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Efficacy of Botulinum toxin in treating Asian Indian patients with masseter hypertrophy: A four years follow-up study

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Abstract:	Background Asian Indians usually have wide lower faces due to masseter hypertrophy. Therefore, they prefer undergoing non-invasive treatments like Botulinum toxin type A (BTA) injections, for the cosmetic reduction of the bulk and volume of the masseter muscle, thereby narrowing the width of the lower face. Methods A total of 50 patients were enrolled in the study & were injected with 30 U Botox ® each side of face, at baseline. 25 patients received second session of BTA injection at 12th week and the other 25 patients received additional third sessions, at 12th & 24th weeks post the first injection respectively. Standardized photography and ultrasonography were performed to assess facial contour and masseter muscle thickness at baseline and to estimate masseter volume reduction at 4th, 12th, 24th, and 36th week, and at 1, 2, 3, and 4 year follow-ups. Results We observed 12% ($p < 0.0001$) average masseter muscle size reduction at 12th week. The patients who received three injections exhibited very high reduction (42.52%, $p < 0.0001$) of masseter volume at 36th week and maintained an average 40.64% ($p < 0.0001$) reduced volume until the 4th year. Three sessions of BTA injections were more effective in long-term maintenance of reduced masseter volume than 2 sessions of injections ($p < 0.0001$). Conclusions BTA treatment is effective for long-term management of bilateral masseter hypertrophy. To the best of our knowledge, this is the first paper evaluating long term effects of BTA injections for treating Masseter hypertrophy.
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Efficacy of Botulinum toxin in treating Asian Indian patients with masseter hypertrophy: A four years follow-up study

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Efficacy of Botulinum toxin in treating Asian Indian patients with masseter hypertrophy: A four years follow-up study

ABSTRACT

Background: Asian Indians usually have wide lower faces due to masseter hypertrophy, leading to loss of aesthetic parameters such as the Golden Ratio. Therefore, they prefer undergoing non-invasive treatments like Botulinum toxin type A (BTA) injections, for the cosmetic reduction of the bulk and volume of the masseter muscle, thereby narrowing the width of the lower face. We evaluated the efficacy of BTA treatment in long-term management of bilateral masseter hypertrophy in Asian Indian patients.

Methods: A total of 50 patients were enrolled in the study & were injected with 30 U Botox ® each side of face, at baseline. Based, on the thickness of the masseter muscle and response to the BTA Injections, 25 patients received second session of BTA injection at 12^{th} week and the other 25 patients received additional third sessions, at 12^{th} & 24^{th} weeks post the first injection respectively. Standardized photography and ultrasonography were performed to assess facial contour and masseter muscle thickness at baseline and to estimate masseter volume reduction at 4^{th}, 12^{th}, 24^{th}, and 36^{th} week, and at 1, 2, 3, and 4 year follow-ups. p-value < 0.05 was considered as statistically significant.

Results: We observed 12% ($p< 0.0001$) average masseter muscle size reduction at 12^{th} week. The maximum reduction (26.6%, $p< 0.0001$) was observed at 24^{th} week for the patients who received two injections and maintained an average 24.43% ($p< 0.0001$) reduction until 4^{th} follow-up year. The patients who received three injections exhibited very high reduction (42.52%, $p< 0.0001$) of masseter volume at 36^{th} week and maintained an average 40.64% (p<

0.0001) reduced volume until the 4th year. Three sessions of BTA injections were more effective in long-term maintenance of reduced masseter volume than 2 sessions of injections ($p < 0.0001$).

Conclusions: BTA treatment is effective for long-term management of bilateral masseter hypertrophy. Doses of BTA repeated at 12 weekly intervals accentuate masseter volume reduction and also help in maintenance of reduced masseter volume for 4 follow-up years, with satisfactory facial contour. To the best of our knowledge, this is the first paper evaluating long term effects of BTA injections for treating Masseter hypertrophy.

INTRODUCTION

Perception of facial beauty is influenced by culture. Asians have a wider lower-third of the face compared to Caucasians, which is aesthetically less acceptable to females,[1] who prefer an oval or almond-shaped face as the epitome of beauty, compared to a round or a square jaw.[2] The contour of the lower face is determined by the thickness of the mandibular bone, the soft tissues, and the masseter muscle. A square face (wide lower third of the face) appearance is commonly due to a prominent mandibular angle or muscle enlargement, i.e. masseter hypertrophy.[1] A Square shaped face, due to symmetrical or asymmetrical increase in the masseter muscle (masseter hypertrophy), is most common in Asian populations aged between 20 to 40 years.[3,4] The aetiology of masseter hypertrophy is still unknown, although several causes are postulated.[3] To achieve a more aesthetically pleasing ovoid facial shape, Asian patients frequently go for aesthetic alteration through surgical resection of the mandibular angle or the masseter muscle.[5] Although aesthetic surgery provides success in reshaping of the lower face, many patients prefer effective minimally invasive alternative therapy.[5]

OnabotulinumtoxinA (BTA, Botox; Allergan Inc., Irvine, CA) was first approved by FDA for treatment of blepharospasm and later it was approved for treatment of cervical dystonia, strabismus, pain syndrome, severe primary axillary hyperhidrosis, and muscle spasm. BTA also got FDA approval for upper face rejuvenation (glabella frown lines and crow's-feet lines).[6,7] Off-label use of BTA injection into the masseter muscle is now extensively used as alternative non-invasive treatment for masseteric hypertrophy.[2] Various studies demonstrate that, use of BTA treatment provides long-term effect on cosmetic reduction of masseter muscle volume, in a dose dependent manner, to narrow the width of the lower face in various ethnicities.[1,2, 4, 8, 9]

The effect of BTA is temporary and repeated injections are required to maintain the reduced masseter volume. [9] A number of studies have been conducted for standardization of BTA dose in effective treatment of masseter hypertrophy, for lower facial remodelling, in various populations, [6,8,9] including the on-going phase-II clinical trial (NCT02010775) [10] of Botox® (Allergan, Irvine, CA, USA). Data suggests that injection of 30 IU BTA per side, significantly reduces gross masseter size.[7]

Width of lower face in Asian Indians is lesser than Southeast Asians, but greater than Caucasians. Therefore, masseter hypertrophy is also less common in Asian Indians than in other Asians.[11]Although, the BTA treatment for masseter hypertrophy and facial remodelling is reported in various populations, limited studies have been done to evaluate the efficacy of masseter hypertrophy reduction in the Indian population with BTA injections. In a study by Sharad, 25 Indian patients of bilateral masseter hypertrophy were treated with BTA and followed-up for up to a year. This study demonstrated that a single injection of 25- 30 U for females and 30- 35 U for males are adequate to maintain cosmetically acceptable reduction of the masseter muscle size, for a year.[12] In a single case study of a male patient, Bhattacharjee et al, observed that 25 U BTA injection maintains appropriate facial contour till 24 months.[13] Therefore, BTA treatment can help to narrow the lower face of Asian Indians too, but the dose and its long-term efficacy needs to be further evaluated.

