants graded the overall efficacy of their BTX treatment (using their experience prior to study inclusion as a baseline) on a scale of -3 to +3 using their daily or weekly logs, where -3 = worst effect ever, -2 = significantly less effective than usual, -1 = slightly less effective than usual, 0 = no change

from usual effect, +1 = slightly more effective than usual, +2 = significantly more effective than usual, and +3 = best effect ever.

Additionally, study participants' duration of treatment effect was compared to effect duration prior to study inclusion by forming a ratio between the length of study and pre-study treatment intervals. The resulting value spanned from -1 (100% shorter than normal) to +1 (100% longer than normal). Finally, all adverse events reported by study participants were recorded and managed as necessary.

Statistical Analysis

Descriptive statistical analyses were performed to determine the mean effect rating and mean increase in duration for each supplementation group (Z50, Z10 and P), and 95% confidence intervals (CI) were calculated for each mean value. Results were considered statistically significant if the 95% confidence interval of the mean did not cross the null value for both duration and effect measures.

Multiple unpaired t-tests were performed to compare each of the study arms regarding duration and effect measurements. These tests were also used to perform subgroup analyses on the Z50 study arm, based upon the indication for treatment with BTX (BH, BC, hemifacial spasm, or facial rhytids), and type of BTX formulation used.

All statistical analyses were performed using SigmaPlot Software (Systat Software Inc., San Jose, California, USA).

Study Limitations

The study design had several limitations. First, participants were unsystematically, randomly distributed among the treatment groups by nursing personnel working at the senior author's private practice, resulting in a sub-optimal treatment group homogenization, as

subconscious methods for allocation may have introduced some degree of bias. However, both study participants and the administering physician were blinded throughout the process, and every participant was able to compare the results of supplementation with their own perceived usual result, reducing the degree to which this unsystematic method may have biased results. Additionally, although patients entered into the study did not alter their usual diet and provided general dietary patterns in a pre-study questionnaire, the projected study sample size was too small to provide meaningful data regarding usual diet and likelihood or degree of benefit from Z50 supplementation.

RESULTS

Participants

From November of 2007 to June of 2009, a total of 44 participants from the senior author's private practice were enrolled in this study. The participants' average age was 65 years (range 35-88 years), and thirty-three (75%) were female. Twenty-three (52%) participants suffered from "hard to treat" Benign Essential Blepharospasm (BH), and 7 (16%) suffered from consistently responsive or "easy to treat" Benign Essential Blepharospasm (BC). Four (9%) participants had hemifacial spasm, while 10 (23%) received interventions for the cosmetic treatment of facial rhytids. Three (30%) participants being treated for rhytids were receiving Dysport®, while two (7%) participants with BH were treated with Myobloc®.

Assignment and Treatment

Participants were unequally randomized to one of four treatment groups. Twenty-three (52%) study participants underwent treatment with Z50 alone (group A), six (14%) study participants underwent treatment with both P and Z50 at separate times (group B), while four (9%) underwent treatment with Z10 and Z50 at separate times (group C). Finally, 11 (25%) of

study participants received all forms of supplementation at separate times (group D) [FIGURE 1]. The average number of Botox® units, Dysport® units, and Myobloc® units per study participant were 48, 120, and 3,000 units, respectively.

Follow-up and Compliance

All participants successfully completed the study with no loss to follow-up, and supplementation compliance was confirmed verbally by all study participants.

Comparisons Between Study Arms

The duration of effect was significantly greater ($p<0.05$) for the Z50 group (mean 23.6%, 95% CI 20.3-26.9%) compared to both the Z10 group (mean 1.2%, 95% CI -2.1-4.5%) and the P group (mean 0.4%, 95% CI -1.5%-2.3%), while no difference was seen between the Z10 and P groups ($p>0.05$). Efficacy ratings were significantly greater for the Z50 study arm (mean +1.6, 95% CI 1.2-1.9) compared to both the Z10 study arm (+0.4, 95% CI 0.1-0.7) and the P study arm (+0.1; 95% CI -0.2-0.3), whereas the difference in effect seen between the Z10 and P groups was not statistically significant ($p>0.05$). [FIGURE 2,3]

Comparisons Based Upon Indications for Treatment

While all four treatment indication groups (BH, BC, hemifacial spasm, and facial rhytids) had significant increases in duration and degree of BTX effect when supplemented with Z50, subjects treated for hemifacial spasm had significantly greater ($p< 0.05$) increases in duration of effect compared to subjects treated for BH (40% increase vs. 20% increase) and facial rhytids (40% increase vs. 25% increase). Comparison of primary outcome variables between the BH, BC, and facial rhytid subgroups, however, did not reveal differences in either efficacy or duration.

