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EFFICACY OF BOTOX-A IN TEMPOROMANDIBULAR DISORDERS REFRACTORY TO THE CONSERVATIVE MANAGEMENT

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ABSTRACT

Aim: The aim of the study was to evaluate the efficacy of botulinum toxin type-A therapy (BTX-A: Allergan Inc, USA) in patients with temporomandibular joint disorders (Both intra-articular & extra-articular pathologies) refractory to the conservative management. **Materials and method**: This prospective, in vivo study was conducted among 11 subjects in the Department of Oral & Maxillofacial Surgery, Maulana Azaad Dental College & Hospital. A clinical proforma was designed along with Numeric Rating Scale (NRS) to record all the pre-operative & post-operative findings in the present study. All non-invasive surgical procedures were performed under aseptic condition by using 5% povidone-iodine solution for skin preparations. Statistical analysis was performed using IBM, SPSS Statistics version 22 (IBM Corp., New York, NY). **Results**: There was significant improvement in subjective facial pain, inter-incisal distance (mm), decrease in the pain scale and decrease in orofacial dysfunction of masticatory muscles at post 6 months intervention ($p<0.05$). **Conclusion**: The injections of BTX-A in masticatory musculatures of TMD patients can be considered as a valuable either first line or second line treatment option refractory to the conservative treatment for controlling complex TMD.

KEYWORDS: Pain, dysfuntion, Botox, TMD.

INTRODUCTION

Botulinium toxin (A 150-kDa protein) produced by the bacterium Clostridium botulinum, is a potent neuromodulator, which works at the neuromuscular junction by inhibiting exocytosis of acetylcholine synaptic vessels.[1] Botulinum toxin (abbreviated either as BTX or BoNT), is subdivided into 7 serotypes i.e., A, B, C [C1, C2], D, E, F, and G produced by different stains of clostridium botulinum. With the exception of C2, they are all neurotoxic. In the oral and maxillofacial region, BoNT has been used to treat oromandibular dystonia, hemifacial spasm, oral dyskinesia, synkinesis following defective healing of the facial nerve, temporomandibular disorders etc.[1]

Temporomandibular disorders (TMD), musculoskeletal disorders of the masticatory system, are common clinical labels for pain in the orofacial area. Successful TMD treatment starts from correctly differentiating the origin of symptoms.[9] Since myofascial pains and mouth opening limitation are the most frequent symptoms in masticatory muscle disorders, directing treatments at the muscular components of TMD could yield therapeutic gains.[2]

Botulinum toxin (BTX) is a valuable non-surgical treatment modality for TMDs, when standard conservative regimen fails to treat the underlying TMDs.[3] Therefore, aim of the present study was to evaluate the efficacy of botulinum toxin type-A therapy (BTX-A: Allergan Inc, USA) in patients with temporomandibular joint disorders (Both intra-articular & extra-articular pathologies) refractory to the conservative management.

MATERIALS AND METHOD

This prospective, in vivo study was conducted in the Department of Oral & Maxillofacial Surgery, Maulana Azaad Dental College & Hospital. Ethical clearance was obtained from the Ethical Committee of the institute. RDC/TMD (Research Diagnostic Criteria/Temporomandibular Disorders) Axis-I criteria[4]

were used to diagnose the TMD's and were further classified under the TMD subtypes proposed by the Japanese Society for the Temporomandibular Joint (JSTMJ) in 2001, where.

a) Category-I: Patients with masticatory muscle disorder
b) Category-II: Patients with capsule-ligament disorder
c) Category-III: Patients with disc disorder
d) Category-IV: Patients with degenerative joint diseases
e) Category-V: Cases not included in types I-IV

A total of 11 subjects with temporomandibular disorders fulfilling the inclusion criteria were selected. All the patients gave the consent and they were also explained about the follow-up protocols which have to be followed by them to be a part of this clinical study.

Inclusion criteria

1. Patients who failed in the non-invasive conservative therapies (Counselling, soft Diet, oral appliances, pharmacotherapy, behavior medicine, physical therapy).
2. Patients who received BTX-A injection therapy during the study period.
3. Patients having complete medical records (if any).
4. Patients with TMD/RDC follow-ups.

Exclusion criteria

1. Any history of atopy or significant allergic reactions
2. Any history of pregnancy or lactation
3. Any known history of hypersensitivity to botulinum toxin
4. Any congenital neuromuscular disorders (eg, myasthenia gravis).