In this study, we assessed the effects of injection of 30 U BTA in long-term management (4 years follow-up) of bilateral masseter hypertrophy in Indian patients.

MATERIALS AND METHODS

Patients

We conducted a prospective interventional trial, with patients treated for lower face reshaping, at The Esthetic Clinics, during May 2014 - May 2018. Subjects below 18 years of age, pregnant and lactating females, patients with local trauma, mental stress, dental problems, bruxism, bony mandibular prominence, cow's milk protein allergy, myasthenia gravis, amyotrophic lateral sclerosis, history of receiving BTA treatment for lower face reshaping in preceding 12 months, and non-Indian origin were excluded from this study. Finally, a total of 50 (29 male, 21 female, mean age 40.5±19.5) bilateral masseter hypertrophy patients of Asian Indian origin, wanting to get a smaller, more aesthetic lower face, were enrolled in this study. Written consent was obtained from all the enrolled patients. Institutional Review Board Approval was obtained for this trial.

Dilution and Dosage

One vial of Onabotulinum toxin A (Botox®, Allergan, Irvine, CA, USA), containing 100 units of lyophilized BTA, was reconstituted in 2 ml of non- preserved normal saline, yielding a final concentration of of 5 U /0.1 ml.

BTA injection

Firstly, a safe area for the injections was established by delimiting a line between the mouth angle and the lower implantation of the ear, with patients strongly grinding their teeth. Anterior and posterior edges of the muscles were also outlined, with the ramus of the mandible being the lower border of the area. This is considered the safety zone, because there are no important anatomical structures under the mouth corner/earlobe line. Using a 26 G 1-inch tuberculin syringe, a total 30 IU of Botox® were injected on each side of face. 10 IU of Botox® was

injected at the center of the muscle and 10 IU each at the upper and the lower points, 1 cm away from the initial point, as shown in **Figure, Supplemental Digital Content 1,** which shows the safe area (marked with black marking) for application of BTA injection, INSERT HYPER LINK.[8,9]

Sessions: The injections were performed at baseline (Session 1), 12th week (Session 2), and 24th week (Session 3) and the patients were followed up for 4 years. The number of injection sessions required for patients were determined based on the initial thickness of the masseter muscle.

Efficacy measurements

Subjective and Objective Scales were used for measurement. Under Objective Assessment,the volume of masseter muscle was measured at baseline, 1, 3, 6 months, 1 year, 2 year, 3 year, and 4 years after treatment, using B-scan ultrasonography (USG) (8 M Hz), and the mean thickness reduction of masseter muscle for both the sides of the face was calculated. Clinician assessment scores and patients' self-assessment scores were used under Subjective Assessment. Standardized photographic documentation was obtained at baseline, 1, 3, 6, 12 months and every yearly follow-up visit thereafter until 4th year, using identical camera settings, lighting, and patient positioning. Independent clinical assessments of masseter reduction were evaluated by three blinded plastic surgeons, by comparing the photographs **(See Figure, Supplemental Digital Content 2,** which shows the change of facial contour after Botulinum toxin type A injection.**A)** Baseline photograph of a 29 years old woman, **B)** After 12 weeks, post first session, **C)** After 12 weeks post second session, **D)** After twenty four weeks post third session. **E)** Baseline photograph 28 years old man, **F)** After 12 Weeks Post first session, **G)** After12 weeks post second session, **H)** After 4 years post second session. Note:- The regain in bulk of muscle. **I)** Baseline photograph of a 21 years old women, **J)** After12 Weeks Post first session, **K)** After

12 weeks post second session, **L)** After 4 years post third session, Note the sustained effect of BTA in maintain the reduction of muscle after 3 sessions of injections. **M)** Baseline Photograph of a 28 years woman, **N)** After 12 Weeks Post first session, **O)** After12 weeks post second session, **P)** After 4 years post second session. Note:- The regain in muscle volume after 2 sessions of BTA injections, INSERT HYPER LINK**).** For patients' self-assessment scores, questionnaires for the assessment of pain, adverse effects, and satisfaction were used on a scale of 0-5, as shown in **Table 1** and **2**.

Statistical analysis

For each patient group, mean thickness of masseter muscle and percentages of masseter reduction were calculated using descriptive statistics. The mean differences of masseter muscle volume reduction between each follow-up visit within one group or between two groups were calculated using paired-samples *t*-test. All statistical analyses were performed using IBM SPSS Statistics 24.0. A p-value < 0.05 was considered statistically significant.

RESULTS

We observed that both of our patient groups, showed an average 8.4% ($p < 0.0001$) and 12% ($p < 0.0001$) masseter muscle reduction from the baseline, at 4^{th} week and 12^{th} weeks respectively.

While we observed a 26.6% ($p< 0.0001$) masseter muscle reduction from baseline at 24^{th} week for the group of patients who received 2^{nd} injection at 12^{th} week, it was 19.81% ($p< 0.0001$) for the other patient group.

However, At 36^{th} week, in the group of patients who received 3^{rd} dose of injection at 24^{th} week, we observed a dramatic reduction (42.52%, $p<0.0001$) of masseter volume (**Table 3**, **Figure 1**). The maximum effect of BTA in reducing the masseter volume was 26.6% ($p< 0.0001$) at 24^{th} week for the patients who received the second dose of BTA at 12^{th} week.

There was significant regain in volume of masseter muscles at 1, 2, 3, and 4 follow-up years for patients who underwent two sessions of BTA injections. However patients who had undergone three sessions of BTA injections, showed a statistically significant ($p < 0.0001$) sustained effect of BTA until 4th year from the baseline. Thus, 3 injections help in long-term management of bilateral masseter hypertrophy, as compared to 2 injections (**Table 3, Figures 1-2**).

No significant side effects were noted, post the injections. There was mild pain noted at the sites of injections, post the injections in 20% patients, especially on mastication. This pain lasted for approximately 24 hours post the injections. Headaches were noted in 2 patients, after the first injection, but these patients did not note headaches post the subsequent injections.

