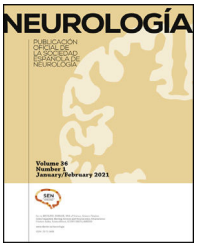
Neurología 38 (2023) 560—565

NEUROLOGÍA

www.elsevier.es/neurologia



ORIGINAL ARTICLE

Effect of botulinum toxin type A in functionality, synkinesis and quality of life in peripheral facial palsy sequelae☆

U. Díaz-Aristizabal*, M. Valdés-Vilches, T.R. Fernández-Ferreras, E. Calero-Muñoz, E. Bienzobas-Allué, L. Aguilera-Ballester, J. Carnicer-Cáceres

Servicio de Rehabilitación y Medicina Física, Xarxa Sanitària i Social Santa Tecla, Tarragona, Spain

Received 18 November 2020; accepted 10 January 2021
Available online 10 July 2023

KEYWORDS
Peripheral facial palsy;
Synkinesis;
Botulim toxin A;
Quality of life;
Face muscle function

Abstract
Objectives: This study aimed to assess the effects of botulinum toxin A (BTX-A) infiltration on face muscle function, synkinesis, and quality of life in patients with sequelae of peripheral facial palsy (PFP).
Material and methods: We present the results of a prospective study including a sample of 20 patients with sequelae of PFP (15 women, 5 men) who underwent BTX-A (Botox© or Xeomin©) infiltration. All patients had previously received personalised treatment with neuromuscular retraining. A clinical assessment was performed before BTX-A infiltration and 4 weeks after treatment. The effect of BTX-A on face muscle function, quality of life, and synkinesis was evaluated using the Sunnybrook Facial Grading System (SFGS), the Facial Clinimetric Evaluation (FaCE) questionnaire, and the Synkinesis Assessment Questionnaire (SAQ), respectively.
Results: Mean SFGS scores increased from 64.8 to 69.9 after BTX-A infiltration ($P = .004$). Increases were also observed in mean total FaCE scores (from 52.42 to 64.5; $P < .001$) and the mean score on the FaCE social function subscale (from 61.15 to 78.44; $P < .001$). Mean SAQ scores decreased from 46.22 to 37.55 after BTX-A infiltration ($P = .001$).
Conclusions: BTX-A infiltration increases face muscle function, improves quality of life, and reduces synkinesis in patients with sequelae of PFP.

DOI of refers to article: https://doi.org/10.1016/j.nrl.2021.01.015.
* Corresponding author.
E-mail address: udiaz@xarxatecla.cat (U. Díaz-Aristizabal).

https://doi.org/10.1016/j.nrleng.2023.07.003

PALABRAS CLAVE
Parálisis facial periférica;
Sincinesia;
Toxina botulínica tipo A;
Calidad de vida;
Funcionalidad facial

Efecto de la toxina botulínica tipo A en la funcionalidad, las sincinesias y la calidad de vida en secuelas de parálisis facial periférica

Resumen
Objetivo: Valorar el efecto del tratamiento con infiltraciones de Toxina Botulínica tipo A (TXB-A) en la funcionalidad facial, las sincinesias y la calidad de vida en pacientes con secuelas de Parálisis Facial Periférica (PFP).
Material y métodos: Presentamos un estudio prospectivo con una muestra de 20 pacientes con secuelas de PFP (15 mujeres, 5 varones), a los que se infiltró TXB-A (Botox© o Xeomin©). Todos los pacientes realizaron previamente un tratamiento personalizado basado en la reeducación neuromuscular. Se realizó una evaluación clínica previa a las infiltraciones y otra al cabo de 4 semanas. El efecto de las infiltraciones sobre la funcionalidad facial fue valorado mediante la escala Sunnybrook Facial Grading System (SFGS). El efecto sobre la calidad de vida se evaluó a través del cuestionario Facial Clinimetric Evaluation Scale (FaCE), y el efecto sobre la reducción de sincinesias se estudió utilizando el cuestionario Synkinesis Assessment Questionnaire (SAQ).
Resultados: La media de los valores del SFGS se incrementó tras el tratamiento con TXB-A, de 64,8 a 69,9 ($P = ,004$). También se incrementó la media de los valores del FaCE Total, de 52,42 a 64,5 ($P < ,001$), y la media de la subescala Social del FaCE, de 61,15 a 78,44 ($P < ,001$). La media de los valores del SAQ disminuyó con las infiltraciones de TXB-A, de 46,22 a 37,55 ($P = ,001$).
Conclusiones: Las infiltraciones de TXB-A incrementan la funcionalidad facial, mejoran la calidad de vida y reducen las sincinesias en pacientes con secuelas de PFP.