Comparisons Based Upon BTX Formulations

Comparisons of primary outcomes with Z50 supplementation between the various BTX formulations used in this study revealed that there was no significant difference ($p>0.05$) in duration of effect or efficacy between the different BTX formulations (Botox®, Myobloc®, and Dysport®).

Safety

Three participants (6.8%) treated for BH in the Z50 study arm suffered from over action of their BTX injections, which led to difficulty with eyelid closure during the term of BTX effect and severe exposure-related dry eye symptoms. Although these dry eye complications were successfully treated with aggressive exogenous lubrication and eye patching at night, all three participants subsequently rated their treatment efficacy as -2.

DISCUSSION

Botulinum toxins (BTXs) are a family of zinc-dependent metalloproteases produced by the bacteria *Clostridium botulinum*. These toxins are used in the treatment of many functional and aesthetic conditions, including Benign Essential Blepharospasm, hemifacial spasm, and facial rhytids. Though the efficacy of BTXs for the management of these conditions is well established,[7, 25-27] a fair degree of variability in treatment effect has been seen both among subjects, and within a single individual's different treatment sessions. Moreover, some subjects never realize a benefit from BTX treatments.[8, 9, 27-29] Interestingly, a correlation between poor- or non-responder rates and age has been suggested, as Botox® non-responder rates as high as 30% have been documented in individuals over the age of 65, versus 9% poor-responder rates reported in patients under the age of 65.[6]

We wondered whether an underlying subclinical zinc deficiency might play a role in the variability of BTX efficacy, as over the years, clinicians have become increasingly aware of the

wide-reaching clinical impact of this often unrecognized condition.[16, 18, 20, 23] Aside from the fact that zinc is an essential direct co-factor for BTX enzymatic activity, it has also been shown to be able to modify the action of various neurotransmitters at their receptors, including acetylcholinergic receptors.[30-34]

Zinc levels in the body are largely dependent upon not only dietary zinc, but dietary phytate intake as well.[35] Phytates, a family of phosphorous-containing compounds that block intestinal absorption of zinc by binding with it in the digestive tract, are found concomitantly in many foods also rich in zinc, including nuts, whole grains, legumes, and preserved foods among others [TABLE 1].[36] Thus, the amount of phytate consumed significantlys reduces the bioavailability of dietary zinc, as the consumption of just 0.26 grams of phytate effectivelyinhibits the absorption of up to 50 mg of zinc.[37-39] A relatively low zinc:high phytate diet may be increasingly prevalent in the United States, especially among the fixed-budget elderly avoiding expensive meats, the weight and cholesterol-conscious, vegetarians, and those who frequently consume preserved foods such as soft drinks with their meals.[40]

Other factors also may play a role in an individual's zinc status [TABLE 2],[41] and while there are homeostatic mechanisms in place to combat the waxing and waning of the body's zinc level, these can maintain stores for only a relatively short period. Consequently, individuals can quickly enter a state of relative zinc deficiency.[42]

Although profound zinc deficiency in infancy and childhood can be blatant,[43] less severe zinc deficiencies in adulthood may be far more subtle. Currently, the exact prevalence of this subclinical problem is unknown because of accuracy, practicality, and financial costs associated with objective zinc level testing.[24, 41] Despite this, roughly half of individuals over the age of 50 consume inadequate amounts of zinc compared to recommended requirements,[15] and nearly 30%

of these individuals show signs of zinc deficiency.[21] This age-related risk for zinc deficiency appears to be caused by a combination of decreased zinc, increased phytate, and competing cation (calcium or iron) intake, although differential absorption may also play a role.[37] Interestingly, the populations based on age and dietary behaviors which are most likely to have an underlying zinc deficiency are also more likely to seek treatment for Benign Essential Blepharospasm, hemifacial spasm, or facial rhytid management, and at least in the advanced age group, have been shown to be more likely to respond more poorly to BTX treatments.[6, 8, 9, 29, 44]