DISCUSSION

The cause of masseter muscle hypertrophy is unknown. Painless enlargement of the angle of the jaw between the ages of 20 to 40 years without any gender specification is the most common presentation, but the literature also describes some patients with localized pain and trismus.[14]

BTA produces its therapeutic effect by acting selectively on peripheral cholinergic motor nerve endings to inhibit the release of the neurotransmitter acetylcholine at the neuromuscular junction.[15] The effectiveness of BTA as an off-label drug in reducing lower facial masseter muscle has been proven by several studies [1, 2,4,8,9] and 20-50 U intra muscle injection of BTA is recommended depending on the masseteric muscle thickness.[16]

However, the efficacy of BTA in reducing masseter muscle volume varies in different studies. While, Kim et al (2003) observed a 22% reduction; Yu et al (2007) reported 31% reduction in masseter volume after BTA treatment.[17, 18] A very low percentage of reduction (11.9%) was observed by Klein et al (2014) in the Brazilian population.[8] Similarly, data suggests that the effect of BTA is temporary and it is diminished within 4 to 6 months after injection.[9] Therefore, repeated injections are required to maintain the reduced masseter volume. A detailed meta-analysis [19] was unable to identify any Randomized Clinical Trials or Controlled Clinical trials assessing the efficacy and safety of intra-masseteric injections of botulinum toxin for people with bilateral benign masseter hypertrophy. The authors emphasised the absence of high level evidence for the effectiveness of this intervention & the need for well-designed, adequately powered trials to prove the efficacy.

These facts suggest that a standardised dose and duration of the effect of BTA in treatment of masseter hypertrophy is yet to be determined.[6,8,9] The on-going phase-II clinical trial (NCT02010775)[10] is aimed to evaluate the safety and efficacy of a range of doses of Botulinum toxin Type A (Botox®) towards the dose standardization in treatment of masseter hypertrophy.

As repeated injections are required to maintain reduced masseter volume and lower facial symmetry, we performed the BTA injections at 12 weekly intervals, in two groups of patients: one group received 2 injections and the other received 3 injections. Similar to previous reports,[8] we observed a statistically significant ($p<0.0001$) reduction of masseter muscle volume after 12 weeks, post initial injection of 30 U BTA per side. In our study, the observed reduction at 12th week was ~12%from the baseline, which is similar to the findings in Brazilian females, who received 90 U BTA.[8]

Although, Yu et al achieved a 31% reduction of masseter volume in Asian women at 6th month after a injecting a single comparable dose of BTA[18]; but they reported gaining of the muscle bulk after nine months period.[18] We achieved maximum reduction of masseter volume of 26.6% ($p < 0.0001$) at 6th month after 2nd injection (**Table 3, Figure 1**).

However, we achieved 42.52% ($p \leq 0.0001$) reduction in masseter volume from the baseline at 36th week in the patients who received 3rd dose of BTA at 24th week. On the other hand, the patients who received 2nd dose of BTA at 12th week exhibited 24.03% ($p < 0.0001$) reduction at 36th week (**Table 3, Figure 2**). These results suggest that, low but repeated dose of BTA can reduce masseter volume more effectively than single dose as reported by Lee et al.[20]

In an Indian study, a 35 years male patient exhibited 22% to 29% reduction of masseter thickness and maintains a satisfactory facial contour at 24 weeks after single BTA injection of 25 IU.[13]However, the sustained effect after 24 months was not reported in this case. Kim et al,[19] who followed up patients until 52 months, reported an increased frequency or repeated injections sustained tong-term BTA effect.

We followed up on our patients until 4 years, and similar to the observation of Kim et al, we found that the patients who received 3 injections maintain better mean reduction (40.64%, $p<0.0001$) of masseter volume, compared to the patients who received 2 injections (24.43%, $p<0.0001$) till 4th year. The difference of the reduction between these two groups is also highly significant ($p<0.0001$) (**Figure 2**) indicating that, BTA can effectively be used for long -term management of bilateral masseter hypertrophy in Asian Indian patients, where 3 injections is a better, more efficacious approach than single dose.

How did the effect of BTA for masseter hypertrophy last so long? The answer to this may be that the mechanism of action of BTA in masseter hypertrophy may be different from the mechanism of action of BTA for hyperkinetic lines & wrinkle treatment. BTA, when injected in high concentrations, may cause cell apoptosis, leading to atrophy of the masseter muscle. Repeated injections may prevent the muscle fibres from regenerating and therefore the muscle atrophy may be semi-permanent or even permanent. This has been proven in multiple animal studies [21, 22] It has also been shown that human jaw muscles are very different from other skeletal muscles and that, post atrophy, the regeneration of these muscles may be limited. [23] The combination of cell apoptosis, occurring in a muscle which has limited regenerative capacities makes BTA for masseter hypertrophy work very well, without any impact on chewing or mastication activities.

CONCLUSION

Botulinum toxin A is equally effective in treating bilateral masseter hypertrophy of Indian patients irrespective of age or gender. Our long-term follow-up analysis of 4 years demonstrates that standard dosages, but three injections at 12 weeks interval, gives better reduction of mean masseter volume, compared to two injections. The repeated injection is also found highly beneficial in long -term management of bilateral masseter hypertrophy, with maintenance of desired facial contour and patient satisfaction. No significant side effects were noted, post the BTA injections. This may be due to our injection technique, deep and into the mass of the masseter muscle. To the best of our knowledge, this is the first clinical study evaluating & analysing the long term effects of BTA injections, for masseter hypertrophy.

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TABLE AND FIGURE LEGENDS

Table 1: Patients Satisfaction Assessment Scores.

Table 2: Pain Assessment Scores

Table 3: The average percentage of masseter volume reduction in two groups of patients at various follow-up times

Figure, Supplemental Digital Content 1. Safe area (marked with black marking) for application of BTA injection, INSERT HYPER LINK.

Figure, Supplemental Digital Content 2. The change of facial contour after Botulinum toxin type A injection.**A)** Baseline photograph of a 29 years old woman, **B)** After 12 weeks, post first session, **C)** After 12 weeks post second session, **D)** After twenty four weeks post third session. **E)** Baseline photograph 28 years old man, **F)** After 12 Weeks Post first session, **G)** After12 weeks post second session, **H)** After 4 years post second session. Note:- The regain in bulk of muscle. **I)** Baseline photograph of a 21 years old women, **J)** After12 Weeks Post first session, **K)** After 12 weeks post second session, **L)** After 4 years post third session, Note the sustained effect of BTA in maintain the reduction of muscle after 3 sessions of injections. **M)** Baseline Photograph of a 28 years woman, **N)** After 12 Weeks Post first session, **O)** After12 weeks post second session, **P)** After 4 years post second session. Note:- The regain in muscle volume after 2 sessions of BTA injections, INSERT HYPER LINK.