Introduction

Sequelae of peripheral facial palsy (PFP) may persist if the facial nerve lesion does not fully resolve. These sequelae may cause severe physical and psychological disorders, negatively affecting patients' quality of life.[1,2]

The main physical sequelae are muscle paresis, hypertonia, sustained muscle contraction (SMC), hemifacial spasm, and synkinesis, in which the voluntary contraction of one muscle is accompanied by the involuntary contraction of another. The most common examples are closure of the eye upon yawning, laughing, or chewing; elevation of the oral commissure upon raising of the eyebrows or closing the eyes; and the appearance of platysma bands when pursing the lips. The pathogenesis of these sequelae is not understood, although it has been suggested that aberrant regeneration of facial nerve fibres and synaptic reorganisation in the facial nerve nucleus may explain synkinesis, spasms, hypertonia, and SMC.[3] These abnormal movements decrease the motility of paretic muscles; thus, in addition to a sensation of stiffness, tension, or pain, patients also display facial asymmetry, both at rest and in movement.

The face is one of the most important parts of the body in the social context, identifying us as individuals and playing a fundamental role in self-image and in social interaction. Therefore, facial involvement due to PFP may provoke a psychological disorder that negatively impacts patients' self-esteem and socialisation.[4]

Botulinum toxin type A (BTX-A) causes reversible muscle paralysis by inhibiting acetylcholine release at the neuromuscular junction, without causing a long-term lesion to the muscle or nerve. For several decades, it has been used to treat a wide variety of diseases, such as strabismus, blepharospasm, spasmodic dysphonia, headache disorders, achalasia, hyperhidrosis, and some sphincter disorders.[5] A large body of research has demonstrated the efficacy of BTX-A infiltrations for reducing abnormal facial movements (spasms, hypertonia, SMC, and synkinesis). Furthermore, the treatment improves facial symmetry at rest and in movement, and facial expressiveness, and is minimally invasive without significant adverse effects.[6—11] Nonetheless, despite the existence of multiple studies on the treatment of PFP sequelae with BTX-A, few researchers have assessed its effects on quality of life.

In the light of the above, the present study aims to evaluate the effect of BTX-A infiltrations as a treatment for PFP sequelae in our setting. In addition to analysing its effects on facial nerve function and on synkinesis, we also address the effect of the treatment on patient quality of life.

Material and methods

We conducted a prospective study of a cohort of 20 patients treated with BTX-A to minimise sequelae remaining after incomplete resolution of PFP; sequelae most frequently consisted in muscle paresis, hypertonia, SMC, spasms, and synkinesis.

The sample included 15 women (75%) and 5 men (25%); PFP affected the left side in 13 patients (65%) and the right in 7 (35%). Regarding aetiology, PFP was caused by surgery in 5 patients (25%; acoustic neuroma in one, meningioma in one, otologic surgery in 2, and parotid tumour in one), Bell's palsy in 11 (55%), herpes zoster infection in 3 (15%), and hyper-

tensive crisis in one (5%). Patients had a mean (standard deviation) age of 58.1 (12.07) years (range, 39—78). Mean disease progression time was 26.5 months (range, 6—164; Q_1—Q_3, 8.25—70.5).

Participants were recruited from among patients attending outpatient consultations at the rehabilitation and physical medicine department of Xarxa Sanitària i Social Santa Tecla in Tarragona (Spain) to receive BTX-A infiltrations, between April 2017 and May 2019.

The inclusion criteria were as follows: age 18 years and above, progression time of at least 6 months, incomplete resolution of PFP, and willingness to participate in the study by completing the questionnaires. All patients had previously completed a tailored programme of neuromuscular re-education, with an initial phase of outpatient therapy followed by a home exercise programme.

