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ORIGINAL INVESTIGATION

# Effectiveness of botulinum toxin type A for pain control in children with spastic cerebral palsy

## *Efectividad de la toxina botulínica tipo A para el control de dolor en niños con parálisis cerebral espástica*

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## RESUMEN

Se realizó un estudio analítico longitudinal prospectivo de antes y después de 12 pacientes pediátricos entre los 2 y los 18 años con parálisis cerebral espástica con limitación para la comunicación, valorándose la presencia de dolor mediante el uso de la escala FLACC; los participantes tenían indicación de aplicación de toxina botulínica tipo A para el control de espasticidad. Posterior a esto se realizó nuevamente la evaluación de la presencia de dolor a la semana y al mes, esto con el objetivo de determinar si hay cambios objetivos en los pacientes que puedan favorecer una mejor calidad de vida.

**Materiales y métodos**: Estudio analítico no experimental longitudinal prospectivo de antes y después para muestras relacionadas de una cohorte de niños entre 0 y 18 años con diagnóstico de parálisis cerebral espástica y presencia de dolor reportado por los padres. Se realizó el test estadístico T-student para muestras relacionadas (emparejadas o apareadas) analizando los resultados de la escala FLACC del dolor.

**Resultados**: Se reunieron 15 pacientes de los cuales por falta en los controles y falta de datos proporcionados por los padres se perdieron 3 casos obteniéndose un total de 12 pacientes incluidos en el estudio, en el cual se encontraron, mediante el uso de la escala FLACC en la primera valoración (FLACC1) siete pacientes (58,3%) con dolor moderado, cuatro (33,3%) con dolor severo y uno (8,3%) con dolor leve; en la segunda valoración, una semana después de la aplicación de material miorelajante (FLACC2) los resultados evidenciaron que cuatro (33.3%) presentaban dolor moderado y ocho (66,7%) dolor leve. Posteriormente, en la tercera valoración al mes del procedimiento (FLACC3) tres (25%) de los pacientes presentaban dolor moderado, ocho (66,7%) dolor leve y uno (8,3%) de ellos ya no presentaba manifestaciones de dolor. Esto demostró que existen diferencias significativas entre los valores de dolor antes y después de la aplicación del material miorelajante, sugiriendo la efectividad del control del dolor con la aplicación de toxina botulínica tipo A.

**Conclusiones**: La aplicación de la escala FLACC a pacientes con parálisis cerebral espástica permite una valoración objetiva del nivel de dolor en los pacientes con limitación para la comunicación y la aplicación de toxina botulínica como material miorelajante tiene un efecto benéfico significativo en la disminución del dolor en este grupo poblacional.

**Palabras clave**: Toxina botulínica tipo A, escala FLACC, dolor en niños, espasticidad, lesión cerebral.
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## ABSTRACT

A prospective longitudinal analytical before and after study was performed in 12 pediatric patients between two and 18 years old with diagnosis of spastic cerebral palsy with limited communication, assessing the presence of pain by using the FLACC scale; the participants had

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indication for the administration of Botulinum Toxin type A for the control of spasticity. After this, the evaluation of the presence of pain was performed a week and a month after de administration of the myorelaxant material, in order to determine if there were any objective changes that may favor a better quality of life.

**Materials and methods**: A Prospective longitudinal non-experimental analytical before and after for related samples study was performed in children between 0 and 18 years of age with a diagnosis of spastic cerebral palsy and presence of pain reported by their parents. The T-student statistical test was performed for related samples analyzing the results of the FLACC pain scale before and after the administration of Botulinum Toxin Type A.

**Results**: A total of 15 patients were met, however, due the absence to controls and insufficient data provided by the parents, 3 cases were lost, obtaining a total of 12 patients included in the study, among them, by using the FLACC scale in the first assessment (FLACC1) seven patients (58.3%) evidenced the presence of moderate pain, four (33.3%) presented severe pain and one (8.3%) had mild pain; In the second assessment, one week after the administration of myorelaxant material (FLACC2), the results showed that four (33.3%) had moderate pain and eight (66.7%) had mild pain. Subsequently, in the third assessment, a month after the procedure (FLACC3), three (25%) of the patients presented moderate pain, eight (66.7%) had mild pain and one (8.3%) of them no longer presented any sign of pain. This showed that there are significant differences between pain values ??before and after the application of myorelaxant material, suggesting the effectiveness of pain control with the administration of Botulinum Toxin type A.