Figure 1. The average percentage of masseter volume reduction in patients at various follow-up times.

Figure 2. Relationship of the maximal effect and the sustained effect of BTA in masseter volume reduction in two groups of patients.

Table 1: Patients Satisfaction Assessment Scores

Scale	Improvement
0	(none or worsening- No Improvement
1	If improvement present, then how much is the improvement in percentage 1-20%
2	21-40%
3	41-60%
4	61-80%
5	81-100%

Table 2: Pain Assessment Scores

Score	Pain
0	No pain
1	Very Mild Pain
2	Mild Pain
3	Moderate Pain
4	Severe Pain
5	Very Severe Pain

Table 3: The average percentage of masseter volume reduction in two groups of patients at various follow-up times

Follow up duration	**2 Sessions** (% of mean MM Vol reduction)	
Weeks / Years	Mean ± SD	**Level of significance** (2 Sessions)
Week 0	14.472 ± 11.2847	p< 0.0001
Week 4		
Week 12		
Week 24		
Week 36		
Year 1	17.745 ± 2.9093	p > 0.0001
Year 2		
Year 3		
Year 4		

Group: I * p< 0.0001 is considered as significant

Follow up duration	(**3 Sessions** % of mean MM Vol reduction)	
Weeks / Years	Mean ± SD	**Level of significance** (3 Sessions)
Week 0	26.87333 ±16.79286	p< 0.0001
Week 4		
Week 12		
Week 24		
Week 36		
Year 1		
Year 2		
Year 3		
Year 4		

Group: II * p< 0.0001 is considered as significant

Figure 1

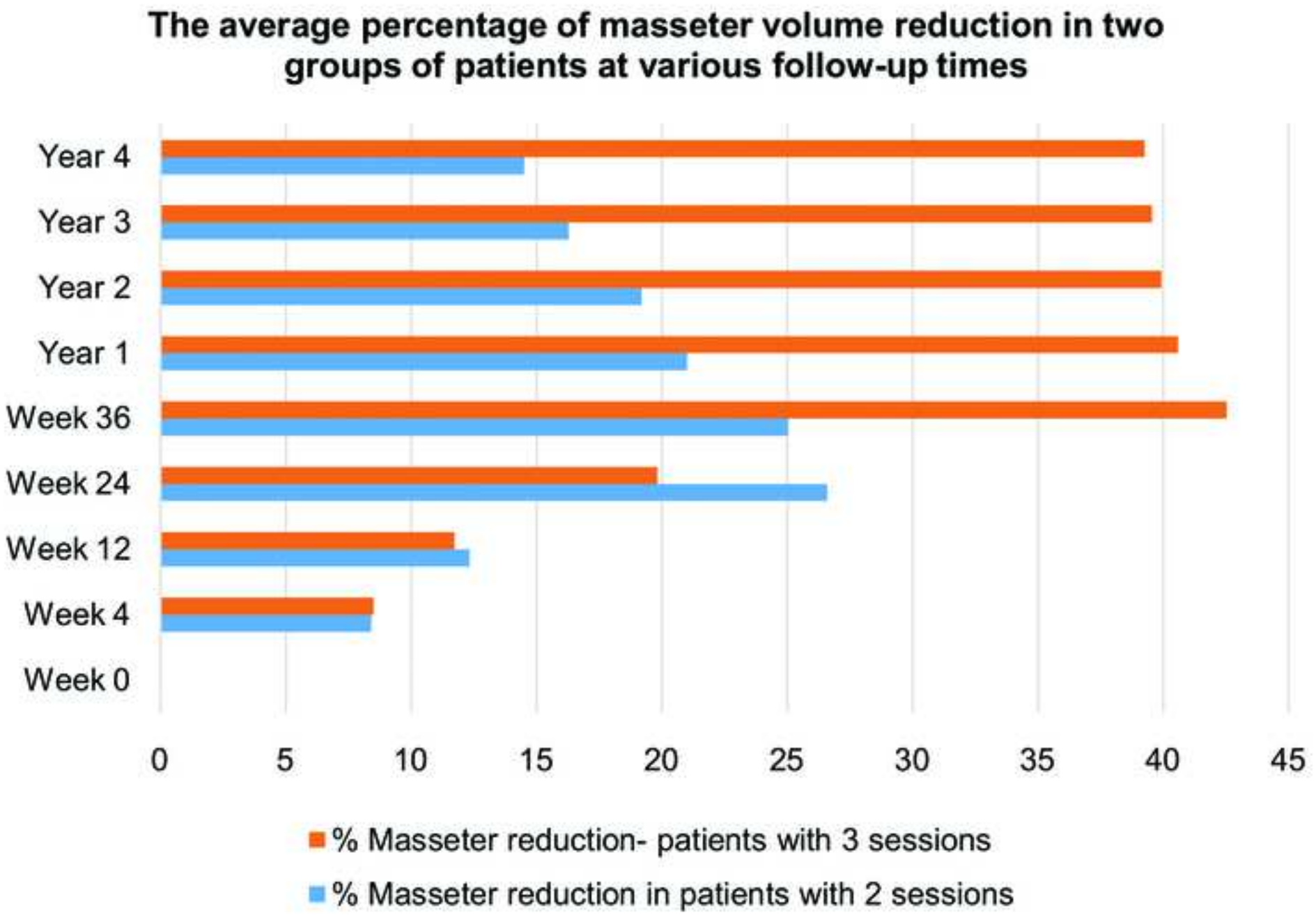
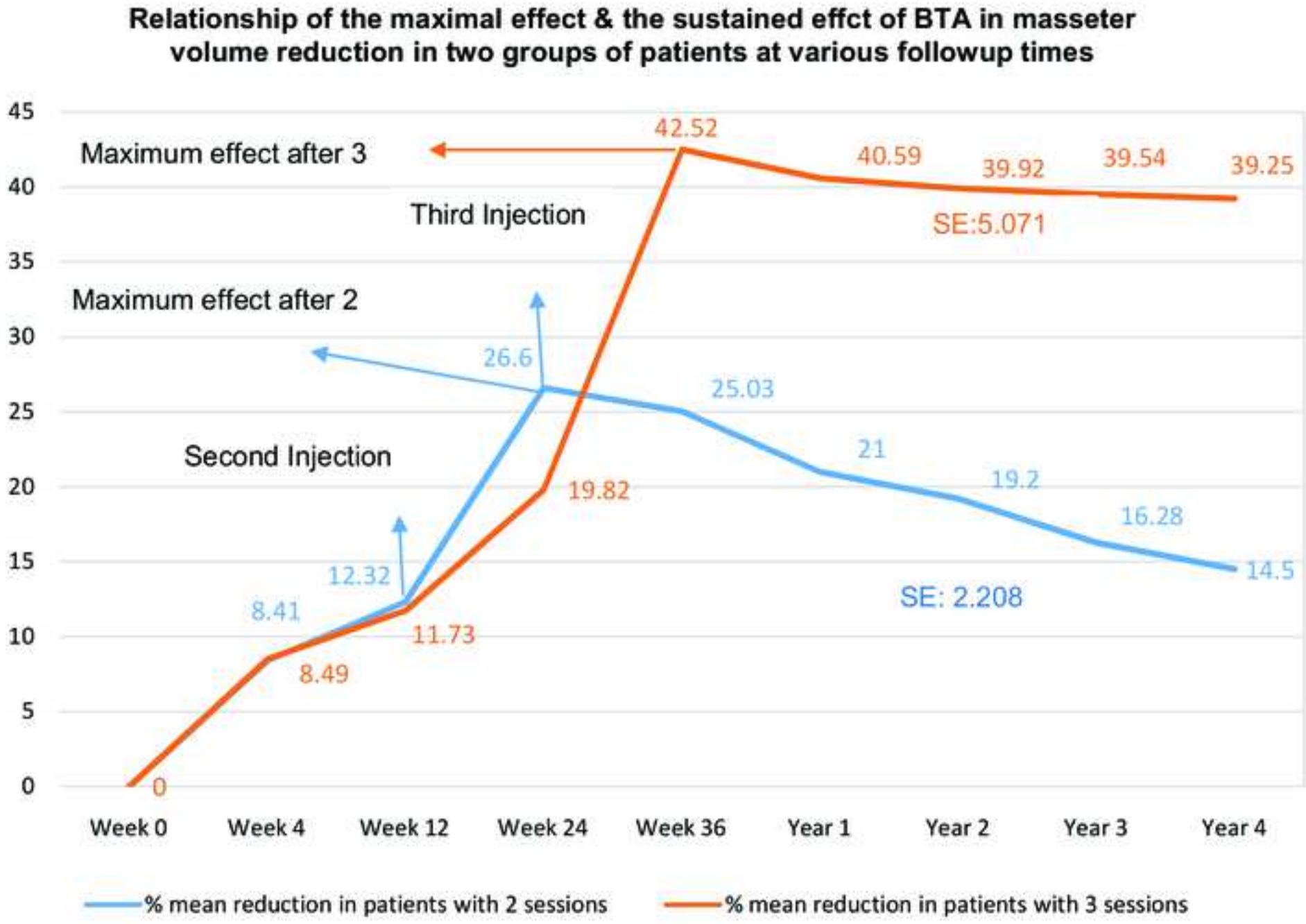