The purpose of this investigation was to determine the relationship between zinc supplementation and BTX treatment efficacy and duration of action. Phytase, which catalyzes the breakdown of phytate, was included in one of the study arms as it has been shown in animal studies to significantly increase the bioavailability of dietary zinc.[45, 46] Subsequently, in this modified double-blind, randomized, placebo-controlled, crossover pilot study, zinc and phytase supplementation appeared to significantly improve the efficacy and longevity of BTX action for the treatment of Benign Essential Blepharospasm, hemifacial spasm, and facial rhytids.

Oral supplementation with Z50 (50 mg of zinc citrate with phytase) resulted in a 24% increase in the duration of BTX effect. The clinical significance of these findings is the potential reduction in the frequency of both medically-indicated and cosmetic treatments required by these patient populations. Supplementation with Z50 also led to a significant increase in mean subjective efficacy, which for some individuals meant the difference between being functionally blind and homebound vs. being able to read, drive, and work at the computer. The increased efficacy of BTX, however, may require new dosing patterns for some individuals.

For three participants supplemented with Z50, using the participant's standard dosing regimen resulted in an excessive clinical effect, caused ocular exposure, and negatively impacted

their overall subjective response. While these complications remain a real concern and should be noted with further clinical management, these outcomes only support our original hypothesis. The purpose of this study was to determine how zinc supplementation affected the efficacy of BTX, and while these participants rated their treatments as being -2 ("Significantly less effective than usual"), their responses commented more on their displeasure from the *overaction* or greatly increased efficacy of BTX, rather than decreased efficacy. If the statistical analysis was performed without these misrepresented outcomes, the efficacy of BTX would have been even greater (mean +1.8; 95% CI +1.6-2.0). This safety issue is important, however, and must be carefully understood by clinicians and patients when undergoing supplementation. Future supplementation with Z50 for the participants experiencing adverse events in this study resulted in a substantial decrease in their dosage.

Supplementation with Z10 (10 mg of zinc gluconate alone), on the other hand, caused a small increase in effect (+0.4), but not a statistically significant increase in duration. Supplementation with P (placebo) did not yield a significant increase in either duration or magnitude of effect.

Although all participants demonstrated an improvement in BTX treatment efficacy and duration with Z50 supplementation on average, secondary outcomes analysis revealed a statistically significant increase in length of duration in participants treated for hemifacial spasm compared to those treated for BH and facial rhytids. The underlying reason for greater improvements in study participants with hemifacial spasm may be related to the often diminished underlying facial nerve function in these individuals.[47, 48]

Finally, the benefits of Z50 supplementation did not appear to differ between different BTX formulations. Although these clinically used BTX formulations differ in terms of their

structure, ancillary carrier proteins, specific site of protein cleavage, and dosing requirements,[4, 9] they are all believed to undergo the same cell-uptake and light chain toxin activation, and perhaps more importantly, all require a zinc cofactor for enzymatic function.

Further observations after the conclusion of this study (unpublished data) suggest that the variability in effect of repeated treatments for each individual is also reduced with repeated pre-injection Z50, potentially indicative of the normal fluctuations in zinc levels in our patients in the absence of supplementation. Additionally, the increased BTX efficacy for some study participants translated into using less BTX to achieve the same treatment goals. In general, reduction in dosing requirements can be beneficial in terms of costs and may be desirable given recent concerns regarding the potential for dose-dependent distant spread of BTX.[49, 50]