The scales and questionnaires used were:

- Sunnybrook Facial Grading System (SFGS). The SFGS measures the degree of impairment caused by PFP. Scores range from 0 to 100, with 100 points indicating normal function; the scale assesses movement, symmetry at rest, and synkinesis.[12]
- Facial Clinimetric Evaluation (FaCE). The FaCE questionnaire evaluates quality of life in patients with PFP. The scale includes several domains (facial movement, facial comfort, oral function, eye comfort, lacrimal control, and social function) and is scored from 0 to 100, with a score of 100 considered normal. In this study, we analysed total FaCE score and the social function subscale.[13]
- Synkinesis Assessment Questionnaire (SAQ). This questionnaire evaluates synkinesis in different muscle groups in patients with PFP sequelae. Scores range from 20 to 100, with higher scores reflecting greater severity.[14]

Patients underwent clinical evaluation and completed questionnaires prior to BTX-A infiltration (on the same day) and at 4 weeks.

The site and dosage of infiltrations were determined on a case-by-case basis, according to the pattern of sequelae in each patient: facial asymmetry, hypertonia, SMC, synkinesis, or overloading of facial muscles. All infiltrations were administered by the same clinician; 18 patients received onabotulinum toxin A (Botox®) and 2 received incobotulinum toxin A (Xeomin®). BTX-A was diluted at 100 IU in 2 mL physiological saline or 50 IU in 1 mL saline, and administered using a 1 mL syringe with a 30 G needle. A dose of 1—5 IU was administered at each injection point, depending on the target muscle.

Statistical analysis was performed using the SPSS statistics software, version 17.0. Data were analysed with the paired sample *t* test; the threshold for significance was set at $P < .05$.

This study was approved by the local clinical research ethics committee (reference no. C.I. 071/2017).

Results

The total BTX-A dose administered ranged from 7.5 to 100 IU. Doses were 7.5 IU in one patient (5%), 45 IU in 2 (10%), 50 IU in 11 (55%), 85 IU in one (5%), 90 IU in 4 (20%), and 100 IU in one (5%).

The target muscles on the unaffected side were the frontalis, zygomaticus major, corrugator, mentalis, and depressor labii inferioris, whereas on the affected side infiltrations targeted the frontalis, corrugator, orbicularis oculi, mentalis, depressor labii inferioris, levator labii superioris, platysma, buccinator, masseter, temporalis, and sternocleidomastoideus muscles. Although the latter 3 muscles are not innervated by the facial nerve, they were hypertonic in some patients, hence the decision to administer BTX-A.

Mean (standard deviation) SFGS score was 64.8 (15.75) prior to infiltration, increasing to 69.7 (16.10) after treatment. We also observed increases in total FaCE score (from 52.42 [22.29] to 64.5 [17.76]) and FaCE social function score (from 61.15 [29.07] to 78.44 [23.25]). Mean SAQ score decreased from 46.22 (12.44) before treatment to 37.55 (10.95) after BTX-A infiltration. All of these changes were statistically significant (Table 1).

Regarding adverse reactions, 3 patients presented a mild increase in weakness of the orbicularis oculi muscle, and a further 2 patients presented slightly increased weakness of the levator labii superioris with drooping of the upper lip.

Discussion

The face is probably the most important part of the body in the social sphere. As noted by Le Breton, ''even the humblest of individuals wears his face as the greatest sign of his difference. It is the most human place in man''[15]: the face is the fundamental element of the body that identifies us as unique individuals, the defining feature that differentiates one person from another. Therefore, PFP can be interpreted as an insult to individual identity, with many patients expressing it in those terms (''I'm not myself any more,'' ''that's not me in the picture''). It also goes against prevailing beauty standards, based on balance, harmony, and geometric proportions.[16] However, the most severely affected area after PFP is social interaction, with the face representing the fundamental part of the body in personal presentation, in everyday conversation and non-verbal communication through facial expressions or the lack thereof.[15,17] Thus, patients with PFP may present social disability, a stigma that will affect all face-to-face interactions, obliging them to employ a series of social strategies including concealment, masking, exhibition, or social withdrawal.[15,17]

It is for this reason that we consider it insufficient to limit the evaluation of PFP to facial nerve function, without considering the psychological effects of the disease or its impact on quality of life. Assessing psychological distress in these patients can be challenging, and questionnaires may present limitations. Therefore, subjective tools such as in-depth interviews may provide more information. We recommend the use of additional instruments to complement the evaluation of facial nerve function, exploring the impact of disease on these patients' quality of life.