A standardized and thorough case history was taken for all the patients. A clinical proforma was designed along with Numeric Rating Scale (NRS) to record all the pre-operative & post-operative findings in the present study. The required clinical armamentarium i.e. diagnostic instruments (probe, mouth mirror, tweezer), drapes, gloves, mouth mask and head cap, botulinum toxin vial (BTX-A) and saline ampules, calibrated tuberculin syringes, cotton swabs and gauze pieces, marking pen and scale was taken. For the present study, following 5 evaluation criteria's were considered as shown in figure 1.

5 CRITERIAS CONSIDERED					
Assessment Intervals (Follow-up)	Subjective Facial Pain ; VAS (0-10)	Range Of Mandibular Motion (Maximum Inter-incisal Opening)	Tenderness Of Masticatory Muscles ; Pain Scale (0-3)	Orofacial Function; {Dysfunction Scale (0-3)}	Facial Harmony (Photographic Evaluation)
Pre-Operative					Pre-Operative
1st Week					
2nd Week					
4th Week					
6th Week					Post-Operative
8th Week					
3 Months					
6 Months					

Figure. 1: Evaluation criteria.

Procedural technique: All non-invasive surgical procedures were performed under aseptic condition by using 5% povidone-iodine solution for skin preparations. BTX-A powders were kept frozen in sterile vials until each use. Preparation of the BTX-A solution was done according to the manufacturer's guidelines. The solution was prepared according to the manufacturer's guidelines by adding 0.9% normal saline without a preservative to the powders until 2 ml of final dilution. In this procedure, injection sites were wiped with 70% ethanol swab, and dry sterile gauze for skin preparations and aspirations were performed before each injection. Calibrated 1 ml tuberculin syringes with 26 gauge needles were used for the injection. The prepared solution was used within an hour of its maximum potency.

The masseter and temporalis muscles were injected on the affected side. Before injections, all the patients were asked to clench their jaws to make the injection sites more prominent. The patients received 25 units of BTX-A divided evenly over 5 sites in the masseter muscle region. All injections were given percutaneous and intramuscular. Similarly, the temporalis muscles were injected with 25 units divided evenly over 5 sites, with diffusion of approximately 1 cm apart from each sites.

a. (VAS) are denoted as

10 – Severe pain (Maximum) & 0 – No pain (Minimum)

b. For tenderness of masticatory muscles, based on the pain scale are denoted as.

3 – Severe discomfort on minimal pressure
2 – Moderate discomfort
1 – Mild discomfort
0 – No discomfort on firm palpation

c. For orofacial function, the dysfunction scale gradings are denoted as:-

3 – Severe discomfort
2 – Moderate discomfort
1 – Mild discomfort

0 – No discomfort

d. For range of mandibular motion, maximum inter-incisal opening is denoted in millimeters (mm).

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM, SPSS Statistics version 22 (IBM Corp., New York, NY). Descriptive data was expressed as mean ± standard deviation (SD). ANOVA was conducted to determine whether there were significant differences in mean test values over the course of 6 months of intervention. A post hoc (Tukey) test was performed using the Bonferroni correction. P value less than 0.05 was considered statistically significant. A Pearson's correlation analysis was done to establish the relation between subjective facial pain (VAS) scale, orofacial dysfunction, masticatory muscles tenderness and inter-incisal opening distance.

RESULTS

The number of valid cases was 11. The mean age of the patients was 35.8 ± 9.1 (range, 26-55, years). There were 6 (54.5%) females and 5 (45.5%) males. The involvement of temporomandibular joint was bilateral in 1(9%), left side in 5 (45.5%) and in right side in 5 (45.5%) cases, respectively (Table 1).

Table 2 shows significant improvement in subjective facial pain at post 6 months intervention ($p<0.001$). Post-hoc analysis with a Bonferroni adjustment revealed that subjective facial pain was statistically significantly decreased at all time points (Table 3).

There was a significant increase in the maximum inter-incisal distance (mm) at 6 months post-intervention ($P<0.05$). Post-hoc analysis with a Bonferroni adjustment revealed that maximal inter-incisal distance statistically significantly increased at 6 months only (Table 4).

There was a significant decrease in the pain scale of masticatory muscles at six months post-intervention ($P<0.001$). Post-hoc analysis with a Bonferroni adjustment revealed a significant change in test values observed at 6w and 6m respectively (Table 5).