Figure 2



18th July 2018

Editor-in-Chief,

Plastic and Reconstructive Surgery.

Respected Editor,

Enclosed herewith is a manuscript **"Efficacy of Botulinum toxin in treating Indian patients with masseter hypertrophy: A four years follow-up study".**for your kind perusal and consideration for publication in your esteemed journal.

This manuscript reports unpublished work that is not currently under consideration for publication elsewhere.

None of the authors have a financial interest in the subject or techniques described in this manuscript.

I certify that I have participated sufficiently in the conception and design of this work and the analysis of the data (when applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe the manuscript represents valid work. I have reviewed the final version of the submitted manuscript and approve it for publication. Neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere.

If requested, I shall produce the data upon which the manuscript is based for examination by the editors or their assignees.

I certify that we have no affiliations with or involvement in any organization or entity with a direct or indirect financial interest in the subject matter or materials discussed in

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The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, to permit this article (if accepted) to be published in Plastic & Reconstructive Surgery.

Thank you for your consideration.

Sincerely,

Debraj Shome, MD, FRCS, FACS, MBA

Corresponding Author

debraj.shome@theestheticclinic.com

Plastic and Reconstructive Surgery

Rod J. Rohrich, M.D., Editor-in-Chief
Brookriver Executive Center
8150 Brookriver Drive
Suite S-415
Dallas, TX 75247

PATIENT PHOTOGRAPHIC AUTHORIZATION, RELEASE AND DISCHARGE

I consent to the taking of photographs, slides, videotapes and other images ("imaging records") by Dr. Debra Thore or his designee of me or of my likeness or parts of my body in connection with the following plastic surgery procedures(s) Bilateral Breast Reduction performed by Dr. Debra Thore on (Date) 2/17/16 and (location) Mandeville. I further consent to the release and transfer of copyright ownership by Dr. Debra Thore to the American Society of Plastic Surgeons ("ASPS") of such imaging records.

I understand that such imaging records may be published by ASPS and/or any party acting under the license and authority of ASPS in any print, visual, electronic or broadcast media, specifically including, but not limited to, medical journals and textbooks, scientific presentations and teaching courses and Internet websites, for the purpose of informing the medical profession or the general public about plastic surgery methods, results, issues, trends, concerns and similar matters. I further understand that the imaging records shall become the property of ASPS.

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I understand that I have the right to revoke this authorization in writing at any time, but if I do so it won't have any effect on any actions taken prior to my revocation. If I do not revoke this authorization, it will expire ten years from the date written below.

I understand that I may refuse to sign this authorization and such refusal will have no effect on the medical treatment I receive from Dr. Debra Thore.

I understand that the information and likeness disclosed, or some portion thereof, may be protected by state law, federal law and/or the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"). I

further understand that, because ASPS is not receiving the information in the capacity of a health care provider or health plan covered by HIPAA, the information described above may no longer be protected by HIPAA and may be redisclosed by ASPS.

I release and discharge Dr. Deby Thomas, ASPS, and all parties acting under their license and authority from all rights that I may have in the imaging records and from any claim that I may have relating to such use in publication, including any claim for payment in connection with distribution or publication of the imaging records in any medium or any claim arising from the distribution or publication by any third party.