**Conclusions**: The application of the FLACC scale to patients with spastic cerebral palsy allows an objective assessment of the level of pain in patients with limited communication and the application of botulinum toxin as myorelaxant material have significant beneficial effects in reducing pain in this population group.

**Key words:** Botulinum Toxin Type A, FLACC scale, children pain, spasticity, brain injury.
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## INTRODUCTION

Cerebral palsy is a group of movement disorders that result from abnormal development or damage to the parts of the brain that control mobility, balance, and posture, and although several risk factors have been identified, including preterm birth, infections during pregnancy, toxicity, and cranioencephalic trauma, there are still cases in which it is not possible to determine the cause of the brain injury[1-3]. This is a condition that has no cure and its treatment is aimed at complications and secondary morbidities since the underlying disease is unchangeable, which is why we should seek to help these patients achieve the best quality of life possible, for which various methods of support are used, such as the use of medications to control abnormal movements or muscle stiffness, surgeries to promote muscle length and avoid deformities and balance difficulties, and therapies to improve functionality and language[1, 4 - 6].

Pain is considered the fifth vital sign, however it is sometimes forgotten or overlooked in patients with Cerebral Palsy, especially in those who do not have the possibility of communicating verbally, and it is precisely because of this difficulty that physicians sought implementation of scales and tools to evaluate this unpleasant sensory experience[7-13].

There are studies that show that, due to the characteristics of botulinum toxin type A, it's possible the interruption of chronic pain and precisely, in patients with cerebral palsy, this medication is occasionally used for the improvement of spasticity[14, 15]

In the study, evaluation and monitoring of pain were performed in patients with cerebral palsy with inability to communicate after the administration of botulinum toxin type A to determine the analgesic effect and clinical changes.

## OBJECTIVE

The aim of the present study was to evaluate the presence or absence of pain in children with cerebral palsy by using the FLACC scale[16, 17], after the application of botulinum toxin type A, in order to guarantee an integral rehabilitation management and improve the quality of life of patients and their caregivers.

For this, it was necessary to initially identify the presence of pain in patients with spastic cerebral palsy before the administration of botulinum toxin type A[18-20], and also one week and one month after this application[21], all using the FLACC scale, which is an interval scale that measures pain in patients between 2 and 7 years old, quantifying it in behaviors with values ??from 0 (painless behaviors) to 10 (behaviors most likely related to pain); there are five categories included in the scale:

- Facial expression
- Legs Movement
- Activity
- Crying
- Comfort

For each category a score of 0 to 2 is given depending on the attitudes observed in the evaluated child[11].

The results are interpreted as follows:

0 = Patient relaxed and comfortable
1-3 = Mild discomfort
4-6 = Moderate pain
7-10 = Severe discomfort, pain or both

## METHODOLOGY

### *Type of study*

Before and after prospective longitudinal non-experimental analytical study for related samples from a cohort of children with a diagnosis of spastic cerebral palsy and the presence of pain reported by the parents, to whom the

FLACC scale was applied prior to the application of botulinum toxin and after her the first week and the first month.

The study population were children with a diagnosis of cerebral palsy evaluated in the Children's Rehabilitation service of the Hospital La Misericordia, a fourth level health institution in the city of Bogotá. The medical assessment was carried out in the "spasticity meeting", in which children with Spastic Cerebral Palsy are evaluated, determining if they are candidates for the administration of Botulinum Toxin type A.

Sample type: sample by convenience.

The inclusion criteria of the study population were:

i. Patients who attend to the spasticity meeting with ages between 2 and 18 years old.

ii. Limitation for the communication to one intelligible word or limitation for phrases.

iii. Diagnosis of spastic cerebral palsy, dyskinesic patients or presence of dystonia.

iv. Suspected pain perceived by caregivers or evidenced during the physical examination.

v. Comply with indications for the administration of myorelaxant material - botulinum toxin.

