ORIGINAL ARTICLE

A novel technique of botulinum toxin injection around skull sutures for chronic migraine: A randomized controlled clinical trial

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Background: Migraine is a chronic headache manifested with attacks. Here we aimed to evaluate and compare the efficacy of 15-point Dysport injection with 31-point Xeomin injections. **Materials and Methods:** This is a randomized clinical trial performed in 2020–2021 in Isfahan on patients with refractory chronic migraine. A total number of 60 patients entered the study. The pain of patients was also determined using headache impact test (HIT) questionnaire. Patients were randomized into two groups: Group 1 underwent 31-point Xeomin injection and Group 2 underwent 1 vial of Dysport injection into 15 points of the scalp. **Results:** Our study revealed that the data regarding aura, nausea, vomit, photosensitivity, sensitivity to sounds and smells did not change significantly between two groups compared to the beginning of the study. Frequency, duration, intensity of headaches, and the mean HIT score of all patients improved significantly within 3 months after interventions. Comparing both groups showed no significant differences ($P > 0.05$). HIT score was decreased from 21.26 ± 3.58 before intervention to 15.51 ± 4.58 after 3 months in Group 1 and 22.23 ± 2.59–10.33 ± 2.26 in Group 2. In both groups, these changes were statistically significant ($P < 0.001$). Although we found more decrease of HIT score in Group 2 comparing with Group 1 (10.33 ± 2.26 vs. 15.51 ± 4.58), this difference was not statistically significant ($P = 0.12$). **Conclusion:** Although Xeomin and Dysport injections are both effective and reduced pain in patients with chronic migraine, our new technique is probably better than the standard technique. Because the injection points are halved, increase patients comfort and reduce overall cost.

Key words: Botulinum neurotoxin, Dysport, migraine, Xeomin

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INTRODUCTION

Migraine is a chronic headache manifested with attacks with a duration of 4–72 h.[1] Epidemiologic data have confirmed that migraine is prevalent among different populations and has a large negative socio-economic influence. Studies in western countries have also shown that migraine affects almost 11% of adult population mostly in the range of 22–55 years of age.[2,3] In Iran, migraine is one of the most common types of headache and Evidences show 9.5% prevalence in South of Iran.[4]

The most important characteristic of migraine is being lateralized, pulsatile with medium to high severity. The severity of migraine is worsened by daily activities and is also correlated with nausea, photophobia, and phonophobia.[5] Patients with migraine have reported aura or premonitory symptoms which is defined as neurologic manifestations before the attacks.[6] Although some patients report no aura before attacks, some others report these manifestations from hours to days before migraine attacks. These premonitory symptoms are fatigue, lack of concentration, neck stiffness, sensitivity to light or sounds, nausea, unclear vision,

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and pallor.[7] Pathophysiological studies on migraine have indicated that constant and sever sensory stimulations or also acute stimulants cause increased sensory entrance to the central nervous system which leads to increased activation of brain stem nuclei.[8] This activation could result in secretion of vasoactive neuropeptides including p-substance and calcitonin gene-related peptide (CGRP) in vascular terminals of the trigeminal nerve. These actions will finally lead to a vascular inflammation.[9] Due to the international classification of headache disorders-3, headaches that occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache named chronic migraine.

The risk factors of chronic migraine are divided into two main groups. Female gender, low socio-economic situation, and lower educational level are some risk factors which could not be changed and on the other hand anxiety, stress, sleep apnea, obesity, and caffeine are other changeable factors.[10] The treatments of migraine are performed by controlling the risk factors along with prophylaxis treatments. The usage of topiramate and onabotulinum toxin A has been approved in many studies for prophylaxis against chronic migraine.[11]