There was a significant decrease in orofacial dysfunction at six months post-intervention ($P<0.001$). Post-hoc analysis with a Bonferroni adjustment revealed that orofacial dysfunction was not statistically significantly improved from pre-intervention to 1-week post-intervention (0.455±0.157, $P=0.454$). Thereafter, a significant change in the test values at 6w (2.18±0.18, $P<0.001$) and 6m (2.27±0.27, $P<0.001$), respectively (Table 6).

On correlation analysis, pre-intervention subjective facial pain (VAS) correlated significantly with orofacial dysfunction (Pearson's correlation coefficient, $r = 0.687$) and inter-incisal opening distance (Pearson's correlation coefficient, $r = 0.465$), respectively (Table 7).

Table. 1: Demographic characteristics and side involvement of the study population.

Variables	N	%
Gender		
Male	6	54.5
Female	5	45.5
Age groups (in years)		
25-35	8	72.7
36.45	1	9.1
>46	2	18.2
Side involved		
Bilateral	1	9
Left	5	45.5
Right	5	45.5
Total	11	100.0

Table. 2: Descriptive Statistics.

Variable	Mean	Std. Deviation
Subjective Facial Pain (PRE)	8.2727	2.05382
VAS1W	6.1818	2.18258
VAS2W	5.2727	2.45320
VAS4W	3.3636	2.37793
VAS6W	2.0000	1.89737
VAS8W	.5455	.93420
VAS3M	1.0909	2.07145
VAS6M	1.1818	2.71360
Maximal Inter Incisal Opening (PRE)	31.6364	7.65863
MIO1W	32.9091	7.66100
MIO2W	33.3636	7.43334
MIO4W	33.8182	7.33237
MIO6W	33.7273	7.44434
MIO8W	33.6364	7.71068
MIO3M	33.6364	7.71068
MIO6M	33.4545	7.84045
Tenderness of Masticatory Muscles (PRE)	2.8182	.40452
TM1W	2.0909	.70065
TM2W	1.3636	.67420
TM4W	.9091	.83121
TM6W	.2727	.46710
TM8M	.1818	.40452
TM3M	.3636	.67420
TM6M	.2727	.64667
Orofacial Dysfunction (PRE)	2.5455	.52223
OFD1W	2.0909	.53936
OFD2W	1.5455	.68755
OFD4W	.9091	.70065
OFD6W	.3636	.50452
OFD8W	.0909	.30151
OFD3M	.2727	.64667
OFD6M	.2727	.64667

Table. 3: Pairwise Comparisons.

Measure: Subjective Facial Pain (VAS)						
(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
PRE	1W	2.091*	.436	.020	.253	3.929
	2W	3.000*	.447	.001	1.115	4.885
	4W	4.909*	.563	.000	2.535	7.284
	6W	6.273*	.604	.000	3.725	8.820
	8W	7.727*	.648	.000	4.996	10.458
	3M	7.182*	.851	.000	3.595	10.768
	6M	7.091*	1.004	.001	2.859	11.323
1W	PRE	-2.091*	.436	.020	-3.929	-.253
	2W	.909	.251	.130	-.147	1.965
	4W	2.818*	.423	.002	1.037	4.599
	6W	4.182*	.672	.003	1.350	7.013
	8W	5.636*	.650	.000	2.895	8.378
	3M	5.091*	.756	.001	1.903	8.278
	6M	5.000*	.894	.006	1.230	8.770
2W	PRE	-3.000*	.447	.001	-4.885	-1.115
	1W	-.909	.251	.130	-1.965	.147
	4W	1.909*	.285	.001	.710	3.109
	6W	3.273*	.619	.010	.663	5.883
	8W	4.727*	.689	.001	1.824	7.630
	3M	4.182*	.818	.013	.733	7.630
	6M	4.091*	.919	.035	.217	7.965
4W	PRE	-4.909*	.563	.000	-7.284	-2.535
	1W	-2.818*	.423	.002	-4.599	-1.037
	2W	-1.909*	.285	.001	-3.109	-.710
	6W	1.364	.527	.758	-.857	3.585
	8W	2.818*	.585	.020	.353	5.284
	3M	2.273	.810	.521	-1.142	5.687
	6M	2.182	.893	.968	-1.580	5.944
6W	PRE	-6.273*	.604	.000	-8.820	-3.725
	1W	-4.182*	.672	.003	-7.013	-1.350
	2W	-3.273*	.619	.010	-5.883	-.663
	4W	-1.364	.527	.758	-3.585	.857
	8W	1.455	.434	.206	-.375	3.284
	3M	.909	.889	1.000	-2.837	4.656
	6M	.818	.998	1.000	-3.390	5.026
8W	PRE	-7.727*	.648	.000	-10.458	-4.996
	1W	-5.636*	.650	.000	-8.378	-2.895
	2W	-4.727*	.689	.001	-7.630	-1.824
	4W	-2.818*	.585	.020	-5.284	-.353
	6W	-1.455	.434	.206	-3.284	.375
	3M	-.545	.666	1.000	-3.351	2.260
	6M	-.636	.834	1.000	-4.152	2.880
3M	PRE	-7.182*	.851	.000	-10.768	-3.595
	1W	-5.091*	.756	.001	-8.278	-1.903
	2W	-4.182*	.818	.013	-7.630	-.733
	4W	-2.273	.810	.521	-5.687	1.142
	6W	-.909	.889	1.000	-4.656	2.837
	8W	.545	.666	1.000	-2.260	3.351
	6M	-.091	.285	1.000	-1.290	1.109
6M	PRE	-7.091*	1.004	.001	-11.323	-2.859
	1W	-5.000*	.894	.006	-8.770	-1.230
	2W	-4.091*	.919	.035	-7.965	-.217
	4W	-2.182	.893	.968	-5.944	1.580
	6W	-.818	.998	1.000	-5.026	3.390