***Exclusion criteria:***

i. Patients with Botulinum Toxin application in the last 3 months.

ii. Presence of adverse effects with the previous application of Botulinum Toxin.

iii. Concomitant use of another myorelaxant medication.

iv. Absence of pain perceived by caregivers or non-identification of pain with the FLACC evaluation.

***Type of variables:***

Quantitative:

- Pain rating according to the FLACC scale
- Age of patients

Qualitative:

- Gender of the patients

Value of pain classification according to the FLACC scale

0. No pain
1. Mild discomfort (relative to value 1-3)
2. Moderate pain (relative to value 4-6)
3. Severe pain or discomfort or both (relative to value 7-10)

Changes in pain rating

0. No changes in the pain rating
1. Changes in less than 3 points in the pain score
2. Changes greater than 3 points in the pain rating[11]

## HYPOTHESIS

Will there be a significant difference between the measures of the FLACC scale before the application of botulinum toxin and after the application of it?

Statistically for this, it was necessary to determine a null hypothesis (Ho) and an alternative hypothesis (Hi) determined as follows:

(Ho): There is no difference in the scale of pain assessment of patients with cerebral palsy before and after the treatment with Botulinum Toxin type A.

(Hi): There is a significant difference in pain assessment in this group of patients before and after treatment with Botulinum Toxin type A.

The alpha level of error of 0.05 (5%) was defined.

The fixed variable are the patients of study and the related variable is the application of botulinum toxin

## ANALYSIS PLAN

The qualitative variables were analyzed by percentages and presented by absolute and relative frequencies, and the quantitative variables through measures of central tendency.

In addition, tests of paired design or repeated measurement design with repeated statistical T student observations were applied to analyze the means of the same participants (paired samples) before and after the intervention.

## RESULTS

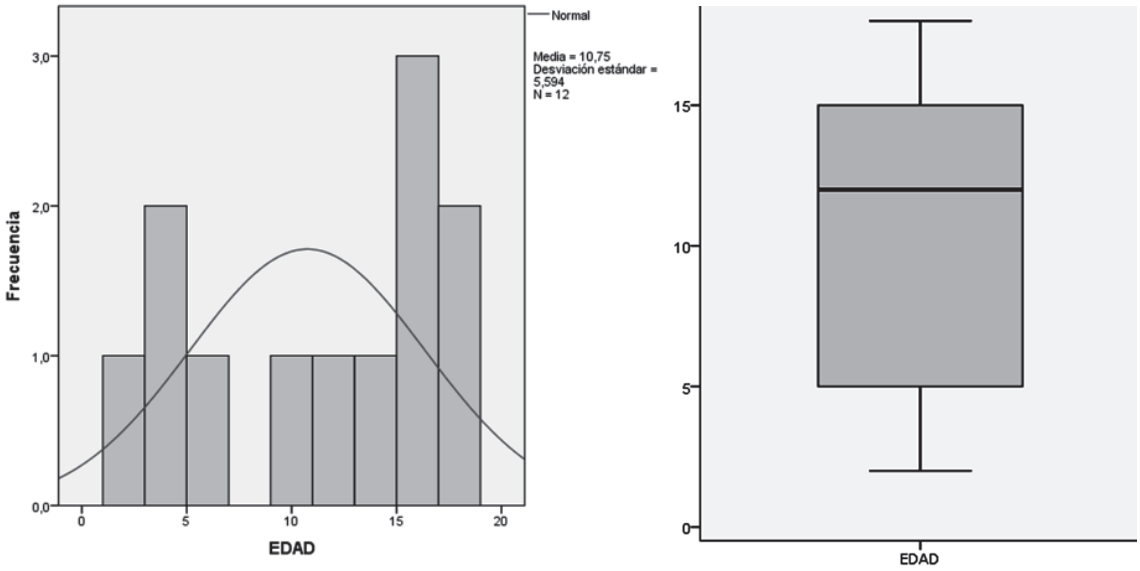
The present study of children and adolescents diagnosed with Spastic Cerebral Palsy was performed at the Hospital de la Misericordia Foundation in the city of Bogotá, meeting 15 patients, one of whom was excluded for presenting a value of 0 on the FLACC scale and other 2 patients did not continue with the study because they did not went to the controls, having a total of 12 patients who were between two and 18 years old, with an average of 10.75 and a median of 12.

