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DE DOCTEUR EN MEDECINE

IMPROVEMENT IN QUALITY OF LIFE AFTER BOTULINUM TOXIN INJECTION FOR TEMPOROMANDIBULAR DISORDER

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Avertissement

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I. INTRODUCTION GENERALE (en français)

Les dysfonctions temporo-mandibulaires (DTM) ont été décrites depuis le 20ème siècle et sont à l'origine de nombreuses études.

L'articulation temporo-mandibulaire ou ATM unit la fosse mandibulaire de l'os temporal avec le condyle de la mandibule par l'intermédiaire d'un disque articulaire. Cette articulation permet des mouvements d'ouverture et de fermeture buccale ainsi que des mouvements de propulsion et de diduction. Un groupe de muscles spécialisés, les muscles manducateurs (comprenant le muscle masséter et temporal), contrôlent également le mouvement de l'articulation.

De multiples facteurs contribuent à l'étiologie des DTM [1]. Deux étiologies sont à différencier ; les DTM d'origine fonctionnelle ou musculaire et les DTM d'origine anatomique ou articulaire [2]. Ces deux étiologies peuvent se combiner. Elles sont sous l'influence de déterminants mécaniques, structurels, systémiques et psychosociaux qui vont être responsables de troubles et de douleurs chroniques affectant la qualité de vie des patients [3].

Différents types de traitements sont proposés dans le cadre des DTM : traitement pharmacologique, physiothérapie, approche comportementale, psychothérapie,

gouttières occlusales, ou traitement chirurgical [4]. Actuellement il n'y a aucun consensus concernant l'approche de traitement la plus efficace. L'infiltration de toxine botulique au niveau des muscles manducateurs est une des modalités thérapeutiques.

La toxine botulique possède une double action sur la jonction neuromusculaire : tout d'abord elle inhibe la libération d'acétylcholine menant à la dégénérescence des terminaisons nerveuses et par conséquent à la paralysie ; et secondairement elle diminue les douleurs inflammatoires en modulant la sécrétions de neurotransmetteurs tels que la substance P ou le glutamate [5].

Une première étude, datant de 1998 [6] [7], a démontré que la toxine botulique réduisait la douleur et améliorait la mobilité articulaire des patients présentant des DTM [8] [9]. Encore aucune étude n'a étudié la qualité de vie après infiltration de toxine botulique chez ces patients ; cela a été, au cours de cette étude prospective, l'objectif de notre travail.

II. INTRODUCTION

Temporomandibular disorders (TMDs) have been known since the 20th century and have been extensively researched. In fact, multiple factors contribute toward its aetiology [1]. TMDs are influenced by several mechanical, structural, systemic and psychosocial determinants which generate chronic disorders and have marked and profound effects on daily life. Varying degrees and types of pain of the temporomandibular joint can originate either from the joint himself or can be secondar to hyperfunctioning of masticatory muscles [2].

Several lines of treatment have already been suggested for TMDs: pharmacological treatment, physiotherapy, behavioural approach, psychotherapy, occlusal splints, or surgical treatment [3]. At present, there is no consensus regarding the most effective treatment approach. Botulinum toxin is one of the treatment modalities proposed in literature. The painful and chronic characteristics of TMDs interfere with the quality of life (QoL) of patients [4]. Botulinum toxin has a double action on the neuromuscular junction: first, inhibition of acetylcholine release leads to degeneration of nerve endings and consequently paralysis; second, botulinum toxin decreases inflammatory pain by inhibiting substance P and glutamate release [5].

The first study, dating back to 1998 [6][7], demonstrated that botulinum toxin reduces pain and improves mobility in patients with dysfunction of the masticatory system [8][9]. However, no study has investigated QoL after injection of botulinum toxin in patients with TDMs; the present retrospective study aimed to evaluate the same.

III. MATERIALS AND METHODS

III.1. Patients

This prospective study was conducted at the Lille University Hospital. Patients with TMDs were recruited from Nov. 2016 to Sept. 2017 to be treated with botulinum toxin A (BTX-A) injections. TMD was assessed using routine clinical examination performed by the same maxillofacial surgeon before injection treatment and entered into the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) [10]. In accordance with RDC/TMD, all patients had at least myofascial pain. Body mass index (BMI) and presence of bruxism were also evaluated in each patient.