	8W	.636	.834	1.000	-2.880	4.152
	3M	.091	.285	1.000	-1.109	1.290
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

Table. 4: Pairwise Comparisons.

Measure: MAXIMUM INTER INCISIAL OPENING						
(I) Time	**(J) Time**	**Mean Difference (I-J)**	**Std. Error**	**Sig.[a]**	**95% Confidence Interval for Difference[a]**	
					Lower Bound	**Upper Bound**
PRE	1W	-1.273	.557	1.000	-3.622	1.077
	2W	-1.727	.619	.536	-4.337	.883
	4W	-2.182	.658	.219	-4.956	.592
	6W	-2.091	.667	.296	-4.901	.720
	8W	-2.000	.739	.616	-5.113	1.113
	3M	-2.000	.739	.616	-5.113	1.113
	6M	-1.818	.761	.05	-5.024	1.388
1W	PRE	1.273	.557	1.000	-1.077	3.622
	2W	-.455	.282	1.000	-1.642	.733
	4W	-.909	.392	1.000	-2.562	.743
	6W	-.818	.400	1.000	-2.506	.870
	8W	-.727	.506	1.000	-2.861	1.406
	3M	-.727	.506	1.000	-2.861	1.406
	6M	-.545	.529	1.000	-2.773	1.682
2W	PRE	1.727	.619	.536	-.883	4.337
	1W	.455	.282	1.000	-.733	1.642
	4W	-.455	.207	1.000	-1.328	.419
	6W	-.364	.203	1.000	-1.220	.493
	8W	-.273	.359	1.000	-1.786	1.241
	3M	-.273	.359	1.000	-1.786	1.241
	6M	-.091	.368	1.000	-1.643	1.461
4W	PRE	2.182	.658	.219	-.592	4.956
	1W	.909	.392	1.000	-.743	2.562
	2W	.455	.207	1.000	-.419	1.328
	6W	.091	.091	1.000	-.292	.474
	8W	.182	.296	1.000	-1.066	1.429
	3M	.182	.296	1.000	-1.066	1.429
	6M	.364	.364	1.000	-1.169	1.896
6W	PRE	2.091	.667	.296	-.720	4.901
	1W	.818	.400	1.000	-.870	2.506
	2W	.364	.203	1.000	-.493	1.220
	4W	-.091	.091	1.000	-.474	.292
	8W	.091	.211	1.000	-.800	.981
	3M	.091	.211	1.000	-.800	.981
	6M	.273	.273	1.000	-.877	1.422
8W	PRE	2.000	.739	.616	-1.113	5.113
	1W	.727	.506	1.000	-1.406	2.861
	2W	.273	.359	1.000	-1.241	1.786
	4W	-.182	.296	1.000	-1.429	1.066
	6W	-.091	.211	1.000	-.981	.800
	3M	.000	.000	.	.000	.000
	6M	.182	.122	1.000	-.332	.696
3M	PRE	2.000	.739	.616	-1.113	5.113
	1W	.727	.506	1.000	-1.406	2.861
	2W	.273	.359	1.000	-1.241	1.786
	4W	-.182	.296	1.000	-1.429	1.066
	6W	-.091	.211	1.000	-.981	.800

	8W	.000	.000	.	.000	.000
	6M	.182	.122	1.000	-.332	.696
6M	PRE	1.818	.761	1.000	-1.388	5.024
	1W	.545	.529	1.000	-1.682	2.773
	2W	.091	.368	1.000	-1.461	1.643
	4W	-.364	.364	1.000	-1.896	1.169
	6W	-.273	.273	1.000	-1.422	.877
	8W	-.182	.122	1.000	-.696	.332
	3M	-.182	.122	1.000	-.696	.332

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Table. 5: Pairwise Comparisons.