The normality test was carried out, for being a sample of less than 30 participants the Shapiro Wilk test was used, a significance for the age of 0.219 was obtained, higher than 0.05 which shows that this variable had a normal distribution (Table 1 and Graphics 1).

Likewise, with the quantitative variables of the FLACC scale, the Shapiro Wilk normality test was performed, which showed that they have a normal distribution (Tables 2 and 3.)

**Table 1**. Age Quantitative Variable, percentiles and Shapiro Wilk normality test

| Prueba de normalidad | | | |
|---|---|---|---|
| | Shapiro Wilk | | |
| | Estadístico | g1 | Significancia |
| Edad | 911 | 12 | 219 |




**Graphics 1**. Histogram and Boxes and Whiskers Diagram. Age Variable

**Table 2**. FLACC Scale Values

| | | Percentiles | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 25 | 50 | 75 | 90 | 95 |
| Promedio ponderado | PUNTFLACCl* | 1 | 1,9 | 5,25 | 7 | 8 | 9 | |
| | PUNTFLACC2** | 1 | 1,3 | 3 | 4 | 5,75 | 6,7 | |
| | PUNTFLACC3*** | 0 | 0,3 | 1 | 2,5 | 4,5 | 5,7 | |
| Bisagras deTukey | PUNTFLACCl* | | | 5,5 | 7 | 8 | | |
| | PUNTFLACC2** | | | 3 | 4 | 5,5 | | |
| | PUNTFLACC3*** | | | 1 | 2,5 | 4 | | |

*Puntaje FLACC 1, **Puntaje FLACC2, ***Puntaje FLACC3.

**Table 3**. Quantitative Variable. FLACC1, FLACC2 and FLACC3 Scores

| Prueba de normalidad | | | |
|---|---|---|---|
| | Shapiro Wilk | | |
| | Estadístico | Gl | Significancia |
| PUNTFIACCl* | 0,900 | 12 | 0.157 |
| PUNTFLACC2** | 0.965 | 12 | 0,855 |
| PUNTFLACC3*** | 0.929 | 1 | 0,370 |

*Puntaje FLACC 1, **Puntaje FLACC2, ***Puntaje FLACC3.

**Table 4.** Categorical Variable, Gender

| Sexo | | | |
|---|---|---|---|
| | Frecuencia | Porcentaje | Porcentaje válido |
| Femenino | 5 | 41,7 | 41.7 |
| Masculino | 1 | 58,3 | 58,3 |
| Total | 12 | 100 | 100 |

**Table 5.** Categorical variable. FLACC1 Score

| FLACCl | | | |
|---|---|---|---|
| | Frecuencia | Porcentaje | Porcentaje válido |
| Dolor leve | 1 | 8,3 | 8,3 |
| Dolor moderado | 7 | 58,3 | 58,3 |
| Dolor severo | 4 | 33,3 | 33,3 |
| Total | 12 | 100,0 | 100,0 |

**Table 6.** Categorical Variable. FLACC2 Score

| FLACC2 | | | |
|---|---|---|---|
| | Frecuencia | Porcentaje | Porcentaje válido |
| Dolor leve | 8 | 66,7 | 66,7 |
| Dolor moderado | 4 | 33,3 | 33,3 |
| Total | 12 | 100,0 | 100,0 |

**Table 7.** Categorical variable. Score FLACC3

| FLACC3 | | | |
|---|---|---|---|
| | Frecuencia | Porcentaje | Porcentaje válido |
| Dolor leve | 1 | 8,3 | 8,3 |
| Dolor moderado | 8 | 66,7 | 66,7 |
| Dolor severo | 3 | 25,0 | 25,0 |
| Total | 12 | 100,0 | 100,0 |

