Botulinum Toxin A in Treatment of Facial Flushing

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Abstract- Flushing is a condition with episodic attacks of redness of the skin with a sensation of warmth or burning, this disease causes emotional and functional problems in patients. There is various treatments for this condition; one of them is the use of botulinum toxin A (BTA). In this prospective pilot study we studied the effect of Botulinum toxin A (BTA) effect on DLQI of patients with facial flushing, we compared the DLQI before and after treatment. The number of 24 women with facial flushing admitted to the department of dermatology of Hamadan Farshchian Hospital, with the age range of 18 to 60 was enrolled in the study. Patients completed Dermatology Quality of life Index questionnaire before and one month after treatment. In our study 1 unit of BTA was injected intracutaneously per square cm in both sides of cheeks, to a total dose of 30 units per session. All of 24 patients completed the study. The mean age was 37.79±13.13. In all patients, DLQI decreased, and in two months follow up, the mean of DLQI improved from 8.08±1.17 to 4.5±1.21 (*P*.value<0.005). Based on this study BTA is an effective and safe treatment for facial flushing.

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Keywords: Flushing; Botulinum toxin A; Injection

Introduction

Flushing is a condition with episodic attacks of redness of the skin with a sensation of warmth or burning of the face, neck and less frequently the upper trunk (1). This is a common complaint of dermatologic patients, and it is more common in the fair skin (2). The term of FLUSH was described in 1882. Flushing can be episodic or constant; repeated attacks lead to fixed erythema, telangiectasia and a cyanotic background of the face (3).

A higher than expected reaction to environmental stimuli in patients who have a lower threshold of reaction also creates the condition in which it is also called Blushing (4).

Erythema confined to blush areas of the face, has the following causes: 1-anatomic evidence for greater capacities in superficial facial cutaneous vasculature 2- less tissue fluid for obscuring the vessels 3-blood vessels of this area are more wider 4- the vessels are closer to the skin in blush area (5).

The mechanism of flushing is complex: postganglionic sympathetic beta-adrenoreceptor stimulation causing vasodilation (6) it can be due to substances which have a direct effect on vascular smooth muscle such as histamine or may be due to vasomotor nerve involvement (1,3).

There are variety of causes for this condition such as: acne rosacea, menopause, hyperthermia and fever, emotional, drugs (such as: all vasodilators, nitroglycerin, calcium channel blockers, morphine and Opiates, cholinergic drugs) and special foods and alcohol consumption and some significant disease such as: carcinoid syndrome, pheochromocytoma, mastocytosis, medullary cell carcinoma of thyroid and renal cell carcinoma (3,7).

The more common causes are menopause, acnea rosacea and emotional or physiologic (1).

Patient history and physical examination are necessary for evaluation of flushing and should be completed with laboratory tests and other investigations based on the clinical suspicion of an underlying cause.

Hypnosis, psychotherapy, and biofeedback have been used in a limited number of patients (8), propranolol and surgical procedure (endoscopic transthoracicsympathectomy) are available too (6) but most of these treatments are unsatisfactory.

One of the new methods of treatment is the use of Botulinum toxin A (BTA). We studied the effect of Botulinum toxin A (BTA) on the treatment of flushing in this article. The aim of our study was to verify the effectiveness and safety of this new method, the

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intradermal injection of botulinum toxin A.

Materials and Methods

Our study was an open-labeled randomized control trial. After clinical evaluation and laboratory tests if necessary, for some condition such as carcinoid syndrome, pheochromocytoma, mastocytosisand *etc*., a total of 24 women with facial flushing referred to Hamadan Farshchian Hospital, department of dermatology as outpatients in 2014 were recruited to the study. A complete medical history was obtained from each patient. Risks, benefits, and al probable side effects were completely explained; informed consent sheet was completed by patients.

The period of our study was two months. The age range was 18 to 60. Exclusion criteria were:

Pregnancy, systemic medication, males, clinical and laboratory abnormalities indicating the secondary flashing and systemic significant disease.

In the first visit all patients completed the DLQI papers that represent the subjective assessment of disability resulting from the symptoms of flushing in the patients. The DLQI includes 10 questions related to work and daily activities, personal relationships, and treatment. The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self-explanatory and the patients can easily fill out the questionnaire (9).

For treatment 1 unit of Botulinum toxin A (BTA) was injected intracutaneously in every square cm, to a total dose of 30 units per session on both sides of cheeks. After one month, papers of DLQI were filled by patients again.