It has been extensively demonstrated that BTX-A infiltration is a safe, efficacious, minimally invasive treatment for PFP sequelae, improving both abnormal facial move-

Table 1 Pre- and post-infiltration scores on the Sunnybrook Facial Grading System, total and social function subscale of the Facial Clinimetric Evaluation, and Synkinesis Assessment Questionnaire.

	Mean (SD)	Difference between means	P*	95% CI
SFGS pre-infiltration	64.80 (15.75)	4.9	.004	1.73—8.07
SFGS post-infiltration	69.70 (16.10)			
FaCE total pre-infiltration	52.42 (22.29)	12.08	< .001	6.63—17.53
FaCE total post-infiltration	64.50 (17.76)			
FaCE social pre-infiltration	61.15 (29.07)	17.29	< .001	10.21—24.37
FaCE social post-infiltration	78.44 (23.25)			
SAQ pre-infiltration	46.22 (12.44)	8.67	.001	3.86—13.47
SAQ post-infiltration	37.55 (10.95)			

CI: confidence interval; FaCE: Facial Clinimetric Evaluation; OR: odds ratio; SAQ: Synkinesis Assessment Questionnaire; SD: standard deviation; SFGS: Sunnybrook Facial Grading System.
* $P < .05$.

ments and facial symmetry at rest and in movement.[5—11] The infiltration begins to take effect after 3 to 7 days, with the benefit lasting approximately 4 months.[8] Weakening the muscles of the non-paralysed side not only improves symmetry, but also enables strengthening and improved functioning of the affected side.[9,10] Attenuation of synkinesis, SMC, and hypertonia can also increase facial motility on the affected side, as abnormal movements do not interfere in the function of paretic muscles[8]; however, motility may also be reduced by the effect of BTX-A.[18]

According to our results, BTX-A infiltration causes a significant improvement in facial nerve function ($P = .001$), as measured with the SFGS, confirming the reports of other authors.[6—8,10,11] However, the improvement observed was not as pronounced as those reported by other researchers. Nonetheless, some authors, such as Couch et al.,[18] have observed a reduction in SFGS scores due to reduced motility secondary to BTX-A.

Our results also show a significant reduction in synkinesis ($P = .004$), as assessed with the SAQ, once more confirming the findings of other authors.[6,7] As with SFGS score, the change in SAQ scores was not as large as those reported in other articles.

Though extensive research has been conducted on the effect of BTX-A infiltrations on PFP sequelae, few studies have evaluated the efficacy of the treatment in improving quality of life. A review by Fuzi et al.[19] that explored this subject only identified 6 eligible studies, concluding that BTX-A infiltration is an effective, minimally invasive treatment that improves the quality of life of patients with PFP sequelae. In one of the studies reviewed, Kleiss et al.[20] observed a statistically significant increase in the social function and facial comfort subscores after treatment with BTX-A; Mehta and Hadlock[21] observed significant improvements in all FaCE subscale scores. Though it is not reviewed by Fuzi et al.,[19] the study by Couch et al.[18] also identified a statistically significant increase in social function and facial comfort scores after BTX-A infiltration. Our study analysed the total and social function subscale scores, omitting the remaining subscales, and confirmed that BTX-A infiltration significantly increases quality of life in patients with PFP sequelae, with greater improvements than those reported by other authors.

Other studies use the Facial Disability Index (FDI) to evaluate quality of life after treatment with BTX-A.[22] Salles et al.[9] reported a statistically significant increase in FDI physical and social function subscale scores at 6 months after infiltration, while Do Nascimento et al.[23] detected a significant increase in FDI social function subscale score after infiltration of onabotulinum toxin A.

The study by De Carvalho et al.[24] used the Body Image Quality of Life Inventory, observing a statistically significant improvement in body image at 6 months after BTX-A infiltration.