Although the data in this study are very compelling, caution should be taken to avoid erroneous extrapolation of the finer points. First, the relatively small study size increases the risk of type II error in our subgroup analysis so that Z50 supplementation may create an equal increase in toxin duration among all individuals, rather than a selectively greater effect in hemifacial spasm study participants. Secondly, the small sample size also limited our ability to investigate the impact of various diets upon primary BTX effect, and so we are unable to do more than speculate about which diets most lend themselves to patients benefitting from Z50 supplementation. Next, other factors may have influenced the severity of the underlying condition treated, and subsequently altered the outcomes of the intervention. For example, stress is well known to affect Benign Essential Blepharospasm severity,[51] and both whole body and dermal hydration affect facial rhytids.[52] So, although Z50 supplementation may resolve an underlying zinc deficiency that limits BTX efficacy and duration of action, there may be many other contributing factors affecting outcomes. Third, it is assumed that the beneficial effect of

phytase in Z50 is to enhance zinc absorption, and it is assumed that zinc supplementation acts directly on the light chain of BTX to increase BTX enzymatic activity, but these putative mechanisms of action remain assumptions requiring further investigation. For example, phytase may provide benefit by increasing the absorption of any number of other dietary cations, and zinc may be acting directly at the neuromuscular junction. [30-34] Fourth, it remains unclear whether the superiority of Z50 compared to Z10 was due to the higher dose of zinc, the addition of phytase, the different organic salt used (citrate vs gluconate), or some combination of the three. Finally, caution is advised against interpreting this data to mean universally that "more zinc is better." Although repeated use of Z50 in a pulse fashion before BTX treatments as often as every six weeks has not been seen to be a problem in our patients (data not shown), prolonged, unrestrained high-dose zinc and / or phytase supplementation on a daily basis can lead to zinc or other cation toxicity.[53, 54]

CONCLUSIONS

This pilot study supports an important role for zinc supplementation in increasing the duration and efficacy of BTX treatments for Benign Essential Blepharospasm, hemifacial spasm, and facial rhytids, potentially decreasing the number of treatments per year, decreasing the total dose of BTX per treatment, and decreasing intertreatment variability for individuals. It is also possible that patients who were previously poor- or non-responders to BTX treatment may recognize new benefit with zinc supplementation.

TABLE LEGEND

Table 1. Zinc and phytate content in common dietary sources.[40]

Table 2. Factors affecting zinc status in humans.

FIGURE LEGEND

Figure 1. Study participants' assignment and treatment. Twenty-three (52%) study participants underwent treatment with Z50 alone (group A), six (14%) study participants underwent treatment with both P and Z50 at separate times (group B), while four (9%) underwent treatment with Z10 and Z50 at separate times (group C). Finally, 11 (25%) of study participants received all forms of supplementation at separate times (group D) (BH = "hard to treat" Blepharospasm, BC = "easy to treat" Blepharospasm, HS = Hemifacial Spasm).

Figure 2. Overall results (with all subgroups included) of efficacy for groups Z50, Z10, and P, using 95% confidence intervals for each mean value (Z50 = zinc citrate 50 mg plus phytase 3,000 PU, Z10 = zinc gluconate 10 mg, P = placebo).

Figure 3. Overall results (with all subgroups included) of duration of effect for groups Z50, Z10, and P, using 95% confidence intervals for each mean value (Z50 = zinc citrate 50 mg plus phytase 3,000 PU, Z10 = zinc gluconate 10 mg, P = placebo)..

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Table 1. Risk Factors for Zinc Deficiency

1. Diet
    a. Vitamin supplements
        i. Poorly absorbed (inexpensive) inorganic zinc forms
        ii. Iron
        iii. Vitamin A
        iv. Calcium
        v. Copper
    b. High phytate intake
        i. Whole grain breads and fiber
        ii. Whole wheat products
        iii. Cereals
        iv. Soy
        v. Oats
        vi. Legumes (including peanuts, peanut butter, peas)
        vii. Beans
        viii. Corn
        ix. Rice
        x. Many pre-prepared foods (preservatives)
        xi. Most beverages (including virtually all carbonated soft drinks)
            1. Phosphate containing compounds
            2. Preservative E391
    c. Alcohol consumption
        i. Decreases Zinc absorption
        ii. Increases urinary excretion
        iii. Many wines contain phytates
    d. Milk-based products containing casein and calcium
    e. Many "fiber enriching" foods and supplements
    f. Vegetarianism (diets low in red meats, poultry, and fish, but high in soy)
    g. Foods containing EDTA preservative
2. Medical conditions
    a. Infections (viral, bacterial, fungal)
    b. Burns
    c. Most chronic illnesses
    d. Malabsorption
        i. Frequent Diarrhea
        ii. Sprue, etc
        iii. Constipation with frequent fiber and/or laxative use
3. Pregnancy
4. Age < 25 or > 65
5. Diuretic use