Results

Twenty four women with facial flushing were evaluated in this study. After statistical evaluation, the following results were obtained:

The age range was 18 to 60. The average age was 37.79±13.13.

Six patients (25%) with rosacea, 10 patients (41.7%) with menopause and 8 patients (33.3%) with idiopathic or physiologic flushing were enrolled into the study.

In all patients DLQI decreased, in two months follow up, the mean of DLQI improved from 8.08±1.17 to 4.5±1.21.

Table 1. DLQI before and after treatment

Patients number	Age	DLQI(1)	DLQI(2)	Patients number	Age	DLQI(1)	DLQI(2)
1	24	7	3	13	18	9	7
2	32	6	4	14	33	8	5
3	33	8	5	15	28	7	4
4	37	7	3	16	49	10	7
5	55	9	4	17	21	9	5
6	48	9	5	18	24	6	4
7	21	8	5	19	58	7	4
8	58	8	4	20	47	8	3
9	52	8	5	21	39	9	3
10	48	10	6	22	29	8	3
11	34	9	5	23	56	10	6
12	42	7	3	24	21	7	5
Mean ofAge=37.79 Sd= 13.13 Min =18 Max = 58		**Mean of DLQI(1)=8.08 Sd=1.176 Min=6 Max=10**				**Mean of DLQI(2)=4.5 Sd=1.215 Min=3 Max=7**	

After using paired samples T test, this 3.58 improvement in DLQI was significant (*P*=0 and <0.005).

The post-treatment appearance of the patients was dramatic, and the patients were highly satisfied with thecosmetic outcome.

Discussion

As mentioned, flushing is due to a variety of disorders, in this study, we had three groups of patients:

1) Acne rosacea, a chronic recurrent inflammatory disease of the skin that occurs in middle-aged patients and is characterized by papules and pustules and erythema of the central region of the face and flushing attacks and is resistant to treatment (10,11).

2) In Menopause, flushing attack is associated with the declining of estrogen levels and can be improved with the use of hormone replacement therapy, but many postmenopausal women do not accept replacement

hormone therapy because of the possible complications associated with them (12). Treatment with Botox injections can be useful and with low risk of complication in these patients (7,12).

3) Patients with idiopathic or unknown cause, mostly due to emotional causes. The emotional role in flushing is specified with reduction of symptoms during sleep (8), and in some patients, thethreshold for this response may be lower (6).

Various treatments have been used to control the flushing. One of the new methods in treatment of this condition is the use of different lasers such as pulsed dye (585 to 595 nm) laser, the long-pulsed KTP (532 nm) laser, the Nd:YAG (1064-nm) laser, and intense pulsed light therapy, for treating fixed facial redness and telangiectasias, but cannot prevent the occurrence of flushing attacks (2).

Botulinum toxin A is being increasingly used in treatment of several disorders and is a new proposed treatment, that can be used to prevent attacks of flushing, that inhibits the release of neurotransmitter acetylcholine (Ach) from the axon terminals of motor neurons, preganglionic sympathetic and parasympathetic neurons, and postganglionic parasympathetic neurons and also prevents the secretion of sweat. Side effects of this therapy are limited and reversible (13-15) and the ultimate effect had a significant impact on hyperfunction of the eccrine gland.

In all of our cases, the injection of botulinum toxin resulted in an obvious improvement in symptoms between the two to three weeks of treatment. No secondary side effects were reported by the patients or noted by the examiners, except for mild discomfort during intradermal injection of the (BTA).

Very different doses of Botox is used to treat flushing in various studies (16-18), And all of them are associated with response to treatment.

In this study, we used 1 unit of Botulinum toxin A (BTA) injection, to a total dose of 30 units per session, in comparison of two different doses (20 units and 75 units) of botulinum toxin A in one study at 2005, higher doses has been associated with faster response and longer treatment (16). Since the follow up period in our study was one month, determination of the time of recurrence was impossible, but the aim of the present study just was to determine the usefulness of BTX (A) response in heterogeneous groups of patients.

According to the previous reports, patients have requested additional injections 4 to 17 months after the first treatment, but there are no explicit criteria for the dose and frequency of the subsequent treatments, it seems that new nerve endings growth within three months after injection of Botulinum toxin A, could be the reason of the need for re-injection (19). Further studies are needed to evaluate this issue.