Medical treatments of migraine are still favorite among patients although some other therapeutic strategies have been developed.[12] Different lines of evidence have confirmed the efficacy of the following drugs for migraine prophylaxis: antidepressants, B-adrenergic blockers, monoamine oxidase inhibitors, and also neuromodulators.[13] Tension headaches are also contributing to chronic migraine in most of the patients. The use of botulinum neurotoxin (BoNT) has been also widely investigated in both chronic migraine and tension headaches which do not respond to common medical treatments.[14] The mechanism of this toxin is by inactivation of motor neural terminals resulting in muscle relaxation. Xeomin is a type A BoNT which is injected into the scalp of patients. Previous studies have shown the beneficial effects of Xeomin injections and the common injection method is 31-point injection of Xeomin in the scalp which is also approved by the Food and Drug Administration (FDA).[15,16]

Dysport is also a type A BoNT mostly used for the treatment of cervical dystonia or cosmetic functions. The use of Dysport injections for the treatments of migraine has been evaluated in different studies but this technique has not been widely used due to a lack of comparative studies.[17] The use of these techniques has been evaluated in few studies and there are still much to be discovered. To the best of our knowledge, no previous study has compared the effects of 31-point Xeomin injections and 15-point Dysport injections in the scalp of patients with chronic migraine. Therefore, we conducted the current study to compare the efficacy of 15-point Dysport injection with 31-point Xeomin injections with the main focus on injection points.

MATERIALS AND METHODS

This is a randomized clinical trial performed from September 2020 to January 2021 in Al-Zahra hospital, Isfahan in Iran. The study population consisted of patients aged 18–60 years with refractory chronic migraine referring to the neurology clinic in our medical center. This study was approved by Research Committee of Isfahan University of Medical Sciences and the Ethical Committee has confirmed it with IR.MUI.MED.REC.1398.116 code. (Iranian Registry of Clinical Trial code (IRCT): IRCT20200217046523N2).

The inclusion criteria were

Age between 18 and 60 years having chronic migraine based on the International Headache Society means headaches that occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, unresponsive to at least 6 months of prophylaxis treatments of migraine (antiepileptic, tricyclic antidepressants, and beta-blockers) and written informed consent to participate in the study.

Exclusion criteria were

Pregnancy or lactation, being under treatments with anti-coagulants, previous exposure to Onabotulinumtoxin A and having any systemic diseases (including diabetes, drug allergies, liver diseases, respiratory diseases, cardiovascular diseases, kidney disorders, myasthenia gravis, and malignancies).

A total number of 60 patients entered the study [Figure 1]. Demographic data of patients were collected. Furthermore, data regarding average consumption of fast foods, average cases of stress in the last month, education, marital status, employment, and menstrual cycles of women were gathered.

The pain of patients was also determined using headache impact test (HIT) questionnaire[18] to evaluate the severity of migraine and its influences on moods of patients and also their daily activities. Data regarding the aura, nausea, vomit, photosensitivity, sensitivity to sounds and smells were also collected in patients.

Randomization was carried out using random generated numbers (Excel Rand) and permuted block randomization approach using block of sizes 4. Group 1 underwent 31-point Xeomin injection. This method was performed using 2 vials of Xeomin 100 units based on the protocol