I hereby warrant that I am over twenty-one years of age, and competent to contract in my own name.

I grant this consent as a voluntary contribution in the interest of public education and certify that I have read the above Authorization, Release and Discharge and fully understand its terms.

Patient Sunny Singh. *Date* 21/2/16.

WITNESS/PHYSICIAN: Dr Reiky Kapoor.

I have read the above Authorization, Release, and Discharge. I am the parent, guardian or conservator of _____, a minor. I am authorized to sign this consent on his/her behalf and I grant this consent as a voluntary contribution in the interest of public education.

Parent/Guardian _____ *Date* _____

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I understand that I may refuse to sign this authorization and such refusal will have no effect on the medical treatment I receive from Dr. Debra Thorne.

I understand that the information and likeness disclosed, or some portion thereof, may be protected by state law, federal law and/or the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"). I

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I release and discharge Dr. Debraj Shome, ASPS, and all parties acting under their license and authority from all rights that I may have in the imaging records and from any claim that I may have relating to such use in publication, including any claim for payment in connection with distribution or publication of the imaging records in any medium or any claim arising from the distribution or publication by any third party.

I hereby warrant that I am over twenty-one years of age, and competent to contract in my own name.

I grant this consent as a voluntary contribution in the interest of public education and certify that I have read the above Authorization, Release and Discharge and fully understand its terms.

Patient Gurpreet Chadha *Date* 28/6/2016.

WITNESS/PHYSICIAN: Dr Debraj Shome.

I have read the above Authorization, Release, and Discharge. I am the parent, guardian or conservator of _____, a minor. I am authorized to sign this consent on his/her behalf and I grant this consent as a voluntary contribution in the interest of public education.

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I consent to the taking of photographs, slides, videotapes and other images ("imaging records") by Dr. Debra Thome or his designee of me or of my likeness or parts of my body in connection with the following plastic surgery procedures(s) Abdominoplasty, Liposuction to be performed by Dr. Debra Thome on (Date) and (Location). I further consent to the **release** and transfer of copyright ownership by Dr. Debra Thome to the American Society of Plastic Surgeons ("ASPS") of such imaging records.

I understand that such imaging records may be published by ASPS and/or any party acting under the license and authority of ASPS in any print, visual, electronic or broadcast media, specifically including, but not limited to, medical journals and textbooks, scientific presentations and teaching courses and Internet websites, for the purpose of informing the medical profession or the general public about plastic surgery methods, results, issues, trends, concerns and similar matters. I further understand that the imaging records shall become the property of ASPS.

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I understand that I may refuse to sign this authorization and such refusal will have no effect on the medical treatment I receive from Dr. Debra Thome.

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I release and discharge Dr. Dr. Priya Khanna, ASPS, and all parties acting under their license and authority from all rights that I may have in the imaging records and from any claim that I may have relating to such use in publication, including any claim for payment in connection with distribution or publication of the imaging records in any medium or any claim arising from the distribution or publication by any third party.

I hereby warrant that I am over twenty-one years of age, and competent to contract in my own name.

I grant this consent as a voluntary contribution in the interest of public education and certify that I have read the above Authorization, Release and Discharge and fully understand its terms.

Patient Priya Khanna *Date* 25/8/17

WITNESS/PHYSICIAN: Dr Priya Khanna

I have read the above Authorization, Release, and Discharge. I am the parent, guardian or conservator of _____, a minor. I am authorized to sign this consent on his/her behalf and I grant this consent as a voluntary contribution in the interest of public education.

Parent/Guardian _____ *Date* _____

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I consent to the taking of photographs, slides, videotapes and other images ("imaging records") by Dr. Debra Thorne or his designee of me or of my likeness or parts of my body in connection with the following plastic surgery procedures(s) Rhinoplasty Jaw Reduction performed by Dr. Debra Thorne, 2012/17, Mentoplasty on (Date) and (Location). I further consent to the **release** and transfer of copyright ownership by Dr. Debra Thorne to the American Society of Plastic Surgeons ("ASPS") of such imaging records.

I understand that such imaging records may be published by ASPS and/or any party acting under the license and authority of ASPS in any print, visual, electronic or broadcast media, specifically including, but not limited to, medical journals and textbooks, scientific presentations and teaching courses and Internet websites, for the purpose of informing the medical profession or the general public about plastic surgery methods, results, issues, trends, concerns and similar matters. I further understand that the imaging records shall become the property of ASPS.

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I understand that I may refuse to sign this authorization and such refusal will have no effect on the medical treatment I receive from Dr. Debra Thorne.

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I release and discharge Dr. Debu Thomas, ASPS, and all parties acting under their license and authority from all rights that I may have in the imaging records and from any claim that I may have relating to such use in publication, including any claim for payment in connection with distribution or publication of the imaging records in any medium or any claim arising from the distribution or publication by any third party.

I hereby warrant that I am over twenty-one years of age, and competent to contract in my own name.

I grant this consent as a voluntary contribution in the interest of public education and certify that I have read the above Authorization, Release and Discharge and fully understand its terms.

Patient Amy Hume *Date* 20/2/17

WITNESS/PHYSICIAN: Dr Debu Thomas

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Parent/Guardian _____ *Date* _____

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I, (We) Dr Debj Shome, Dr Mk Khare, Dr Rinky Kapoor have submitted for publication in *Plastic and Reconstructive Surgery*® a manuscript entitled:

Dr Debj Shome, Dr Mk Khare, Dr Rinky Kapoor

I, (We) hereby certify, that:

No financial support or benefits have been received by me or any co-author, by any member of my (our) immediate family or any individual or entity with whom or with which I (we) have a relationship from any commercial source which is related directly or indirectly to the scientific work which is reported on in the article except as described below.

I (we) understand an example of such a financial interest would be a consulting relationship or stock interest in any business entity which is included in the subject mater of the manuscript or which sells a product relating to the subject matter of the manuscript.

In addition to filling out and signing this declaration, *I acknowledge that I (we) also made complete disclosure in the manuscript itself*, stating all sources of funds that have supported this work and also a statement of financial interest, if any. Each author on the manuscript has disclosed any commercial association or financial disclosure that might pose a conflict of interest with information presented in this manuscript. *If the authors have no financial interest or commercial association with any of the subject matter or products mentioned in our manuscript, that too will be indicated.* I (we) hereby agree that such disclosures will be printed with the manuscript if it is accepted.