III.2. Botulinum toxin A injection technique

Type-A botulinum toxin was Botox reconstituted with 1 mL physiological saline for 100 U of Botox. Patients received a total of 150 U of BTX-A injections into bilateral masseter and temporalis muscles [11][12]: 50 U per masseter muscle was divided into three injection sites and 25 U per temporalis muscle was divided into two injection sites (Fig. 1).

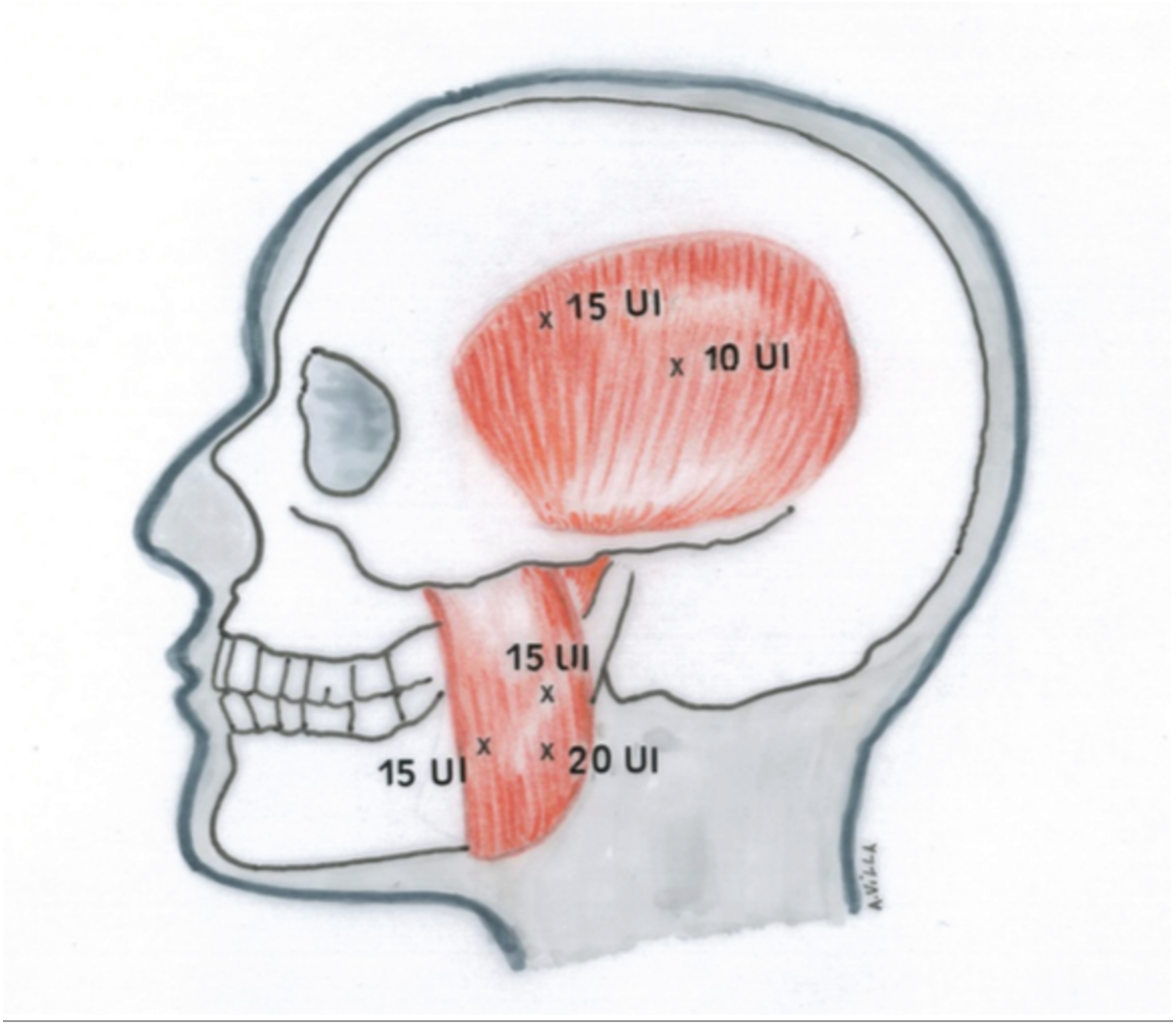

Fig. 1. BTX-A injection distribution in temporal and masseter muscles

III.3. Quality of life evaluation

Various approaches can be used to measure oral health-related QoL. We selected two QoL questionnaires.