Within the study, seven male and five female patients were obtained, with a relative frequency of 58.3% and 41.7% respectively. The value of the FLACC scale in the first assessment (FLACC1) showed that of the 12 participants, seven (58.3%) had moderate pain, four (33.3%) severe pain and one (8.3 %) mild pain; In the second assessment, one week after the administration of myorelaxant material (FLACC2), the results showed that four patients (33.3%) presented moderate pain and eight (66.7%) mild pain, observing that within the sample, there were no longer participants with severe pain. Subsequently, in the third assessment after one month of the procedure (FLACC3), three of the patients (25%) presented moderate pain, eight (66.7%) had mild pain and one (8.3%) of them no longer presented pain. (Tables 4, 5, 6 and 7)

As for the FLACC score, the three assessment times are described before the

administration of myorelaxant material, and one week and one month after (FLACC1, FLACC2 and FLACC3 respectively). Within the normality tests of Shapiro Wilk, the normal distribution is supported. (Table 4)

We also analyzed the differences in the scores between the different moments in which the pain scale was performed, comparing the scores in the first and second evaluation, in the second and third evaluation and finally between the first and third evaluation (DifpuntFLACC1 y 2, DifpuntFLACC2 y 3 and DifpuntFLACC1 y 3 respectively); as for the variables mentioned above, the Shapiro Wilk normality test was used, obtaining a significance value of 0.160, 0.234 and 0.917 respectively, demonstrating a normal distribution in each of the moments. (Table 8)

When comparing the results of the three evaluations in which the FLACC scale was carried out, it was observed that between the second and third evaluation (one week and one month after the administration of botulinum toxin type A), the most significant change in the values ??was observed. Being this the most important moment of the study (Graphics2).

A comparison was made between the means of the scores in evaluations 1, 2 and 3. In the FLACC1 and FLACC2 comparison a significance of 0.001 was obtained. At this moment, the null hypothesis is rejected and the alternative hypothesis is accepted, that means that there were significant differences between the first and second moments of pain assessment with the scale before and one week after the application of myorelaxant material (Table 9).

Subsequently, the results of the FLACC2 and FLACC3 scores were compared, presenting one more time a significance value of 0.001, rejecting once again the null hypothesis (Table 10).

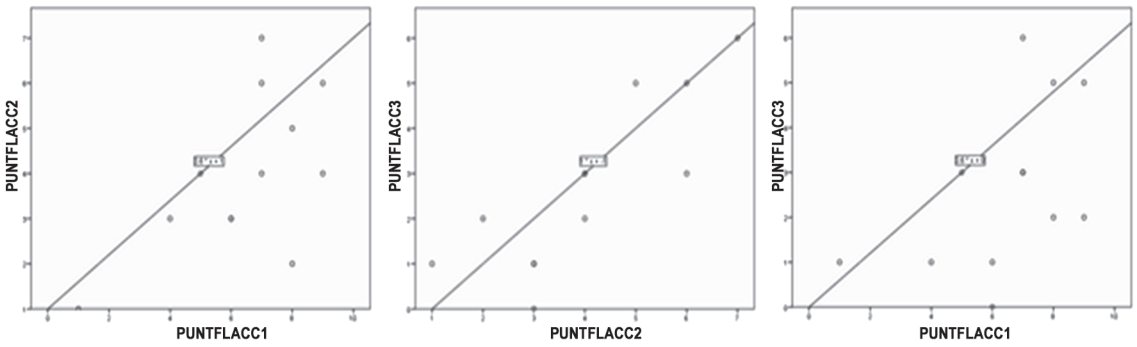
The scores were evaluated again in the first and third moment of the FLACC scale evaluation (ie FLACC1 and FLACC3) obtaining a value of significance of 0.000, rejecting the null hypothesis and reinforcing the theory that there is a significant improvement in the Pain rating in patients who received botulinum toxin (Table 11).