Furthermore, I (we) understand that potential sanctions may be imposed by *Plastic and Reconstructive Surgery* for violation of this complete disclosure policy. I (we) understand that potential disciplinary actions may include warning letters, refusal to publish an article in question, retraction of a published paper, notification to our primary institution, and/or exclusion from publication in *Plastic and Reconstructive Surgery* for a specified time frame.

The corresponding author has the obligation of having any and all co-authors sign this form and date his or her signature.

Debj 3/7/18
Signature and Date

Mk 3/7/18
Signature and Date

Rinky 3/7/18
Signature and Date

CHICAGO/#2123828.3

______________________________ PRS-D.__-____
Enkwell Corresponding Author Last Name (Please Print) Enkwell Number

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2. Some of the material in this paper has been, or is being published elsewhere. Details are in the appended letter.

Signed: ______________________

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Signed: ______________________ Date: 3/2/18
Signed: ______________________ Date: 3/2/18
Signed: ______________________ Date: ______
Signed: ______________________ Date: ______
Signed: ______________________ Date: ______
Signed: ______________________ Date: ______

CHICAGO/#2139023.2

Declaration of Authorship for *(title)* "Efficacy of Botulinum toxin in treating Asian Indian Patients with Mentalis hyperactivity: A four years follow up study". for Plastic and Reconstructive Surgery

Author Name	Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (initial here)	Drafting the work or revising it critically for important intellectual content; (initial here)	Final approval of the version to be published; (initial here)	Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; (initial here)	By placing my SIGNATURE below, I attest that I meet all four criteria of authorship for this article and am legally responsible for the content here in.
① Dr Debraj Shome.	Shome	Shome	Shome	Shome.	Debraj
② Dr Ketki Khare.	Khare	Khare	Khare	Khare	Ketki
③ Dr Rishi Kapoor	Kapoor	Kapoor	Kapoor	Kapoor	Rishi

Enkwell Corresponding Author Last Name (Please Print)

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Signed: Debraj Date: 3/7/18

Signed: Date: 3/7/18

Signed: Date: 3/7/18

Signed: Date:

Signed: Date:

Signed: Date:

Signed: Date:

_____ PRS-D-___-_____

Enkwell Corresponding Author Last Name (Please Print) Enkwell Number

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Signed: _____ Date: 3/7/17

Signed: _____ Date: _____

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Signed: _____ Date: _____

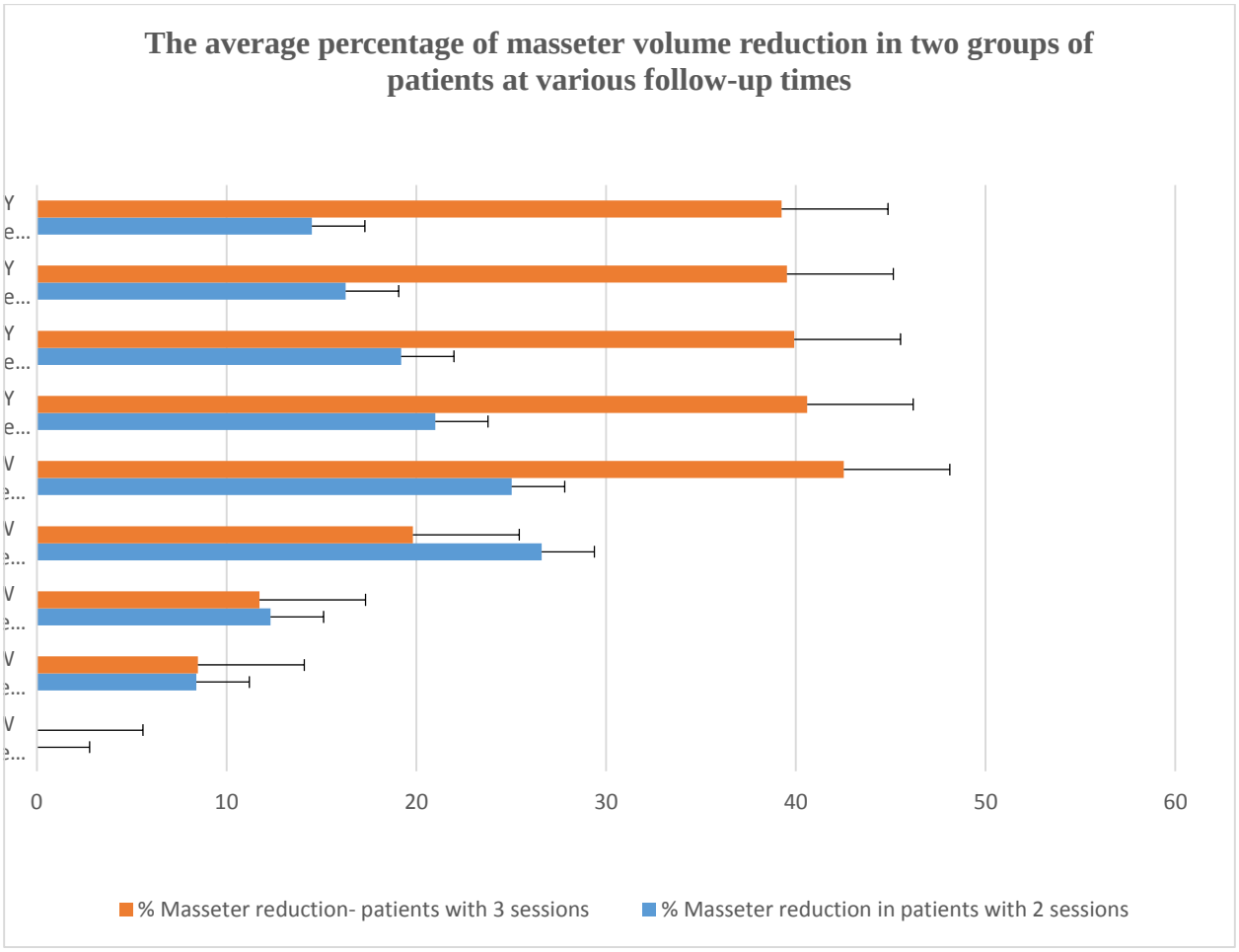
Signed: _____ Date: _____

Reply to Reviewers

Reviewer #4: This article evaluated the efficacy of BTA treatment in long-term management of bilateral masseter hypertrophy among Indian patients. I have several comments regarding the statistical analysis.

1. In Table 3, the SDs should be included with the corresponding means.

DS: Included.