The first was an adaptation of the Oral Health Impact Profile questionnaire (OHIP-14) (Table 1). OHIP-14 is a questionnaire designed to measure self-reported discomfort, functional limitation and disability due to oral conditions. It is derived from an original version of 49 items developed by the World Health Organization and adapted for oral health by Locker [13]. The scores range from 10 to 50.

The second questionnaire was an adaptation of the temporomandibular joint replacement quality of life questionnaire (TMJ-QoL) (Table 2). It consists of 12 questions, which cover physical, functional and psychosocial aspects of patients' lives [14]. The scores range from 12 to 60.

Treatment efficacy was evaluated by measuring pain on a visual analogue scale (VAS), with scores ranging from 0 to 10.

All patients answered both questionnaires and VAS before BTX-A injection, at 1 month after injection and at 3 months after injection. Any reduction in scores represented improvement in QoL. No missing data was reported for any of the recruited patients. All patients provided written informed consent for data collection and presentation.

III.4. Statistical analysis

Quantitative variables were described using mean and standard deviation. Normality of distributions was verified with the help of graphs and the Shapiro–Wilk test. On the other hand, qualitative variables were described using frequencies and percentages.

Evolution of patients' QoL (TMJ-QoL and OHIP-14) and pain (VAS) from baseline (injection) to 1 and 3 months after injection was appreciated using longitudinal mixed models.

Correlation between age, BMI and QoL was calculated using Pearson's correlation coefficients. Moreover, correlation between sex, bruxism and QoL was assessed using student's t-tests. In case of non-normality of data, nonparametric Wilcoxon tests were used.

The threshold for significance was set at 0.05. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC, USA).

IV. RESULTS

In total, 28 patients with TMD (17 women, 11 men) were included. The mean patient age was 45.0±14.0 (range: 18–68) years, and the average BMI was 25.4±6.2. All patients presented myalgia of masticatory muscles. Associated to TMD, the most commonly diagnosed condition was disc displacement (32%), followed by TMD-related headache (10.5%) and arthralgia (7%). Disc displacement without reduction was the least common Axis I diagnosed condition (3.5%). Bruxism was noted in 21 patients. None of the patients reported any adverse effects after injection.

IV.1. Quality of life assessment

Significant improvement in QoL (TMJ-QoL and OHIP) was noted at 1 ($p<0.0001$) and 3 months after BTX-A injection ($p<0.001$) (Fig. 2).

