BOTULINUM TOXIN TYPE A IN THE MANAGEMENT OF RESISTANT RAYNAUD'S PHENOMENON SECONDARY TO AUTOIMMUNE SYSTEMIC CONNECTIVE TISSUE DISEASES

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ABSTRACT

AIM: The objectives of our study was to assess the efficacy of botulinum toxin type A in recalcitrant secondary Raynaud's phenomenon with respect to complete pain relief, healing of digital ulcer, improvement in tissue oxygenation, improvement in activities of daily living and prevention of recurrence.

METHODS: 20 female patients with recalcitrant secondary Raynaud's were divided into 2 equal groups - 10 in group A who received up to 100 units of botox in both hands (5 units/site) and 10 in Group B received placebo injection (normal saline).

RESULTS: Patients in group A had a statistically significant improvement as compared to group B in visual analogue scale for pain (p=0.02) and oxygen saturation (p=0.04). Group A had an improvement in quick Disabilities of Arm, Shoulder and Hand (DASH) score, but was not statistically significant (p=0.34).

CONCLUSION: Botulinum injection rapidly reduces the pain, frequency of attacks, and reduces the disability associated with Raynaud's phenomenon.

INTRODUCTION

Raynaud's phenomenon (RP) is a vasospastic disorder of the palmar and digital vessels of the hand and feet that can lead to ischemic ulcers, pain, and loss of function. Primary vasospastic disease can be termed Raynaud's disease or primary Raynaud's phenomenon. Secondary vasospastic disease can be termed Raynaud's syndrome or secondary Raynaud's phenomenon. In severe cases, it can lead to gangrene. Outcomes in primary and secondary RP are related to the structural differences in blood vessels occurring in the secondary RP. The aim of our treatment is to prevent exaggerated vasospasm, improve the vasodilatatory response, increase the red cell deformation to adjust to the decreased calibre of the vessel. Current accepted medical and surgical treatments are not uniformly successful, have their inherent morbidities and are limited by efficacy, side effects, and polypharmacy concerns. Botulinum toxin A has conventionally been used in the upper extremity to treat spasticity resulting from stroke, paraplegia, and dystonia. Recently, it has been used to relieve symptoms of vasospasm in Raynaud's phenomenon. Botulinum toxin A (Botox) functions by blocking the depolarization of vascular smooth muscles and vasoconstriction. It also blocks the central stimuli for vasocostriction. We report the results of the treatment of recalcitrant Raynaud's secondary to autoimmune connective tissue diseases with Botox in our institution.

PATIENTS AND METHODS

This prospective interventional pilot study was conducted on 20 consecutive adult female patients attending our outpatient department from May 2015 to November 2015. After obtaining Institutional Ethical Committee clearance, 20 female patients with recalcitrant secondary RP were chosen for the study after obtaining informed and written consent. Recalcitrant RP was considered in those patients who had either frequent or severe attacks (including non-obstructive pre gangrene of digits and digital ulcers) not responding to a combination of nifedipine, fluoxetine, and sildenafil in maximum permissible doses for a period of 3 months. Endothelin receptor antagonists were not tried due to non-availability in our hospital. 15 patients with systemic sclerosis (SSc) and 5 with mixed connective tissue disorder (MCTD) were included in this study.

Table 1. Patient demographic data (GROUP A)

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<th>Units of botox inj</th>
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There was statistically significant difference in the mean SpO2 score at groups at 3 months (p=0.34). Statistical significance in the quick DASH score between the two score at baseline and after 3 months (p = 0.06) in group B. There was no statistical significance between the two groups in the mean VAS score at baseline and after 3 months (p = 0.008) in group A. The mean quick DASH score in group A at 3 months was 61.2 ± 17.6 (2SD). There was statistically significant difference in the quick DASH score in group A and B at 3 months.

SPSS 21 software was used for statistical analysis. Student t test was used to compare the mean of each group pre and post treatment. Unpaired Student t test was used to compare the mean of group A and B at 3 months.

RESULTS
All 20 patients were females. The mean age of group A was 34.5 ± 13.7 (2SD). The mean age of group B was 30.6 ± 9.58 (2SD). Baseline demographic parameters were comparable. The mean quick DASH score in group A at baseline was 89.6 ± 4.64 (2SD) (table 1). The mean quick DASH score at baseline was 70.7 ± 29.24 (2SD) (table 2). There was no statistical significance between the two groups in the mean VAS score at baseline (p = 0.82). The mean visual analogue scale (VAS) (inj) in group A was 7.8 ± 1.84 (2SD). The mean VAS in group B at baseline was 8.3 ± 1.9 (2SD). There was no statistical significance between the two groups in the mean VAS score at baseline (p = 0.02). The mean oxygen saturation (SpO2) in group A at baseline was 88.4 ± 3.68 (2SD). The mean oxygen saturation (SpO2) in group B at baseline was 87.6 ± 4.64 (2SD). There was no statistical significance between the two groups in the mean SpO2 at baseline (p = 0.06). 50 units of reconstituted botox was injected per hand (10 sites per hand; 5 units per site).