				Placebo			Zinc 10			Zinc 50 + P		
ID	**SEX**	**AGE**	**DZ**	**D_P**	**E_P**	**T_P**	**D_{Z10}**	**E_{Z10}**	**T_{Z10}**	**D_{Z50P}**	**E_{Z50P}**	**T_{Z50P}**
1	M	39	BH							0	1	B
2	M	56	BH							0.23	2	B
3	M	71	BH	0	0	B				0.15	2	B
4	M	76	BH							0.12	2	B
5	M	78	BH	0.07	1	B	0.07	1	B	0.23	3	B
6	F	68	BH							0.12	0	B
7	F	70	BH				0	0	B	0.23	2	B
8	F	71	BH				-0.15	0	B	0.23	2	B
9	F	73	BH							0.23	2	B
10	F	73	BH	0	-1	B				0.16	2	B
11	F	73	BH	-0.07	0	M	0	1	M	0.23	2	M
12	F	76	BH							0.31	3	B
13	F	76	BH							0.31	2	B
14	F	77	BH	-0.06	0	M	0.07	1	M	0.16	2	M
15	F	77	BH							0.35	-2*	B
16	F	77	BH							0.23	0	B
17	F	80	BH							0.35	3	B
18	F	80	BH	0.06	-1	B	0	0	B	0.16	2	B
19	F	82	BH							0	2	B
20	F	84	BH	0	0	B				0.07	2	B
21	F	84	BH				0.07	1	B	0.23	3	B
22	F	85	BH							0.23	2	B
23	F	88	BH	0.07	1	B	0	0	B	0.23	2	B
24	F	58	BC							0.31	-2*	B
25	F	61	BC							0.15	2	B
26	F	63	BC	0	0	B	0	0	B	0.23	-2*	B
27	M	72	H							0.31	2	B
28	F	65	H				0	0	B	0.47	2	B
29	F	38	C							0.47	2	B
30	F	43	C							0.31	2	B
31	F	54	C	0	0	B	0	0	B	0.23	2	B
32	F	57	C							0.15	1	B
33	M	43	H							0.33	1	B
34	M	47	H							0.5	0	B
35	F	64	BC	0	0	B				0.23	2	B
36	F	69	BC	0	0	B	0.12	1	B	0.31	3	B
37	M	73	BC	0	0	B	0	0	B	0.23	2	B
38	M	74	BC	0	1	B	0	0	B	0.23	2	B
39	F	35	C	0	0	B				0.25	2	B
40	F	39	C	0	0	B	0	1	B	0.25	1	B
41	F	43	C	0	0	B				0	1	B
42	F	44	C							0.25	1	D
43	F	56	C							0.31	2	D
44	M	52	C							0.31	1	D

Figure 1. Results of supplementation with placebo, low dose zinc, or high dose zinc with phytase for four days prior to botulinum toxin injection. ID = patient ID number, Sex = gender, M = male, F = female, Age = patient's age in years at commencement of the study, DZ = condition for which the patient was being treated, BH = "hard to treat blepharospasm", BC = "easy to treat" blepharospasm with consistent response to toxin injections, H = hemifacial spasm, C = cosmetic rhytids, Placebo = lactulose capsules, Zinc 10 = 10 mg zinc gluconate, Zinc 50 + P = 50mg zinc citrate and 3,000 Units Phytase, D_P = duration of effect of toxin treatment after placebo supplementation, E_P = degree of effect of toxin treatment after placebo supplementation, TP = type of botulinum toxin used in patient's treatment, B = botulinum toxin type A (Botox), D = botulinum toxin type A (Dysport), M = botulinum toxin type B (Myobloc), D_{Z10} = duration of effect of toxin treatment after Zinc 10 supplementation, E_{Z10} = degree of effect of toxin treatment after placebo supplementation, T_{Z10} = type of botulinum toxin used in patient's treatment, D_{Z50P} = duration of effect of toxin treatment after Zinc 50 + P supplementation, E_{Z50P} = degree of effect of toxin treatment after Zinc 50 + P supplementation.