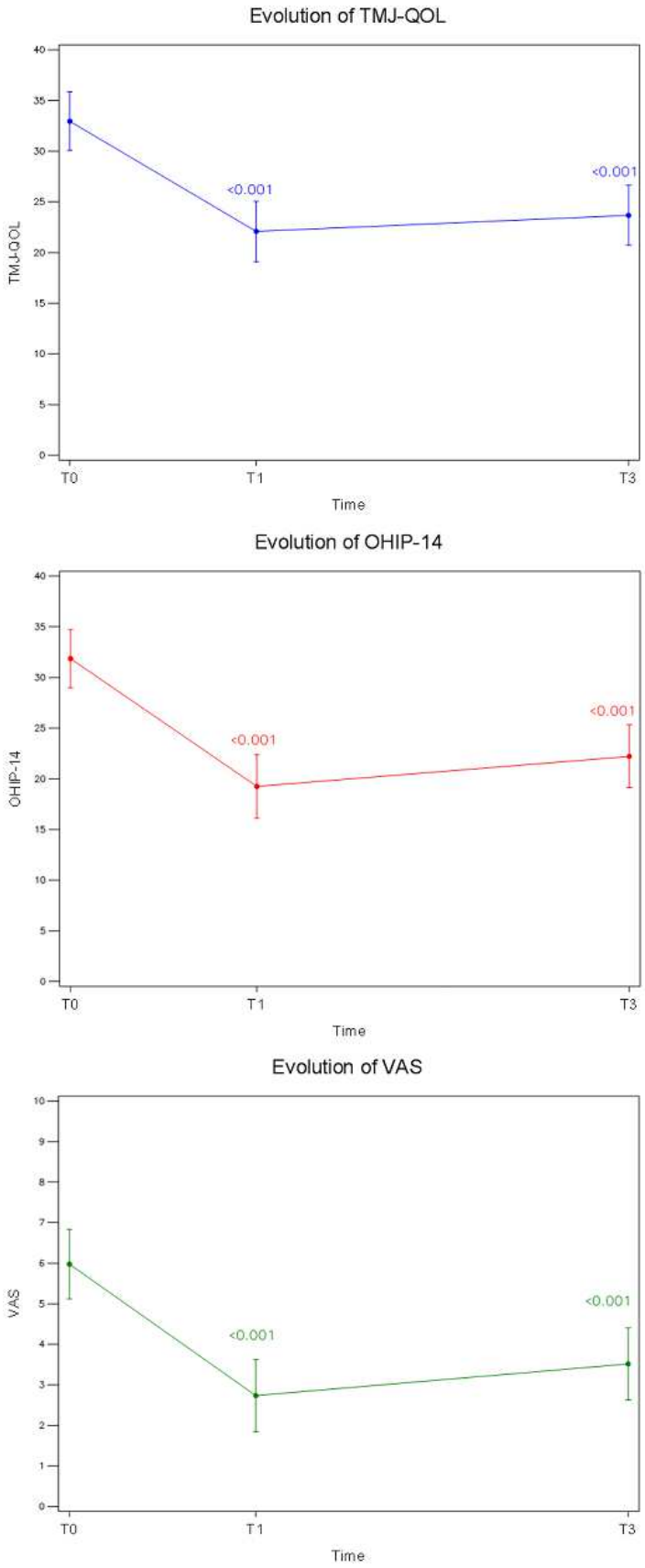

Fig. 2. Evolution (mean and 95% confidence intervals) of the two QoL questionnaires (OHIP and TMJ-QoL) and VAS from injection (T0) to 1 month after injection (T1) and 3 months after injection (T3) with p values of comparison with T0

IV.2. Pain assessment

All patients reported significant improvements in VAS scores ($p<0.001$) at 1 and 3 months after BTX-A injection (Fig. 2).

IV.3. Association between quality of life and other factors: bruxism, age, sex and BMI

No significant association was identified between improvement in QoL after BTX-A injection and age, sex and bruxism. However, a significant positive but moderate correlation (Pearson Correlation Coefficient of 0.45) was noted between TMJ-QoL before BTX-A injection and BMI ($p=0.016$), indicating the relative importance of BMI. As the correlation is positive, hight BMI would be associated with hight TMJ-QoL scores before BTX-A injection, which, in turn, would indicate a worse QoL (Table 3).

		OHIP T0	**OHIP T1**	**OHIP T3**	**TMJ-QoLT0**	**TMJ-QoLT1**	**TMJ-QoLT3**
AGE	PCC	-0.05	0.18	0.31	-0.14	0.08	0.19
	p value	*0.79*	*0.35*	*0.10*	*0.47*	*0.69*	*0.34*
BMI	PCC	0.32	-0.17	-0.04	0.45	-0.03	-0.02
	p value	*0.10*	*0.3878*	*0.8504*	***0.016***	*0.89*	*0.90*

Table 3. Correlation between QoL scores and age and BMI by using Pearson correlation coefficient (PCC)

V. DISCUSSION GENERALE (*en français*)

Notre étude, comme plusieurs autres publications, confirme l'amélioration de la douleur après infiltration de toxine botulique [15]. Une corrélation entre la sévérité de la DTM et l'impact sur la qualité de vie avait déjà par le passé été mise en évidence [16]. L'amélioration de la qualité de vie était significativement plus importante 1 mois après infiltration qu'à 3 mois après infiltration. Ces résultats sont cohérents avec les données actuelles de la littérature où l'effet maximal du traitement est obtenu après 1 à 4 semaines et dure pendant 3 à 6 mois selon les différents patients [17].

L' OHIP est reconnu comme étant spécifique aux fonctions orales [18]. Aucune version française n'étant disponible, une traduction aussi précise que possible a été réalisée. On note cependant quelques inconvénients à ce score comme le manque de clarté concernant certaines questions. La nuance entre l'incapacité, l'inconfort et la limitation est parfois difficile à saisir et peut interférer dans l'interprétation des résultats. Néanmoins, l'OHIP a été choisi comme outil d'évaluation en raison de sa reconnaissance internationale et de son utilisation dans plusieurs études récentes [19]. Le second questionnaire, le TMJ-QoL, a été choisi en raison de sa plus grande spécificité concernant les symptômes affectant l'articulation temporo-mandibulaire, mais ce questionnaire n'a actuellement aucune validité internationale.