Measure: TENDERNESS OF MASTICATORY MUSCLES						
(I) Time	**(J) Time**	**Mean Difference (I-J)**	**Std. Error**	**Sig.[b]**	**95% Confidence Interval for Difference[b]**	
					Lower Bound	**Upper Bound**
Pre	1W	.727	.237	.333	-.272	1.726
	2W	1.455*	.207	.001	.581	2.328
	4W	1.909*	.251	.001	.853	2.965
	6W	2.545*	.157	.000	1.882	3.209
	8W	2.636*	.203	.000	1.780	3.493
	3M	2.455*	.207	.000	1.581	3.328
	6M	2.545*	.207	.000	1.672	3.419
1W	PRE	-.727	.237	.333	-1.726	.272
	2W	.727*	.141	.012	.134	1.321
	4W	1.182*	.182	.002	.415	1.948
	6W	1.818*	.122	.000	1.304	2.332
	8W	1.909*	.211	.000	1.019	2.800
	3M	1.727*	.195	.000	.905	2.549
	6M	1.818*	.226	.000	.864	2.772
2W	PRE	-1.455*	.207	.001	-2.328	-.581
	1W	-.727*	.141	.012	-1.321	-.134
	4W	.455	.157	.454	-.209	1.118
	6W	1.091*	.163	.001	.405	1.776
	8W	1.182*	.226	.011	.228	2.136
	3M	1.000*	.234	.045	.016	1.984
	6M	1.091*	.251	.040	.035	2.147
4W	PRE	-1.909*	.251	.001	-2.965	-.853
	1W	-1.182*	.182	.002	-1.948	-.415
	2W	-.455	.157	.454	-1.118	.209
	6W	.636	.203	.299	-.220	1.493
	8W	.727	.273	.662	-.422	1.877
	3M	.545	.207	.703	-.328	1.419
	6M	.636	.244	.731	-.392	1.665
6W	PRE	-2.545*	.157	.000	-3.209	-1.882
	1W	-1.818*	.122	.000	-2.332	-1.304
	2W	-1.091*	.163	.001	-1.776	-.405
	4W	-.636	.203	.299	-1.493	.220
	8W	.091	.163	1.000	-.595	.776
	3M	-.091	.163	1.000	-.776	.595
	6M	.000	.191	1.000	-.804	.804
8W	PRE	-2.636*	.203	.000	-3.493	-1.780
	1W	-1.909*	.211	.000	-2.800	-1.019
	2W	-1.182*	.226	.011	-2.136	-.228
	4W	-.727	.273	.662	-1.877	.422
	6W	-.091	.163	1.000	-.776	.595

	3M	-.182	.182	1.000	-.948	.585
	6M	-.091	.163	1.000	-.776	.595
3M	PRE	-2.455*	.207	.000	-3.328	-1.581
	1W	-1.727*	.195	.000	-2.549	-.905
	2W	-1.000*	.234	.045	-1.984	-.016
	4W	-.545	.207	.703	-1.419	.328
	6W	.091	.163	1.000	-.595	.776
	8W	.182	.182	1.000	-.585	.948
	6M	.091	.091	1.000	-.292	.474
6M	PRE	-2.545*	.207	.000	-3.419	-1.672
	1W	-1.818*	.226	.000	-2.772	-.864
	2W	-1.091*	.251	.040	-2.147	-.035
	4W	-.636	.244	.731	-1.665	.392
	6W	.000	.191	1.000	-.804	.804
	8W	.091	.163	1.000	-.595	.776
	3M	-.091	.091	1.000	-.474	.292

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Table. 6: Pairwise Comparisons.