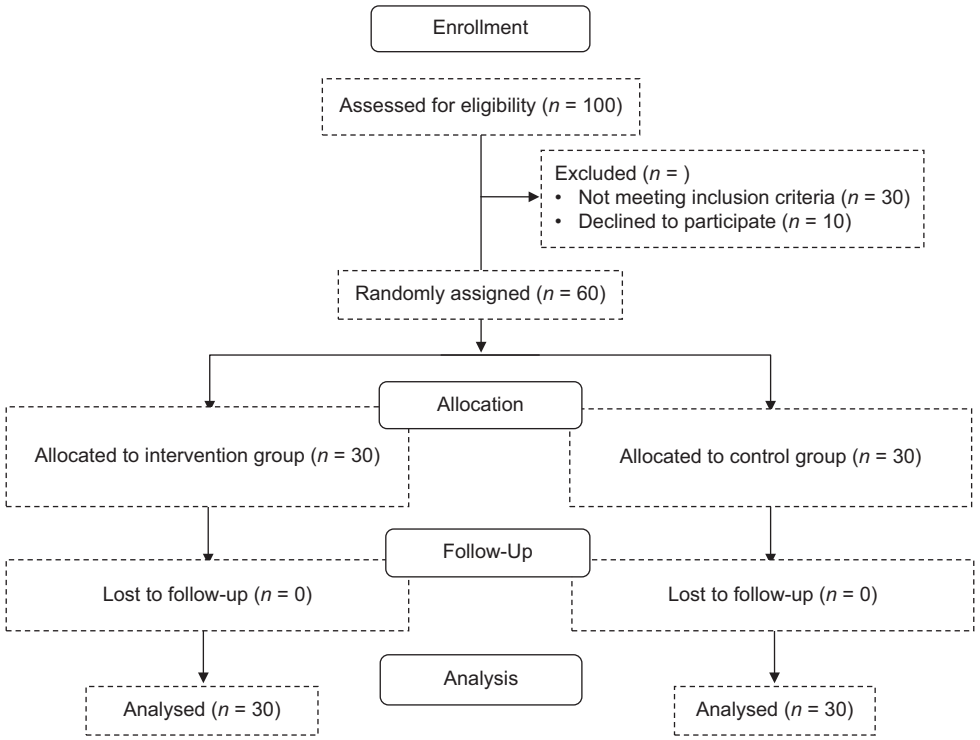

Figure 1: Patients flow diagram

approved by the FDA. The points are described in the study by Ion I *et al*.[19]

The other groups underwent 300 units of Dysport was reconstituted with 1.5 ml of 0.9% NaCl to present a solution containing 200 units/ml. The injection sites of Dysport were determined using the skull sutures. Dysport was injected into 15 points of the scalp which are located on the skull sutures.

The Dysport injection sites on the skull sutures were as follows:

- Six points on squamous suture (3 each side)
- Four points on lambdoid suture (2 each side)
- Two points on sagittal suture.

Three points on the forehead (1 point between eyebrows and 2 points on superior-medial side of each orbit) [Figure 2].

Patients were then followed and visited 1 month after interventions. Data regarding the aura, nausea, vomit, photosensitivity, sensitivity to sounds and smells were collected 1 month after interventions and compared to the beginning. Furthermore, pain and headache of patients were assessed using HIT questionnaires along with the duration of headache based on days and number of headaches per month based on days. Data regarding HIT questionnaires and duration of headache and number of headaches per month were investigated again 2 months and 3 months after interventions.

Data were collected and analyzed using IBM SPSS statistics due to version 24 (IBM, USA). Kolmogorov–Smirnov test was used to explore normality distribution of variables. We used independent samples test, Chi-square, repeated measure analysis, and McNemar's test for data analysis, and the $P < 0.05$ was considered as a significance threshold.

RESULTS

Sixty patients including 20 (33.3%) males and 40 (66.6%) females with refractory chronic migraine entered the study based on inclusion and exclusion criteria. The mean age of patients was 34.16 ± 10.6 years old.

Patients were divided randomly into Group 1 (Xeomin injection) and Group 2 (Dysport injection). Demographic data, data regarding average consumption of fast foods, average cases of stress in the last month, education, marital status, employment, and menstrual cycles of women were analyzed. There were no significant differences between patients of both groups regarding the mentioned information ($P > 0.05$) [Table 1].

This study also revealed that the data regarding aura, nausea, vomit, photosensitivity, sensitivity to sounds and smells did not change significantly between the two groups compared to the beginning of the study. No significant differences were also observed between two Groups ($P > 0.05$). These data are summarized in Table 2.