Notre étude présente certaines limites. Il s'agit d'une étude monocentrique avec un échantillon de petite taille. L'interprétation parfois subjective des questionnaires a pu modifier certains résultats. De plus, plusieurs autres facteurs qui pourraient avoir affecté la qualité de vie, n'ont pas été pris en considération, comme par

exemple la prise d'autres traitements concomitante aux infiltrations de TXB-A ou encore la présence de pathologies multiples autres que les DTM. Le muscle ptérygoïdien latéral n'a pas été pris en compte. Ce muscle fait en effet parti des muscles manducateurs et sont hypercontractilité joue un rôle dans les DTM. Cependant sa topographie profonde le rend difficile d'accès, et les infiltrations intramusculaires sans guidage, tel que l'électromyographie ou l'IRM, sont hasardeuses.

VI. DISCUSSION

Management of TMD, a multi-factorial and polysymptomatic pathology, cannot be univocal and must be customized on case-by-case basis. Permanent muscle involvement in various mechanisms of the temporomandibular joint and consequently TMD justifies the use of multiple muscle-relaxant therapies such as botulinum toxin. Although botulinum toxin has not been proven superior over other treatments for TMD, it is a part of the therapeutic arsenal with a good risk-to-benefit ratio. Treatment for TMD aims to relieve algebraic attacks and break the vicious cycle of chronic pain.

Findings from our study, like various other publications, confirmed improved pain relief after botulinum toxin injections [15]. A previous study proved a correlation between severity of TMD and its impact on QoL [16]. In the present study, improvement in QoL was significantly greater at 1 month after injection compared with at 3 months after injection; this finding was consistent with reports from previous studies, wherein the maximum effect of treatment was obtained after 1–4 weeks, which lasted for up to 3–6 months depending on individual patients [17].

The World Health Organization defined Health (1947) as ‘a state of complete physical, mental and social well-being, and not only as the absence of disease’. This definition incorporates both social and psychological aspects. Thus, level of health must be assessed within the larger framework of QoL.

In general, health-related QoL takes into account not all dimensions of QoL but only those which can be modified by the disease, including the physical condition of the patient, somatic sensations (symptoms, therapeutics, pain, sequelae), psychological

state (emotionality, anxiety, depression) and social relations (relation to the family environment, friendly or professional).

OHIP is recognised as being specific to oral functions [18]. As no French version is available, we created a translated version (as accurate and faithful as possible) of the same. This questionnaire included 10 questions grouped into seven domains: functional limitation, physical pain, psychological discomfort, physical incapacity, psychological incapacity, social incapacity and handicap.

However, as a disadvantage, the OHIP scoring system lacks clarity regarding certain issues. Nuances between discomfort and disability are sometimes difficult to grasp, and inaccurate interpretation could affect the scores obtained. Nevertheless, OHIP was chosen as an assessment tool because of its international recognition and its use in several recent studies [19]. The second QoL questionnaire TMJ-QoL was chosen because of its greater specificity regarding symptoms, which affect the temporomandibular joint, but this questionnaire has not yet been validated. In our study, improvement in pain levels had, independent of associated psychopathological comorbidities, a reverberating impact on daily life by improving somatic sensations, psychological state as well as social relations, and consequently QoL on the whole.

In a previous study, TMD was more prevalent in women than in men, but no gender differences were noted in terms of its impact on QoL [16]. However, in the present study, no correlation was identified between age, gender, as well as bruxism and improvement in QoL after BTX-A injections, which could probably be explained by the insufficient statistical power of the study. On the other hand, a positive correlation was observed between high BMI and lower QoL in patients with TMD. Several studies have investigated the relationship between TDM and obesity with discordant

results. In a recent study, Rhim *et al*. found that TMD was associated with low BMI and abdominal obesity in women [20], whereas no such correlation has been found in other studies [21][22].

Our study had certain limitations. It is a monocentric study with a small sample size. In addition, subjective interpretation of questionnaires could have altered the results. Furthermore, several other factors, which could have affected QoL, were perhaps not taken into account, such as patients taking treatments other than BTX-A injections and presence of multiple pathologies other than TMDs.