Measure: OROFACIAL FUNCTION (DYSFUNCTION SCALE)						
(I) Time	**(J) Time**	**Mean Difference (I-J)**	**Std. Error**	**Sig.[b]**	**95% Confidence Interval for Difference[b]**	
					Lower Bound	**Upper Bound**
Pre	1W	.455	.157	.454	-.209	1.118
	2W	1.000*	.191	.011	.196	1.804
	4W	1.636*	.244	.001	.608	2.665
	6W	2.182*	.182	.000	1.415	2.948
	8W	2.455*	.207	.000	1.581	3.328
	3M	2.273*	.273	.000	1.123	3.422
	6M	2.273*	.273	.000	1.123	3.422
1W	PRE	-.455	.157	.454	-1.118	.209
	2W	.545	.157	.170	-.118	1.209
	4W	1.182*	.182	.002	.415	1.948
	6W	1.727*	.141	.000	1.134	2.321
	8W	2.000*	.191	.000	1.196	2.804
	3M	1.818*	.263	.001	.708	2.929
	6M	1.818*	.226	.000	.864	2.772
2W	PRE	-1.000*	.191	.011	-1.804	-.196
	1W	-.545	.157	.170	-1.209	.118
	4W	.636	.152	.053	-.005	1.278
	6W	1.182*	.182	.002	.415	1.948
	8W	1.455*	.207	.001	.581	2.328
	3M	1.273*	.273	.025	.123	2.422
	6M	1.273*	.195	.002	.451	2.095
4W	PRE	-1.636*	.244	.001	-2.665	-.608
	1W	-1.182*	.182	.002	-1.948	-.415
	2W	-.636	.152	.053	-1.278	.005
	6W	.545	.157	.170	-.118	1.209
	8W	.818*	.182	.032	.052	1.585
	3M	.636	.244	.731	-.392	1.665
	6M	.636	.152	.053	-.005	1.278
6W	PRE	-2.182*	.182	.000	-2.948	-1.415
	1W	-1.727*	.141	.000	-2.321	-1.134
	2W	-1.182*	.182	.002	-1.948	-.415
	4W	-.545	.157	.170	-1.209	.118
	8W	.273	.141	1.000	-.321	.866

	3M	.091	.211	1.000	-.800	.981
	6M	.091	.163	1.000	-.595	.776
8W	PRE	-2.455*	.207	.000	-3.328	-1.581
	1W	-2.000*	.191	.000	-2.804	-1.196
	2W	-1.455*	.207	.001	-2.328	-.581
	4W	-.818*	.182	.032	-1.585	-.052
	6W	-.273	.141	1.000	-.866	.321
	3M	-.182	.122	1.000	-.696	.332
	6M	-.182	.122	1.000	-.696	.332
3M	PRE	-2.273*	.273	.000	-3.422	-1.123
	1W	-1.818*	.263	.001	-2.929	-.708
	2W	-1.273*	.273	.025	-2.422	-.123
	4W	-.636	.244	.731	-1.665	.392
	6W	-.091	.211	1.000	-.981	.800
	8W	.182	.122	1.000	-.332	.696
	6M	.000	.135	1.000	-.568	.568
6M	PRE	-2.273*	.273	.000	-3.422	-1.123
	1W	-1.818*	.226	.000	-2.772	-.864
	2W	-1.273*	.195	.002	-2.095	-.451
	4W	-.636	.152	.053	-1.278	.005
	6W	-.091	.163	1.000	-.776	.595
	8W	.182	.122	1.000	-.332	.696
	3M	.000	.135	1.000	-.568	.568
Based on estimated marginal means						
*. The mean difference is significant at the .05 level.						
b. Adjustment for multiple comparisons: Bonferroni.						

Table 7: Correlations.

		VAS-PRE	MIO-PRE	TM-PRE	OFD-PRE
Subjective Facial Pain (pre)	Pearson Correlation	1	.465	-.055	.687*
	Sig. (2-tailed)		.150	.873	.020
	N	11	11	11	11
Maximum Inter Incisal (pre)	Pearson Correlation	.465	1	-.217	.130
	Sig. (2-tailed)	.150		.521	.704
	N	11	11	11	11
Tenderness of Masticatory Muscles (pre)	Pearson Correlation	-.055	-.217	1	.516
	Sig. (2-tailed)	.873	.521		.104
	N	11	11	11	11
Orofacial Dysfunction (pre)	Pearson Correlation	.687*	.130	.516	1
	Sig. (2-tailed)	.020	.704	.104	
	N	11	11	11	11

DISCUSSION

Botox (Allergan Inc, USA): BTX-A (originally called 'Oculinum') was first used in humans in 1968 to treat strabismus.[5] BTX has evolved from a poison to a versatile clinical tool for a growing list of conditions resulting from muscular hyperfunction. Temporomandibular joint disorders (TMD) occur in 10% of population and about 20-25% of them seek professional care[6]. Muscular disorders are thought to possibly play a causative role in degenerative disease of the TMJ[7]. So in the present study, the efficacy of BTX-A therapy in patients with temporomandibular joint disorders is evaluated refractory to the conservative management.