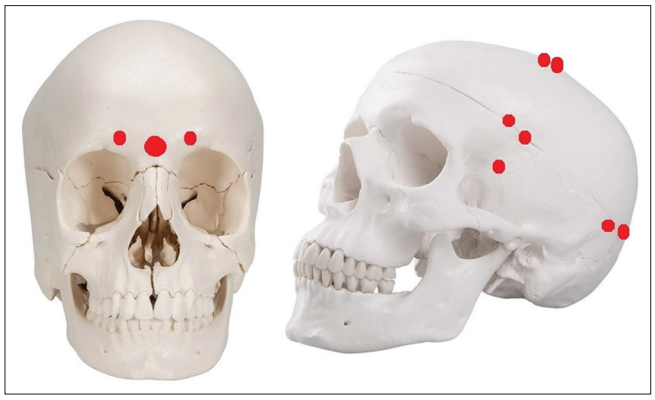

Figure 2: Locations of botulinum toxin injection for chronic migraine headache

Our data also showed that the frequency of headaches, their duration and intensity and the mean HIT score of all patients improved significantly within 3 months after interventions (all $P < 0.05$). A comparison of both groups showed no significant differences among them regarding the mentioned variables [Table 3].

Results of our study demonstrated that HIT score was decreased from 21.26 ± 3.58 before intervention to 15.51 ± 4.58 after 3 months in Group 1 and 22.23 ± 2.59 to 10.33 ± 2.26 in Group 2. In both groups, these changes were statistically significant ($P < 0.001$).

Although we found more decrease in HIT score after 3 months in Group 2 comparing with Group 1 (10.33 ± 2.26 vs. 15.51 ± 4.58), this difference was not statistically significant ($P = 0.12$).

Headache frequency was decreased from 7.99 ± 1.67 days/month before intervention to 4.63 ± 0.92 after 3 months in Group 1 and 8.06 ± 1.99 to 3.90 ± 1.26 in Group 2.

The duration of headache also decreased significantly in both groups after intervention (1.43 ± 0.83–0.69 ± 0.29 in Group 1 and 1.44 ± 0.75–0.61 ± 0.31 in Group 2.

DISCUSSION

Here, in the present study, we evaluated and compared the results of Xeomin and Dysport injections in patients with chronic migraine and showed that data regarding aura, nausea, vomit, photosensitivity, sensitivity to sounds and smells did not change significantly between two groups compared to the beginning of the study. However, on the other hand, we showed a significant improvement in the frequency of headaches, their duration and intensity and the mean HIT score of all patients. On the other hand, we did not observe any significant differences between two groups of patients. The lower points for injection were used to increase patients' comfort and lower overall cost.

Table 1: Analysis of demographic data and other variables

Variable	Group 1	Group 2	*P*
Age (year), mean±SD	35.16±11.85	33.16±9.20	0.46*
Times of fast food consumption, mean±SD	3.53±2.43	3.96±2.57	0.52*
Times of having stress in month, mean±SD	4.23±1.79	5.10±2.12	0.09*
Sex, *n* (%)			
Female	19 (31.7)	21 (35)	0.58**
Male	11 (18.3)	9 (15)	
Education, *n* (%)			
Without	2 (3.3)	2 (3.3)	0.98**
Diploma	15 (25)	16 (26.7)	
Bachelor	4 (6.7)	5 (8.3)	
Doctorateandmore	9 (15)	7 (11.7)	
Marriage, *n* (%)			
Single	13 (21.7)	10 (16.7)	0.29**
Married	17 (28.3)	18 (30)	
Widow/divorced	0	2 (3.3)	
Occupation, *n* (%)			
Employed	16 (26.7)	18 (30)	0.76**
Unemployed	14 (23.3)	12 (20)	
Menstrual cycles, *n* (%)			
Menopause	3 (7.5)	1 (2.5)	0.50**
Regular	10 (25)	12 (30)	
Irregular	6 (15)	8 (20)	