No deaths were reported for cosmetic cases and the most commonly reported side effects following the injection of (BTA) are similar to those that occurred among therapeutic cases, and are reported mainly relate to pain on injection and also includes headaches, focal facial paralysis, muscle weakness, dysphagia, flu-like syndromes, and allergic reactions (20,21). None of the above was reported by patients in our study because these side effects usually occur in patients who received higher doses and also have complicated underlying diseases.

Although this treatment is also minimally invasive, but can be well tolerated, and can be repeated with no loss of efficacy as a simple office procedure, and our data suggest that (BTA) can be recommended as a treatment of flushing because it is highly effective and safe, and can provide long-lasting symptom relief.

References

1. Boloux PM. Sweating and flushing: evaluation and management. ENDO 2003. (Accessed March 3, 2016, at http://sessions.endocrine.org/s/2013an/endo/M58).
2. Yuraitis M, Jacob CI. Botulinum Toxin for the Treatment of Facial Flushing. Dermatol Surg 2004;30:102-4.
3. Izikson L, English JC, Zirwas MJ. The flushing patient: Differential diagnosis, workup, and treatment. J Am Acad Dermatol 2006;55:193-208.
4. Oh YJ, Lee NY, Suh DH, Koh JS, Lee SJ, Shin MK. A split-face study using Botulinum Toxin type B to decrease facial Erythema index. J Cosmet Dermatol 2006;5:268-72.
5. Wilkin JK. Why is flushing limited to a mostly facial cutaneous distribution. J Am Acad Dermatol 1988;19:309-12.
6. Sterodimas A, Nicolaou M, Paes TRF. Successful use of Botulinum toxin A for the treatment of neckand anterior chest wall flushing. Clin Exp Dermatol 2003:28:592-4.
7. Friedman BS, Germano P, Miletti J, Metcalfe DD. A clinicopathologic study of ten patients with recurrent unexplained flushing. J Allergy ClinImmunol 1994;93:53-60.
8. Hashmonai M, Kopelman D, Assalia A. The Treatment of Primary Palmar Hyperhidrosis: A Review. Surg Today 2000;30:211-8.
9. Companati A, Penna L, Guzzo T, Menotta L, BSilvestri B, Lagalla G, et al. Quality of life assessment in patients

with hyperhidrosis before and after treatment with Botulinum toxin: Result of an open label study. Clin Ther 2003;25:298-308.

10. Parish LC, Witkkowski JA. Acne rosacea and Helicobacter pylori betrothed. Int J Dermatol 1995;34:237-8.
11. Jansen T, Plewig G. Rosacea: classification and treatment. J R Soc Med 1997;90:144-50.
12. Kim WO, Kil HK, Yoon KB, Yoo JH. Treatment of Generalized Hyperhidrosis with Oxybutynin in Postmenopausal Patients. ActaDermVenereol 2010;90:291-3.
13. Matarasso SL. Treatment of facial chromhidrosiswithbotulinum toxin type A. J Am Acad Dermatol 2005;52:89-91.
14. Cote TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type A injections: Adverse events reported to the US Food and Drug Administrationintherapeutic and cosmetic cases. J Am Acad Dermatol 2005;53:407-15.
15. Cohen AA, Blitzer A. Botulinum toxin treatment for symptomatic Frey's syndrome. Otolaryngol Head Neck Surg 2000;122:237-40.
16. Ferraro G, Altieri A, Grella E, D'Andrea F. Botulinum toxin: 28 patients affected by FREY's syndrome treated with intradermal injections. Plastic and Reconstructive Surgery 2005;115:344-345.
17. Geddoa E, Matar HE, Paes TRF. The use of botulinum toxin A in the management of neck and anterior chest wall flushing: pilot study. Int J Dermatol 2013;52:1547-50.
18. Dayan SH, Pritzker RN, Arkins JP. A New Treatment Regimen for Rosacea: OnabotulinumtoxinA. J Drugs Dermatol 2012;11:76-9 .
19. Hekmann M, Ceballos Baumann AO, Plewig G. Botulinum toxin A or axillary hyperhidrosis (excessive sweating). N Engl J Med 2001:344:488-93.
20. Cote TR, Mohan AK, Polder JA, Walton MK, Braun M. Botulinum toxin type A injections: Adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. J Am Acad Dermatol 2005;53:407-15.
21. Laing TA, Laing ME, O'Sullivan ST. Botulinum toxin for treatment of glandular hypersecretory disorders. J Plast Reconstr AesthetSurg 2008;61:1024-8.