Other authors have developed ad hoc questionnaires that address physical, psychological, and social factors to evaluate the effect of BTX-A infiltrations on quality of life, social interactions, and self-perception, and report statistically significant improvements in all these areas. However, their results should be interpreted with caution as the questionnaires used are not validated.[10,11,25]

Both the FDI and the FaCE were developed and validated for evaluating the impact of PFP sequelae on quality of life; however, there is no unanimous agreement on which tool should be used.[19,20] Several of the studies discussed used the FaCE,[18,20,21] whereas others used the FDI[9,23] and some used ad hoc tools.[10,11,25] The main issue with ad hoc tools is reproducibility; similarly, no validated Spanish-language version is available for the FaCE and SAQ scales. A validated Spanish-language version of these scales would constitute a significant advance in the study of quality of life in patients with PFP in our setting. We recommend that one of these instruments be used in clinical practice in addition to measures of facial nerve function, and particularly the FaCE scale for assessing quality of life. Despite the lack of a validated Spanish-language version, the scale shows a strong correlation with scales measuring facial nerve function (SFGS), disability (FDI), and psychological distress (Hospital Anxiety and Depression Scale).[4]

With respect to infiltration technique, it is important to note that BTX-A infiltration is a highly personal and individualised treatment, and each patient presents a specific set of sequelae within a pattern of aberrant reinnervation including muscle paresis, hypertonia, SMC, spasms, and synkinesis, with considerable variability between individual patients. Furthermore, not all patients attribute the same importance to the same aspects of these sequelae; thus, patients' sub-

jective perception should inform decisions about the pattern of BTX-A infiltration. The experience of the professional administering the treatment is also of fundamental importance. Dosage must be determined carefully due to the risk that, in attempting to reduce hypertonia, SMC, and synkinesis, we may exacerbate the weakness of the paretic muscles. Special attention must be paid to specific muscles, such as the zygomaticus major and levator labii superioris, which often simultaneously present both hypertonia and paresis, and should be treated with very low doses of BTX-A (up to 1.5 IU).[8,9] In our study, 2 patients presented slightly increased weakness of the levator labii superioris, with drooping of the upper lip, following infiltration of 1.25 IU of BTX-A; this symptom resolved within 3 weeks.

Many patients with PFP sequelae also present hypertonia of muscles not innervated by the damaged facial nerve, such as the masseter, temporalis, and sternocleidomastoideus. We administered BTX-A infiltrations to these muscles in affected patients, observing a considerable improvement in pain and in the sensation of stiffness. The physiological mechanism causing the increased tone in these muscles is unknown, and our literature search yielded no articles on the subject. We suggest that PFP with permanent sequelae may cause a biomechanical alteration in facial activities such as chewing, gesticulation, or speech, resulting in overloading of other muscles not innervated by the facial nerve, and potentially leading to tension or pain.

The adverse reactions observed in 5 participants (mild exacerbation of orbicularis oculi weakness in 3 and mild exacerbation of the levator labii superioris weakness with drooping of the upper lip in 2) are consistent with those reported in the literature, which include difficulty speaking, eating, and drinking.[8,9,19,23] As reported in the literature, adverse effects are mild and transient, and are outweighed by the benefit for patients' quality of life. The adverse reactions observed in our study were mild and resolved within 3 to 4 weeks. No patient presented such complications as ptosis, dry eyes, keratitis, lagophthalmos, or systemic symptoms.

Our study presents certain limitations, and the results should be interpreted with caution. Firstly, we should mention the relatively small sample size and lack of a control group. Secondly, no validated Spanish-language version of the FaCE and SAQ questionnaires is available. Finally, quality of life was evaluated using a questionnaire, which provides very limited information on such a complex domain as quality of life.

Conclusions

BTX-A infiltrations improve facial nerve function and reduce synkinesis in patients with PFP sequelae.