**P*-value using independent samples test; ***P*-value using Chi-square. SD=Standard deviation

Table 2: Data regarding associated factors with headache among both groups

Variable	Before, *n* (%)	After, *n* (%)	*P**	*P***
Aura				
Group 1	9 (30)	8 (26.7)	1.00	1.00
Group 2	8 (26.7)	8 (26.7)	1.00	
Nausea				
Group 1	8 (26.7)	8 (26.7)	1.00	0.57
Group 2	10 (33.3)	10 (33.3)	1.00	
Vomit				
Group 1	2 (6.7)	1 (3.3)	1.00	0.55
Group 2	3 (10)	2 (6.7)	1.00	
Photosensitivity				
Group 1	17 (56.7)	17 (56.7)	1.00	0.19
Group 2	12 (40)	12 (40)	1.00	
Sensitivity to sounds				
Group 1	6 (20)	6 (20)	1.00	0.75
Group 2	7 (23)	7 (23)	1.00	
Sensitivity to smells				
Group 1	6 (20)	5 (16.7)	1.00	0.44
Group 2	5 (16.7)	3 (10)	1.00	

*P-value using McNemar's test, **P-value using Chi-square

The use of Xeomin injections in the scalp for the prophylaxis of chronic migraine has been well studied. Green and Rothrock reported that Xeomin injections are effective and beneficial which is also approved by FDA but also declared that this

Table 3: Comparison of headache characteristics among both groups

Variable	Mean±SD				*P** (time)	*P** (time×intervention)	*P** (intervention)
	Before	1 month	2 months	3 months			
Headache frequency (month)							
Group 1	7.99±1.67	7.20±1.60	5.90±1.34	4.63±0.92	<0.001	0.24	0.62
Group 2	8.06±1.99	7.26±2.01	5.77±1.74	3.90±1.26	<0.001		
*P***	0.83	0.88	0.68	0.26			
Duration of headache (day)							
Group 1	1.43±0.83	1.34±0.74	0.80±0.38	0.69±0.29	<0.001	0.34	0.69
Group 2	1.44±0.75	1.24±0.57	0.78±0.45	0.61±0.31	<0.001		
*P***	0.98	0.52	0.87	0.34			
Headache intensity							
Group 1	8.08±1.59	7.30±1.48	6.96±1.65	4.20±0.84	<0.001	0.32	0.01
Group 2	7.97±1.62	6.63±1.37	5.76±1.35	3.06±0.90	<0.001		
*P***	0.81	0.07	0.06	0.06			
HIT score							
Group 1	21.26±3.58	18.90±2.78	17.63±3.44	15.51±4.58	<0.001	0.12	0.001
Group 2	22.23±2.59	17.33±2.61	14.56±2.17	10.33±2.26	<0.001		
*P***	0.19	0.12	0.14	0.07			

*P-value using repeated measure test, **P-value using independent-t-test. SD=Standard deviation, HIT=Headache impact test

method is associated with pain and requires an expert physician.[20] The usage of Xeomin injections for treatments of chronic migraine has been also shown to be useful in some other studies.[21,22] Another study was conducted by Escher *et al*. in 2017 on patients with chronic migraine. They showed that 31-point Xeomin injections are well tolerated in patients and are associated with no complications except injection pain they also showed that this method might have no significant effects on the aura in patients.[14] These results are in line with the findings of our study emphasizing on the effectiveness of Xeomin injections. As mentioned, injection of Xeomin in 31 points in the scalp is approved by FDA and its efficacy has been well established by previous studies. Usage of Dysport injection in the scalp was also associated with improvements in chronic migraine.[23]

The key point of the current study was that we used a new technique for injections in the scalp. We used Dysport and injected this agent into 15 points of the scalp.

Ravenni *et al.* also showed that both Dysport and Xeomin injections are associated with pain relief in chronic migraine but they could not compare the two methods.[24]

Here, we compared the injection of Dysport with Xeomin and showed that both methods are beneficial and no significant differences could be observed.