The mean VAS score in group A at 3months was 6.7 ± 2.12 (2SD). The mean VAS score in group B at 3months was 7.9 ± 2.2. There was a statistically significant difference in the mean VAS between the two groups at 3 months (p=0.02). 3 patients in group A reported pain relief in 1 day. The remaining 7 patients were pain free within 3 days of Botox injection. Patients in group B reported complete pain relief in 8 days (average). All patients in group A had a mean pain free period of 3 months after single dose of Botox injection. There were no further attacks in the 3months follow up period in group A. In group B, the mean pain free period with drugs and placebo was 1.5 months. Average units of Botox needed to produce a clinically meaningful response in group A was 88 ± 7.9.

The mean quick DASH score in group A at 3months was 61.2 ± 17.6 (2SD). There was statistically significant difference in the quick DASH score at baseline and after 3 months (p = 0.008) in group A. There was no statistically significant difference in the quick DASH score at baseline and after 3 months (p = 0.06) in group B. There was no statistically significant difference in the quick DASH score between the two groups at 3 months (p=0.34).

DISCUSSION
Raynaud's phenomenon involves a mismatch between constriction and dilation of the small arteries of the upper extremity[10]. It occurs secondary to autoimmune systemic connective tissue disorders like scleroderma, mixed connective tissue disorder, systemic lupus erythematosus, rheumatoid arthritis, Sjogrens syndrome and myositis. Symptoms range from digital blanching and cyanosis to reactive hyperemia, to pain and dysesthesias. Prolonged RP can result in severe

With the needle tip perpendicular to the pulp and deep to the palmar fascia, the area adjacent to the proper digital arteries at base of both sides of fingers was injected. This was followed by a massage of the injected sites to make the drug evenly distribute throughout the region. Group B received normal saline in a similar procedure (table 2).

Table 2. Patient demographic data (GROUP B)

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**FOLLOW UP**
All patients were followed up at days 1, 3, 7 and monthly thereafter for 3 months. Disability was assessed using Quick DASH (Disabilities of Arm, Shoulder and Hand) score at baseline and after 3 months in both the groups. All patients were allowed to continue the medications which they were on previously.

**STATISTICS**
SPSS 21 software was used for statistical analysis. Student t test was used to compare the mean of each group pre and post treatment. Unpaired Student t test was used to compare the mean of group A and B at 3 months.

The mean VAS score in group A at 3months was 6.7 ± 2.12 (2SD). The mean VAS score in group B at 3 months was 7.9 ± 2.2. There was a statistically significant difference in the mean VAS between the two groups at 3 months (p=0.02). 3 patients in group A reported pain relief in 1 day. The remaining 7 patients were pain free within 3 days of Botox injection. Patients in group B reported complete pain relief in 8 days (average). All patients in group A had a mean pain free period of 3 months after single dose of Botox injection. There were no further attacks in the 3months follow up period in group A. In group B, the mean pain free period with drugs and placebo was 1.5 months. Average units of Botox needed to produce a clinically meaningful response in group A was 88 ± 7.9.

The mean quick DASH score in group A at 3months was 61.2 ± 17.6 (2SD). There was statistically significant difference in the quick DASH score at baseline and after 3 months (p = 0.008) in group A. There was no statistically significant difference in the quick DASH score at baseline and after 3 months (p = 0.06) in group B. There was no statistically significant difference in the quick DASH score between the two groups at 3 months (p=0.34).

There was statistically significant difference in the mean SpO2 score at baseline and after 3 months (mean 94.2 ± 2.28; p = 0.007) in group A. There was no statistically significant difference in the mean SpO2 score at baseline and after 3 months (mean 89.2 ± 1.88; p = 0.82) in group B. There was a statistically significant difference in the mean SpO2 between the two groups at 3 months (p=0.04).

In group A, 2 patients with systemic sclerosis had no occlusive gangreneous changes which resolved completely at 1 month after botox injection (Figure 1).

**Figure 1 : Left – shows a patient with MCTD and severe Raynauds, not responding to conventional drugs, progressed to gangrene of right 5th digit; Right – same patient after 1st injection of botox showing complete resolution of gangrene**

Only 2 patients had active digital ulcers, which healed completely within a month. The remaining 8 had digital pitted scars (Figure 2).

**Figure 2 : Left – showing a patient with digital pitted scars; Right - same patient after 1st injection of botox showing complete healing of pitted scars**

1 patient in group B had digital ulcer, which healed over 3 months. No one had pregangrene in group B. No patient had procedure related complications.

**DISCUSSION**
Raynaud's phenomenon involves a mismatch between constriction and dilation of the small arteries of the upper extremity[10]. It occurs secondary to autoimmune systemic connective tissue disorders like scleroderma, mixed connective tissue disorder, systemic lupus erythematosus, rheumatoid arthritis, Sjogrens syndrome and myositis. Symptoms range from digital blanching and cyanosis to reactive hyperemia, to pain and dysesthesias. Prolonged RP can result in severe
digital vascular compromise, ulceration, digital infarction which may require amputation.