VII. CONCLUSION

Clinical injection of BTX-A in masticatory muscles of patients with TMD can be considered as a useful supportive treatment option to control pain and improve QoL. However, additional studies with larger samples are required to extrapolate these results, perhaps a randomised, double-blind, placebo-controlled trial testing a null hypothesis.

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IX. ANNEXES

Because of problems with your teeth, mouth, or dentures…	Never	Hardly ever	Occasionally	Fairly often	Very often
Have you had painful?	1	2	3	4	5
Have you found it uncomfortable to eat any food?	1	2	3	4	5
Have you been a bit embarrassed?	1	2	3	4	5
Have you felt tense?	1	2	3	4	5
Has your diet been unsatisfactory?	1	2	3	4	5
Have you had to interrupt meals?	1	2	3	4	5
Have you found it difficult to relax?	1	2	3	4	5
Have you had difficulty doing your usual jobs?	1	2	3	4	5
Have you felt that life in general was less satisfying?	1	2	3	4	5
Have you been totally unable to function?	1	2	3	4	5

Table 1. Adaptation of the Oral Health Impact Profile-14 (OHIP-14)

	No difficulty	Mild difficulty	Moderate difficulty	Severe difficulty	Unable
Having a conversation	1	2	3	4	5
Eating	1	2	3	4	5
Yawning	1	2	3	4	5
Sleeping	1	2	3	4	5
Recreational activities	1	2	3	4	5

	Never	Rarely	Once a day	Regularly	Pain not controlled
How often do you have to take medication to control your pain?	1	2	3	4	5

	Never	Seldom	Quite often	Very often	Always
How often do you feel depressed because of your TMJ problems?	1	2	3	4	5

	Not at all	Slightly	Moderately	Quite a bit	Extremely
Do you feel your mouth improved?	1	2	3	4	5

Do you feel your facial appearance has been affected?	1	2	3	4	5
How have your TMJ problems affected your social life?	1	2	3	4	5
How have your TMJ problems limited your daily activities?	1	2	3	4	5

	Very poor	Poor	Neither poor or good	Good	Extremely good
How would you rate your quality of life?	1	2	3	4	5

Table 2. Adaptation of the TemporoMandibular Joint replacement Quality Of Life questionnaire (TMJ-QoL)

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Date de Soutenance : 27 septembre 2018

Titre de la Thèse : Improvement in quality of life after botulinum toxin injection for temporomandibular disorder

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Cadre de classement : Chirurgie Maxillo-Faciale et Stomatologie

DES + spécialité : *DES de Chirurgie Générale, Chirurgie Maxillo-Faciale et Stomatologie*

Mots-clés : quality of life, botulinum toxin type A, temporomandibular disorder

Résumé :
Background: Temporomandibular disorders (TMDs) cause chronic pain and interfere with quality of life (QoL). Botulinum toxin is one of the treatment modalities popularly used for TMDs. The primary objective of this prospective study was to evaluate improvement in QoL after botulinum toxin injections in patients with TMD.
Methods: Twenty-eight patients diagnosed with TMD were included in this study. In accordance with the Research Diagnostic Criteria for Temporomandibular Disorders, all patients had myofascial pain. They received botulinum toxin A (BTX-A) injections in temporalis and masseter muscles. QoL was measured using a French translated version of the validated Oral Health Impact Profile-14 (OHIP-14) and a second questionnaire, which was an adaptation of the temporomandibular joint replacement QoL questionnaire (TMJ-QoL). Patients answered both questionnaires and a visual analogue scale (VAS) before the injection, at 1 month after the injection and at 3 months after the injection. Relationship between QoL and factors such as bruxism, age, sex and body mass index (BMI) were also evaluated.
Results: All patients reported significant improvements in QoL (OHIP-14 and TMJ-QoL) and VAS scores at 1 and 3 months after BTX-A injections ($p<0.0001$). A significant moderate positive correlation was noted between TMJ-QoL before BTX-A injections and BMI ($p=0.016$).
Conclusion: Overall, QoL in patients with TMD improved significantly at 1 and 3 months after BTX-A injections. BTX-A injection in masticatory muscles of patients with TMD can be a useful supportive therapy to control pain and improve QoL.

Composition du Jury :

Président :
Monsieur le Professeur Joël Ferri
Assesseurs :
Madame le Professeur Brigitte Benzacken
Monsieur le Professeur Gwenaël Raoul
Directeur de Thèse :
Monsieur le Docteur Romain Nicot