We believe that 15-point Dysport injection is an easier technique and associated with less injection pain in patients compared to 31-point injections. As previously indicated, CGRP receptors are mostly concentrated on the skull sutures[25,26] which leads to increased drug effectiveness in Dysport injections. This issue was indicated by Blumenfeld in 2017 they showed that 15-point BoNT injections on sutures are associated with beneficial results due to CGRP receptors concentration.[27] We also believe that the other reasons of the same results between Xeomin and Dysport injections are due to the molecular characteristics of Dysport.[28] Based on the evidence, Dysport spreads to a wider area compared to Xeomin because of smaller molecular size while on the other hand, effects of Xeomin injections are limited to a smaller area.[29] The concentration of CGRP receptors of the skull sutures and molecular characteristics of Dysport led to similar therapeutic effects of this agent compared to Xeomin.

In the current study, we showed that the frequency of headaches, their duration and intensity and the mean HIT score improved in all patients after Xeomin and Dysport injections. This was in line with the findings of previous studies but we also recommend that neurologists should pay more attention to 15-point Dysport injections due to less injection's sites and also fewer injection pain. The key point of this study was that we compared both 31-point Xeomin and 15-point Dysport injection techniques and reported that the both methods are beneficial. As explained, the Dysport molecules are better distributed compared to Xeomin and bring the highest efficacy when injected into the skull suture due to CGRP receptors concentrations. This technique is a novel therapeutic procedure for chronic migraine that has the same efficacy compared to 31-point injections of Xeomin.

This study has some limitations. First, due to the small sample size of our study further studies with a larger population are needed to confirm our findings. Second, despite several adjustments, further control for confounding variables such

as previous prophylactic medication, medical history, and psychosocial factors will be needed to reach an independent association between pain control and method of injection.

Third, maybe it would be better to evaluate patients after multiple courses of botulinum toxin injection.