Both vascular and neural abnormalities play a role in the pathogenesis of RP. Vascular abnormalities include both structural and functional problems[5]. There is an imbalance between vasodilators (nitric oxide) and vasoconstrictors (endothelin). Endothelial hyperplication causes structural vascular derangements and contributes to further narrowing of vessel wall. Microthrombi have been demonstrated in the small vessels, which further reduces the blood flow. Neural alterations may also contribute by affecting the autoregulation of vascular tone through either an overproduction of alpha-andrenergic receptors and subsequent vasoconstriction or a decrease in vasodilatory stimuli (calcitonin gene related peptide)[5].

Botulinum toxin type A is produced by the bacterium Clostridium botulinum. Botulinum toxin A has been used as a treatment modality to reverse the vasoconstriction in Raynaud's phenomenon. It blocks the transmission of the norepinephrine vesicle, preventing sympathetic vasoconstriction of the vascular smooth muscle. Additionally it blocks recruitment of specific α2-adrenoceptor (alpha 2c), which decreases the activity of chronically upregulated C-fiber nociceptors. This leads to a subsequent reduction in cold induced vascular smooth muscle constriction and pain[2].

The QuickDASH is a short version of the DASH Outcome Measure. The QuickDASH uses 11 items to measure physical function and symptoms in people with any or multiple disorders of the upper limb. The QuickDASH outcome measure is a valid, reliable and is used for clinical and research purposes.

Bedarida et al[7] reported a reduced vasodilatory response to bradykinin (endothelium-dependent) in comparison with sodium nitroprusside (endothelium-independent) in patients with primary Raynaud's phenomenon, which points to a defect in the endothelium-dependent mechanism.

Calcium channel blockers have been validated as a first line agent to reduce the frequency of Raynaud's attacks. Other drugs that are tried include angiotensin II inhibitors, selective serotonin reuptake inhibitors, angiotensin converting enzyme (ACE) inhibitors, alpha-blockers, oral and topical nitrates, intravenous prostaclin, endothelin receptor blockers, phosphodiesterase inhibitors[5].

Fregene et al[5] in 2009 injected an average of 77 units of botox in the digits (38%), distal palm (83%) and proximal hand (13%). They could observe a statistically significant improvement in the pain score and digit transcutaneous oxygen saturation measurements after treatment. They noted intrinsic hand muscle weakness in 6 patients (23%) and dysesthesia in 1 (4%), which resolved within 5 months. We used an average of 88 units of botox. We targeted only the base of fingers. We did not inject in the palms or proximal hand. We did not have any intrinsic muscle weakness in both the groups. With regards to pain score, our study had a comparable effect with this study. We did not measure the transcutaneous oxygen measurement. Instead we chose to measure the SpO2 (though unreliable, it was chosen for the ease of its measurement and its non-invasiveness).

Neumeister et al[5] in 2009 injected 50 to 100 Units hand in all digits at A1 pulley/metacarpophalangeal joint level. They noted intrinsic weakness in 3 patients (16%), which resolved within 2 months. We used a similar dose but did not have complications.

Sycha et al[8] in 2004 administered 1 to 10 U/site only in the affected digits (18%) and digital and superficial arch (82%). They found that injecting Botox reduced patient's rest pain, promoted healing of digit ulcerations, and reduced overall the frequency of the attacks. They also noted mild intrinsic weakness in 3 (27%) patients. In our study, we injected 10 sites per hand and 5 units per site at base of both sides of affected fingers.

Neumeister et al[5] in 2009 showed that botulinum toxin appears to improve perfusion of the hand by administering in 33 patients with RP and showed that all but 5 patients experienced improved vascularity and relief of pain and that Laser Doppler illustrated notable improvement in perfusion. Five patients had repeat injections for recurrent pain. Our patients responded well to a single injection of botox. Due to financial constraints, we could not use Laser Doppler for perfusion study.

Zhang et al[9], in China administered 20 u/ml botox (guided by ultrasonography) to ten patients with RP who had intractable pain and were non-responsive to conservative and/or medical therapy and showed a great improvement in artery flow velocity (P< 0.01), surface temperature (P<0.01), ulcer and VAS for clinical symptoms.

Our study demonstrated a statistically significant reduction in the pain (reduction in VAS for pain), activities of daily living (as evidenced by improvement in the quick DASH score), provided a symptom free period of 3 months and improvement in the SpO2.

**CONCLUSION**

We conclude that botulinum toxin administration provides immediate pain relief, prevents further attacks and improves the quality of life particularly in patients who are not responsive to conventional medications. Botox could be used as a good alternative to sympathectomy. Further large scale studies and long follow up is needed to assess the long term efficacy of botox. Till date, botox is tried when conventional medications fail. Its role as a first line drug (avoiding cumbersome polypharmacy) has to be studied in future.

**LIMITATIONS OF THE STUDY**

1. This study was a pilot study involving 20 patients. Further large scale studies are needed to prove the role and efficacy of botox in the management of resistant Raynauds.

2. Short duration of follow up.

3. Endothelin receptor antagonists were not tried due to non availability in our centre.

**REFERENCES**