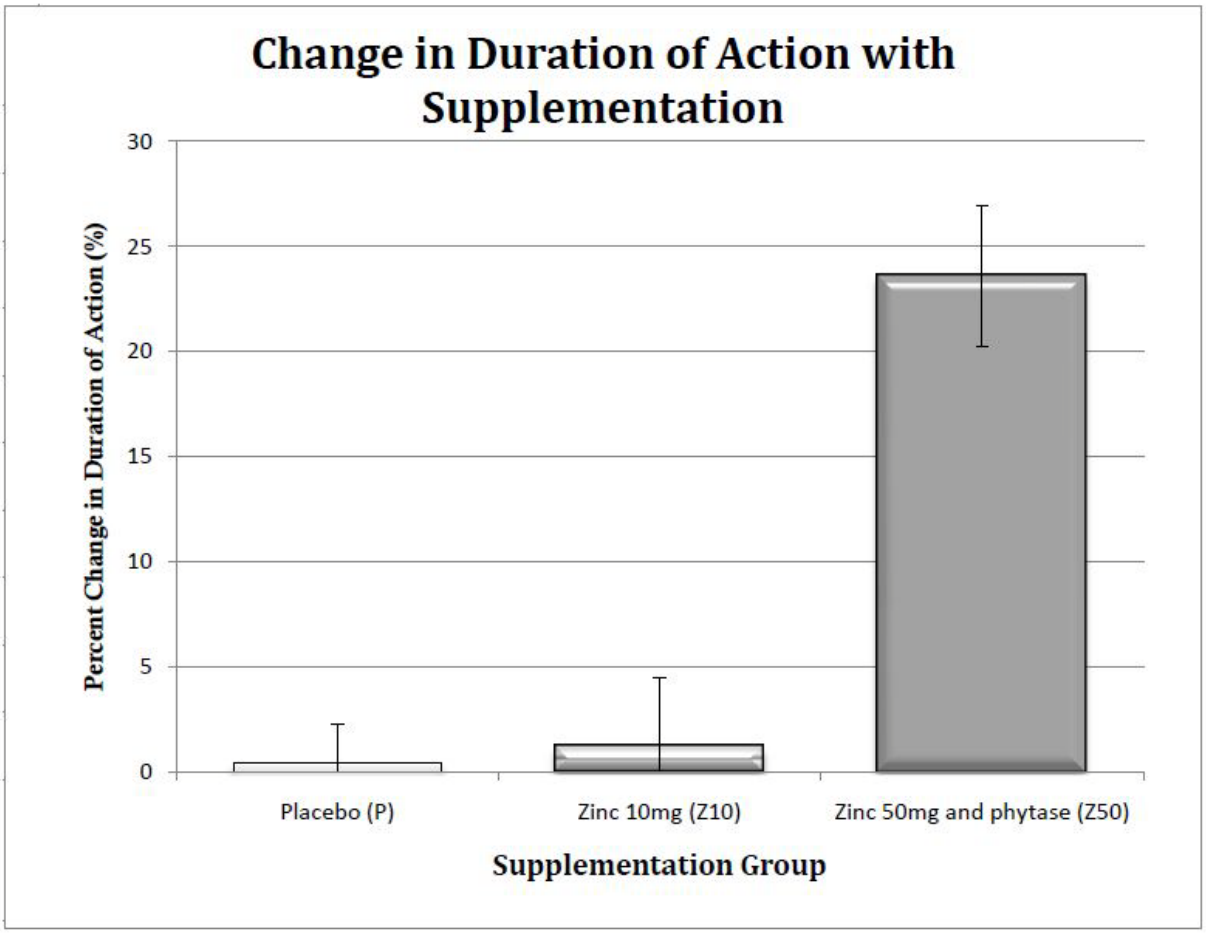

Figure 2. Patient-specific change in duration of botulinum toxin effect compared to no supplementation following pre-injection supplementation with lactulose placebo (P), 10 mg zinc gluconate (Z10), or 50 mg zinc citrate and 3,000 U phytase (Z50).