CONCLUSION

Taken together, we showed that Xeomin and Dysport injections are both effective and lead to reduced pain and symptoms in patients with chronic migraine. These results were in line with the previous studies but we believe that 15-point Dysport injections have priority compared to 31-point Xeomin injections due to fewer injection sites and injection pain. We also suggest that neurologists should pay more attention to BoNT injections techniques for treatments and prophylaxis of chronic migraine.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: A disorder of sensory processing. Physiol Rev 2017;97:553-622.
2. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, burden, and comorbidity. Neurol Clin 2019;37:631-49.
3. Scher AI, Buse DC, Fanning KM, Kelly AM, Franznick DA, Adams AM, *et al*. Comorbid pain and migraine chronicity: The Chronic Migraine Epidemiology and Outcomes Study. Neurology 2017;89:461-8.
4. Sadeghi O, Maghsoudi Z, Askari G, Khorvash F, Feizi A. Association between serum levels of homocysteine with characteristics of migraine attacks in migraine with aura. J Res Med Sci 2014;19:1041-5.
5. Martami F, Togha M, Seifishahpar M, Ghorbani Z, Ansari H, Karimi T, *et al*. The effects of a multispecies probiotic supplement on inflammatory markers and episodic and chronic migraine characteristics: A randomized double-blind controlled trial. Cephalalgia 2019;39:841-53.
6. Charles A. The migraine aura. Continuum (Minneap Minn) 2018;24:1009-22.
7. Karsan N, Bose P, Goadsby PJ. The migraine premonitory phase. Continuum (Minneap Minn) 2018;24:996-1008.
8. Haanes KA, Edvinsson L. Pathophysiological mechanisms in migraine and the identification of new therapeutic targets. CNS Drugs 2019;33:525-37.
9. Scuteri D, Adornetto A, Rombolà L, Naturale MD, Morrone LA, Bagetta G, *et al*. New trends in migraine pharmacology: Targeting calcitonin gene-related peptide (CGRP) with monoclonal antibodies. Front Pharmacol 2019;10:363.
10. May A, Schulte LH. Chronic migraine: Risk factors, mechanisms and treatment. Nat Rev Neurol 2016;12:455-64.
11. Barbanti P, Ferroni P. Onabotulinum toxin A in the treatment of chronic migraine: Patient selection and special considerations. J Pain Res 2017;10:2319-29.
12. Long R, Zhu Y, Zhou S. Therapeutic role of melatonin in migraine prophylaxis: A systematic review. Medicine (Baltimore) 2019;98:e14099.
13. Danesh A, Gottschalk PC. Beta-blockers for migraine prevention: A review article. Curr Treat Options Neurol 2019;21:20.
14. Escher CM, Paracka L, Dressler D, Kollewe K. Botulinum toxin in the management of chronic migraine: Clinical evidence and experience. Ther Adv Neurol Disord 2017;10:127-35.
15. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. Toxins 2016;8:65.
16. Spiegel LL, Ostrem JL, Bledsoe IO. FDA approvals and consensus guidelines for botulinum toxins in the treatment of dystonia. Toxins (Basel) 2020;12:E332.
17. Field M, Splevins A, Picaut P, van der Schans M, Langenberg J, Noort D, *et al*. AbobotulinumtoxinA (Dysport®), OnabotulinumtoxinA (Botox®), and IncobotulinumtoxinA (Xeomin®) neurotoxin content and potential implications for duration of response in patients. Toxins (Basel) 2018;10:E535.
18. Nachit-Ouinekh F, Dartigues JF, Henry P, Becg JP, Chastan G, Lemaire N, *et al*. Use of the headache impact test (HIT-6) in general practice: Relationship with quality of life and severity. Eur J Neurol 2005;12:189-93.
19. Ion I, Renard D, Le Floch A, De Verdal M, Bouly S, Wacongne A, *et al*. Monocentric prospective study into the sustained effect of Incobotulinumtoxin A (XEOMIN®) botulinum toxin in chronic refractory migraine. Toxins 2018;10:221.
20. Green MW, Rothrock JF. An academic debate: OnabotulinumtoxinA for chronic migraine: PREEMPT-derived vs. "customized" dosing/injection paradigm. Toxicon 2018;147:116-9.
21. Mimeh H, Fenech Magrin AM, Myers S, Ghanem AM. A critical review of botulinum toxin type A in the prophylactic treatment of chronic migraine in adults. Aesthet Surg J 2019;39:898-907.
22. Kaye R, Binder WJ, Blitzer A. Botox for migraine headaches and facial pain. InDiagnosis and Management of Head and Face Pain. Springer, Cham. 2018. p. 171-86.
23. Hollanda L, Monteiro L, Melo A. Botulinum toxin type a for cephalic cutaneous allodynia in chronic migraine: A randomized, double-blinded, placebo-controlled trial. Neurol Int 2014;6:5133.
24. Ravenni R, De Grandis D, Mazza A. Conversion ratio between Dysport and Botox in clinical practice: An overview of available evidence. Neurol Sci 2013;34:1043-8.
25. Eltorp CT, Jansen-Olesen I, Hansen AJ. Release of calcitonin gene-related peptide (CGRP) from guinea pig dura mater *in vitro* is inhibited by sumatriptan but unaffected by nitric oxide. Cephalalgia 2000;20:838-44.
26. Baillie LD, Ahn AH, Mulligan SJ. Sumatriptan inhibition of N-type calcium channel mediated signaling in dural CGRP terminal fibres. Neuropharmacology 2012;63:362-7.
27. Blumenfeld AM. Suture Line Administration Technique Using Botulinum Toxins. Google Patents; US20090252764A1.
28. Pickett A. Dysport®: Pharmacological properties and factors that influence toxin action. Toxicon 2009;54:683-9.
29. Frevert J. Content of botulinum neurotoxin in botox®/vistabel®, dysport®/azzalure®, and xeomin®/bocouture®. Drugs R D 2010;10:67-73.