This treatment is minimally invasive, causes no relevant adverse effects, and improves quality of life in these patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Fu L, Bundy C, Sadig SA. Psychological distress in people with disfigurement from facial palsy. Eye. 2011;25:1322—6.
2. Volk GF, Granitzka T, Kreysa H, Klingner CM, Guntinas-Lichius O. Nonmotor disabilities in patients with facial palsy measured by patient-reported outcome measure. Laryngoscope. 2016;126:1516—23.
3. Celik M, Forta H, Vural C. The development of synkinesis after facial nerve paralysis. Eur Neurol. 2000;43:147—51.
4. Díaz-Aristizabal U, Valdés-Vilches M, Fernández-Ferreras TR, Calero-Muñoz E, Bienzobas-Allué E, Moracén-Naranjo T. Correlación entre deficiciencia, afectación psicológica, discapacidad y calidad de vida en la parálisis facial periférica. Neurologia. 2019;34:423—8.
5. Laskawi R. The use of botulinum toxin in head and face medicine: an interdisciplinary field. Head Face Med. 2008;4:5.
6. Filipo R, Spahiu I, Covelli E, Nicastri M, Bertoli GA. Botulinum toxin in the treatment of facial synkinesis and hyperkinesis. Laryngoscope. 2012;122:266—70.
7. Wei LA, Diels J, Lucarelli MJ. Treating buccinator with botulinum toxin in patients with facial synkinesis: a previously overlooked target. Ophtalmic Plast Reconstr Surg. 2016;32:138—41.
8. Toffola ED, Furini F, Redaelli C, Prestifilippo E, Bejor M. Evaluation and treatment of synkinesis with botulinum toxin following facial nerve palsy. Disabil Rehabil. 2010;32:1414—8.
9. Salles AG, Toledo PN, Ferreira MC. Botulinum toxin injection in long-standing facial paralysis patients: improvement of facial symmetry observed up to 6 months. Aesthetic Plast Surg. 2009;33:582—90.
10. Choi KH, Rho SH, Lee JM, Jeon JH, Park SY, Kim J. Botulinum toxin injection of both sides of the face to treat postparalytic facial synkinesis. J Plast Reconstr Aesthet Surg. 2013;66:1058—63.
11. Kim J. Contralateral botulinum toxin injection to improve facial asymmetry after acute facial paralysis. Otol Neurotol. 2013;34:319—24.
12. Ross BG, Fradet G, Nedzelski JM. Development of a sensitive clinical facial grading system. Otolaryngol Head Neck Surg. 1996;114:380—6.
13. Kahn JB, Gliklich RE, Boyev KP, Stewart MG, Metson RB, McKenna MJ. Validation of a patient-graded instrument for facial nerve paralysis: the FaCE scale. Laryngoscope. 2001;111:387—98.
14. Mehta RP, WernickRobinson M, Hadlock TA. Validation of the Synkinesis Assessment Questionnaire. Laryngoscope. 2007;117:923—6.
15. Le Breton D. Rostros. Ensayo de antropología. Buenos Aires: Editorial Letra Viva; 2010.
16. Blanco Dávila F. Las proporciones divinas. Cir Plást. 2005;15:118—24.
17. Goffman E. Estigma. La identidad deteriorada. Buenos Aires: Amorrortu Editores; 1963.
18. Couch SM, Chundury RV, Holds JB. Subjective and objective outcome measures in the tratment of facial nerve synkinesis with onabotulinumtoxinA (Botox). Ophthalmic Plast Reconstr Surg. 2014;30:246—50.
19. Fuzi J, Taylor A, Sideris A, Meller C. Does botulinum toxin therapy improve quality of life in patients with facial palsy? Aesthetic Plastic Surg. 2020;44:1811—9.
20. Kleiss IJ, Hohman MH, Susarla SM, Marres HA, Hadlock TA. Health-related quality of life in 794 patients with a peripheral facial palsy using the FaCE Scale: a retrospective cohort study. Clin Otolaryngol. 2015;40:651—6.
21. Mehta RP, Hadlock TA. Botulinum toxin and quality of life in patients with facial paralysis. Arch Facial Plast Surg. 2008;10:84—7.

22. VanSwearingen JM, Brach JS. The Facial Disability Index: reliability and validity of a disability assessment instrument for disorders of the facial neuromuscular system. Physical Ther. 1996;76:1288—98.
23. do Nascimento Remigio AF, Salles AG, de Faria JC, Ferreira MC. Comparison of the effificacy of onabotulinumtoxinA and abobotulinumtoxinA at the 1: 3 conversion ratio for the treatment of asymmetry after long-term facial paralysis. Plast Reconstr Surg. 2015;135:239—44.
24. de Carvalho VF, Vieira APS, Paggiaro AO, Salles AG, Gemperli R. Evaluation of the body image of patients with facial palsy before and after the application of botulinum toxin. Intern J Dermatol. 2019;58:1175—83.
25. Moraleda S, Hachoue Z, Abdel-Muti E, Ruiz G, Díez Sebastián J, Lasaletta L. Encuesta de satisfacción del paciente con secuelas de parálisis facial periférica en tratamiento con toxina botulínica A. Rehabilitación. 2020;54:254—9.