In females the chances of seeking treatment increases by 77% with the use of supplemental estrogen in the postmenopausal years, or by 19% in subjects on oral contraceptives[8], female hormones have been implicated in the modulation of pain. In general, females tend to report more pain and exhibit a higher incidence of joint noise and mandibular deflection with movement than do male counterparts. Functional estrogen receptors have been identified in the female TMJ[9,10], but not in the male TMJ.[11] Estrogen may also promote degenerative changes in the TMJ by increasing the synthesis of specific cytokines. However, gender differences in health services use and symptom perception are insufficient to explain the greater involvement of women.[12] Similarly, in our study, the mean age of patients with temporomandibular disorders was 36 years and female

subjects (54.5%) were more compared to male subjects (45.5%).

Sidebottom AJ et al[13] in his study concluded that botulinum toxin is a valuable non-surgical treatment method for masticatory myofascial pain associated with TMDs. Girdler[14] also reported an improvement in pain symptoms in 2 patients with chronic facial pain and muscle spasms. A study[15] had proved that pain pressure threshold can be slightly increased by the use of acupuncture therapy and occlusal splint therapy in TMD patients, whereas wearing splint alone for 3 months had no significant difference for TMJ arthralgia. This study confirmed no major decrease of pain pressure threshold in patients treated with nonsurgical procedures for TMDs. On the contrary, in the present study, after the BTX-A therapy, the overall improvement in subjective facial pain just after 1 week was found to be decreased by 25% and when re-evaluated at 6-month time interval, the mean reduction in pain was found to be decreased by 87.5%.

In a small series, von Linder et al[16] treated 7 patients with unilateral and bilateral masseter and temporalis muscle hypertrophy with BTX-A injections into the specific muscles. The authors noted marked decrease in the size of the affected musculature. Patients received 1, 2, or 3 sets of injections depending on the clinical response. Studies showed all patients were followed up for minimum of 25 months, with no relapse of the muscular hypertrophy. In the present study, one patient presented with bilateral masseter muscle hypertrophy with TMJ arthralgia where after 24 months follow-up, and after administering 2 doses of BTX-A in masseter muscle at time intervals of 12 months, the second dose was only injected to augment the effect of the first injection. Although pain was relieved by single dosage only, the repeat injection was performed only to attain adequate reduction of affected masticatory musculature.

Freund et al[17] in his study concluded that BTX-A injections produce a statistically significant improvement in subjective facial pain, orofacial function, mouth opening and tenderness without any side effects. The present study coincides with the reported study in the literature and found that 25 U of BTX-A is sufficient enough to treat TMDs associated with musculoskeletal disorders. Post one-week BTX-A therapy, the mean of tenderness in masticatory muscles was reduced by 25.8% whereas at 6-month time interval, it was found to be reduced by 90%. It was noted that after one-week post BTX-A therapy, mean improvement in orofacial function was found to be 17%, whereas at 6 month time interval, 89.3% improvement in orofacial function was observed.

The safety of botulinum toxin use during pregnancy has not been tested in clinical trials. BTX-A has officially been labelled by the FDA as pregnancy category C, meaning there is a lack of studies in pregnant women, but animal studies may have described harm to the fetus. The toxin is lactation category L3, meaning there are no controlled studies in breastfeeding women and potential unknown risks to the baby might exist.[18] In the present study, as a safety precautionary measure, pregnant and lactating subjects were excluded from the study.

Binder et al[19] had reported that even chronic headaches were completely or partially improved on the patients who regularly received BTX-A treatment in the facial areas. In the present study, one patient reported with tension type headache in right temporalis muscle region, who was then administered BTX-A in only temporal region and pain subsided eventually after 48-72 hours, as reported by the patient. Studies have found that maximal effects of Botox are observed at 5 to 6 weeks post injection[18]. The results of the present study also clearly demonstrates that subjects who were evaluated at 6 weeks post-injection reported significantly more clinical improvement compared to subjects who were evaluated at 5 weeks or less post injection.