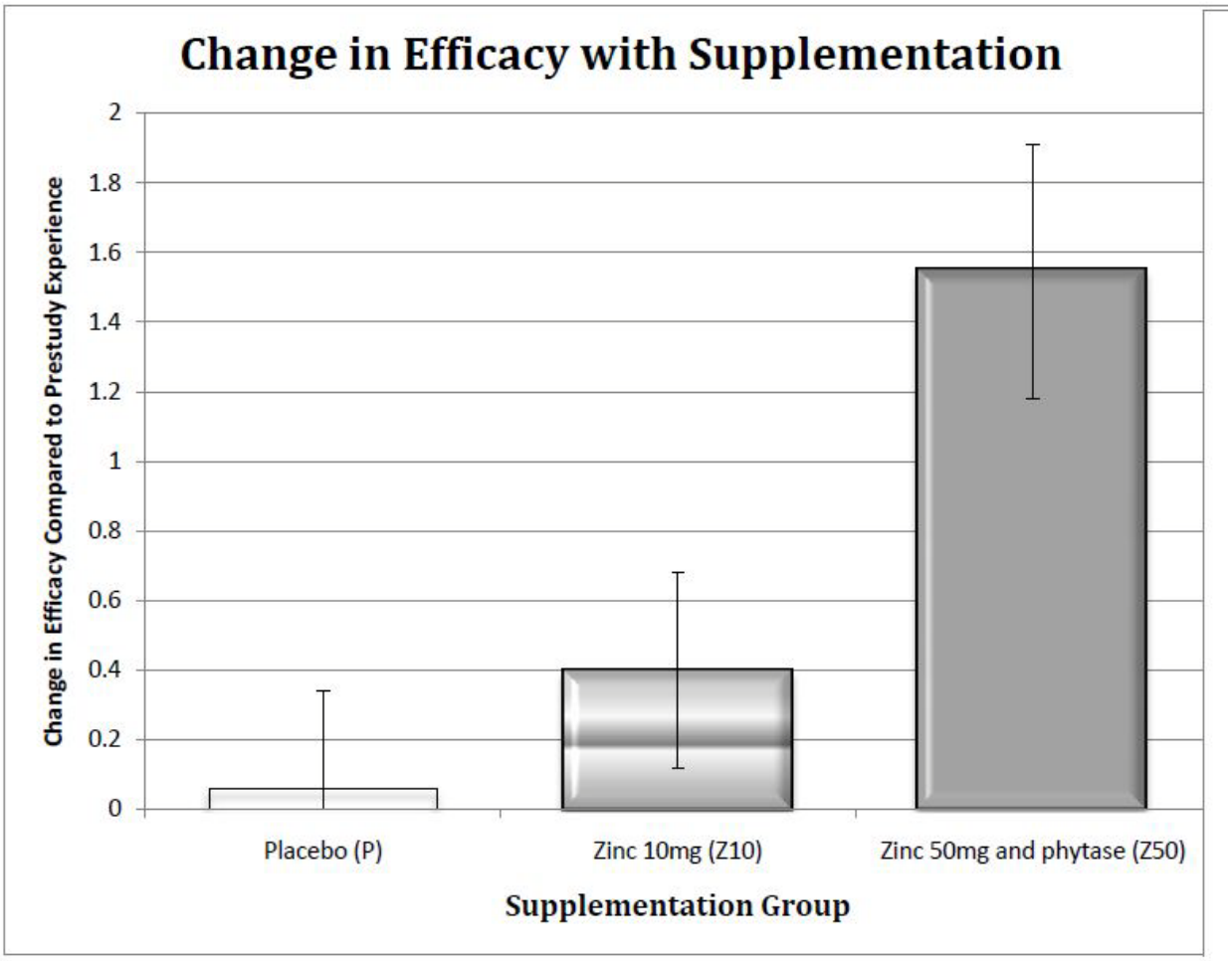

Figure 3. Patient-specific, patient-determined change in efficacy of botulinum toxin effect compared to no supplementation following pre-injection supplementation with lactulose placebo (P), 10 mg zinc gluconate (Z10), or 50 mg zinc citrate and 3,000 U phytase (Z50).