2. In Statistical Analysis, the authors stated that "The mean differences … between each follow-up visit within one group or between two groups were calculated using paired-samples t-test.". It is not clear how the paired-sample t-test could compare samples from two different groups (like p-values in the last column of Table 3).

DS: According to the data normality test, our data was distributed normally. Paired tests are used when there are two measurements on the same experimental unit. Hence, we chose a parametric test & the two groups were calculated using the paired-samples t-test. Regarding p values, they

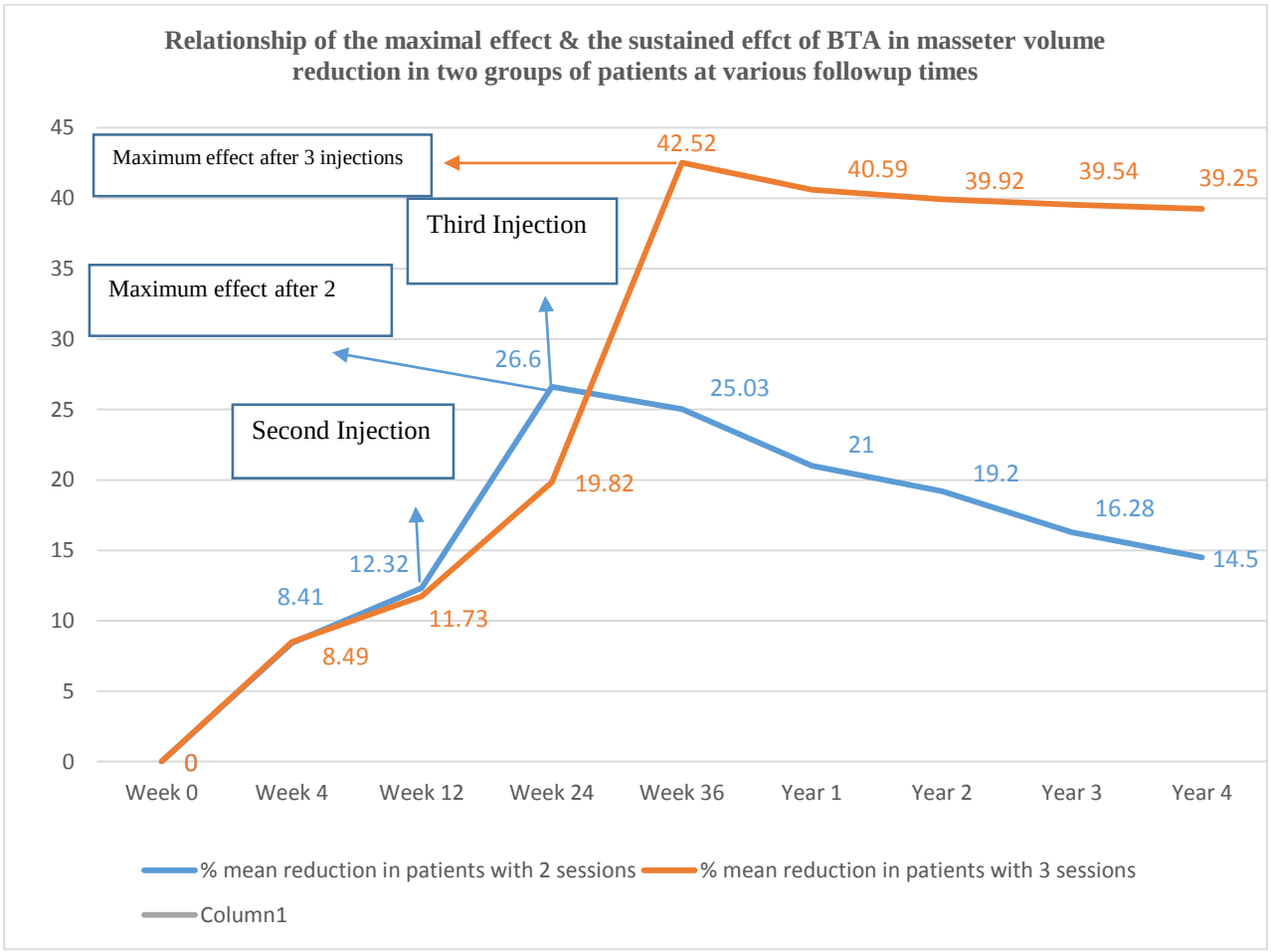
were repeated multiple times. So,mwe revised the table for better understanding and interpretation.

3. In Figure 3, the standard error (SE) bars should be included on top of their corresponding means.

DS: Included, as above.

4. In Figure 4, it would be informative if the means with the SEs are included at the time points.

DS: Included.



Reviewer Q4: In Figure 4, it would be informative if the means with the SEs are included at the time points.

DS: Suggested changes done.

Plastic and Reconstructive Surgery

Rod J. Rohrich, M.D., Editor-in-Chief
Brookriver Executive Center
8150 Brookriver Drive
Suite S-415
Dallas, TX 75247

PATIENT PHOTOGRAPHIC AUTHORIZATION, RELEASE AND DISCHARGE

I consent to the taking of photographs, slides, videotapes and other images ("imaging records") by Dr. Debraj Shome or his designee of me or of my likeness or parts of my body in connection with the following plastic surgery procedures(s) Botox for masseter Hypertrophy to be performed by Dr. Debraj Shome on 23/11/2017 and Mumbai. I further consent to the **release** and transfer of copyright ownership by Dr. Debraj Shome to the American Society of Plastic Surgeons ("ASPS") of such imaging records.

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I understand that I have the right to revoke this authorization in writing at any time, but if I do so it won't have any effect on any actions taken prior to my revocation. If I do not revoke this authorization, it will expire ten years from the date written below.

I understand that I may refuse to sign this authorization and such refusal will have no effect on the medical treatment I receive from Dr. Debraj Shome.

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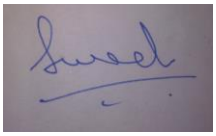
I hereby warrant that I am over twenty-one years of age, and competent to contract in my own name.

I grant this consent as a voluntary contribution in the interest of public education and certify that I have read the above Authorization, Release and Discharge and fully understand its terms.

Patient  *Date* 23/11/2017

WITNESS/PHYSICIAN: Dr. Debraj Shome

I have read the above Authorization, Release, and Discharge. I am the parent, guardian or conservator of _____, a minor. I am authorized to sign this consent on his/her behalf and I grant this consent as a voluntary contribution in the interest of public education.

Parent/Guardian _____ *Date* _____

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