It is logical to accept the effectiveness of BTX-A with this time-based correlation. The injection of BTX-A into the masseter and temporalis muscles of patients with TMD reduced subjective facial pain and tenderness in most of the patients coincident with the objective and subjective weakening of the masticatory muscles and not before. In the present study, no complications were reported by the subjects.

CONCLUSION

In our study, the injections of BTX-A in masticatory musculatures of TMD patients can be considered as a valuable either first line or second line treatment option refractory to the conservative treatment for controlling complex TMD and improving its associated symptoms. In the present study, positive outcomes was reported in majority of the cases, yet more studies need to be performed on a larger sample size, with longer follow-up periods in order to scrutinize and evaluate the full effects of BTX-A injections.

REFERENCES

1. Yoshida K. Botulinum Neurotoxin injection for the treatment of recurrent temporomandibular joint dislocation with and without neurogenic muscular hyperactivity. Toxins, 2018; 10: 174.
2. Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. Cranio, 2008; 26(2): 126-135.
3. Sidebottom AJ, Patel AA, Amin J. Botulinum injection for the management of myofascial pain in the masticatory muscles. A prospective outcome study. Br. J Oral Maxillofac. Surg, 2013; 51: 199-205.
4. Dworkin SF. Research diagnostic criteria for temporomandibular disorders: review, criteria,

examinations and specifications, critique. J Craniomandib Disord, 1992; 6: 301-355.
5. Scott AB, Rosenbaum AR, Collins CC. Pharmacologic weakening of extraocular muscles. Invest Ophthalmol, 1973: 12: 924-927.
6. Carlsson GE. Epidemiology and treatment need for temporomandibular disorders. J Orofac. Pain, 1999; 13(4).
7. Sunil Dutt C, Ramnani P, Thakur D, Pandit M. Botulinum Toxin in the Treatment of Muscle Specific Oro-Facial Pain: A Literature Review. J Oral Maxillofac. Surg, 2014; 14(2): 171-175.
8. Tolvanen M, Oikarinen VJ, Wolf J. A 30-year follow-up study of temporomandibular joint meniscectomies: a report on five patients. Br J Oral Maxillofac. Surg, 1988; 26(4): 311-316.
9. Aufdemorte TB, Van Sickels JE, Dolwick MF, Sheridan PJ, Holt GR, Aragon SB, Gates GA. Estrogen receptors in the temporomandibular joint of the baboon (Papio cynocephalus): an autoradiographic study. Oral Surg. Oral Med. Oral Pathol, 1986; 61(4): 307-314.
10. Abubaker AO, Raslan WF, Sotereanos GC. Estrogen and progesterone receptors in temporomandibular joint discs of symptomatic and asymptomatic persons: a preliminary study. J Oral Maxillofac. Surg, 1993; 51(10): 1096-1100.
11. Milam SB, Aufdemorte TB, Sheridan PJ, Triplett RG, Van Sickels JE, Holt GR. Sexual dimorphism in the distribution of estrogen receptors in the temporomandibular joint complex of the baboon. Oral Surg. Oral Med. Oral Pathol, 1987: 64: 527.
12. Eriksson L, Westesson PL. Long-term evaluation of meniscectomy of the temporomandibular joint. J Oral Maxillofac. Surg, 1985; 43(4): 263-269.
13. Sidebottom AJ, Patel AA, Amin J. Botulinum injection for the management of myofascial pain in the masticatory muscles. A prospective outcome study. Br. J Oral Maxillofac. Surg, 2013; 51: 199-205.
14. Girdler NM. Use of botulinum toxin to alleviate facial pain. Br J Hosp Med., 1994: 52: 363.
15. Conti PC, Corrêa AS, Lauris JR, Stuginski-Barbosa J. Management of painful temporomandibular joint clicking with different intraoral devices and counseling: a controlled study. J App. Oral Sci., 2015; 23(5): 529-535.
16. Von Lindern JJ, Niederhagen B, Berge S, et al: Type A botulinum toxin in the treatment of chronic facial pain associated with masticatory hyperactivity. J Oral Maxillofac. Surg. 2003: 61: 774-778.
17. Freund B, Schwartz M, Symington JM. The use of botulinum toxin for the treatment of temporomandibular disorders: preliminary findings. J Oral Maxillofac Surg. 1999; 57(8): 916-920.
18. Tan M, Kim E, Koren G, Bozzo P. Botulinum toxin type A in pregnancy. Can. Fam. Physician. 2013; 59(11): 1183-1184.
19. Binder WJ, Brin MF, Blitzer A, Pojgoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine. Semin Cutan Med Surg. 20: 93-100.