From the statistical point of view, a P value of less than 0.05 is evidenced in all the variables examined in the patients at moments 1 and 2, 2 and 3, and 1 and 3. These findings

**Table 8**. Quantitative Variable. Score FLACC1y2, FLACC2y3 and FLACC1y3 Differences and Shapiro Wilk normality tests

| Prueba de normalidad | | | |
|---|---|---|---|
| | Shapiro Wilk | | |
| | Estadístico | Gl | Significancia |
| DIFFPUNTFLACClY2* | 0,900 | 12 | 0.160 |
| DIFFPUNTFLACC2Y3** | 0.891 | 12 | 0,123 |
| DIFFPUNTFLACC1Y3*** | 0.971 | 12 | 0,917 |

* Difference between FLACC Scores 1 and 2, ** Difference between FLACC Scores 2 and 3, *** Difference between FLACC Scores 1 and 3.




**Graphics 2**. Significance of FLACC1-2, FLACC2-3 and FLACC1-3 comparison scores

**Table 9**. T-Student statistical test. Scores FLACC1 and FLACC2

| Prueba de muestras emparejadas | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Diferencias emparejadas | | | | | t | gl | Significancia (bilateral) |
| | Media | Desviación estándar | Media de error estándar | 95% de intervalo de confianza de la diferencia | | | | |
| | | | | Inferior | Superior | | | |
| PUNTIFLACC1* PUNTIFLACC2** | 2.417 | 1.881 | 543 | 1.222 | 3.612 | 4.451 | 11 | 0,001 |

*Puntaje FLACC1, **Puntaje FLACC2

**Table 10**. T-Student statistical test. FLACC2 and FLACC3 Scores.

| Prueba de muestras emparejadas | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Diferencias emparejadas | | | | | t | gl | Significancia (bilateral) |
| | Media | Desviación estándar | Media de error estándar | 95% de intervalo de confianza de la diferencia | | | | |
| | | | | Inferior | Superior | | | |
| PUNTIFLACC2* PUNTIFLACC3** | 1,333 | 1.073 | 0,310 | 0,652 | 2,015 | 4.304 | 11 | 0,001 |

*Puntaje FLACC2, **Puntaje FLACC3

**Table 11**. T-Student statistical test. FLACC1 and FLACC3 Scores.

| Prueba de muestras emparejadas | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Diferencias emparejadas | | | | | t | gl | Significancia (bilateral) |
| | Media | Desviación estándar | Media de error estándar | 95% de intervalo de confianza de la diferencia | | | | |
| | | | | Inferior | Superior | | | |
| PUNTIFLACC1* PUNTIFLACC3** | 3,750 | 2,094 | 0,605 | 2,419 | 5,081 | 6,203 | 11 | 0,000 |

*Puntaje FLACC1, **Puntaje FLACC3

conject a statistically significant change in the means of the compared variables, demonstrating that the administration of botulinum toxin in patients with pain was statistically significant in the improvement of pain measured with the FLACC scale.

## DISCUSSION

During the evaluation of the participants as part of the data collection, it was evident that as time passed, during the first month of the administration of the botulinum toxin, patients presented fewer activities that, according to the interpretation of the FLACC scale, were related as a manifestation of pain; The aforementioned statistical support reinforces the idea that this improvement is significant, supporting the alternative hypothesis that the administration of botulinum toxin improves pain in patients with spastic cerebral palsy.

In 2011, The Korean Journal of Pain published an article that analyzed the mechanism of action of botulinum toxin and mentioned how it could be used for myofascial pain syndrome, chronic low back pain, headache, arthralgia, chronic pelvic pain, and neuropathic pain[22].

Likewise, in 2017 The Journal of Headache and Pain published an article in which information was collected on the use of botulinum toxin type A for other types of headaches other than trigeminal neuralgia and migraine, this latter already approved as an indication of administration of botulinum toxin in our country, and concluded that this is an emerging treatment for the control of headaches and other painful conditions, mentioned as prophylactic pain management[23]

With the aforementioned articles, the results evidenced in the present study can be complemented respecting to the benefits in the administration of botulinum toxin for the management of pain independently to the presence or absence of spasticity.

As explained above, the findings of this study are consistent with the analgesic effects of Botulinum Toxin type A [22-27], reinforcing the fact that it can be used for purposes other than spasticity, [28-33] or migraine[23] as they are the indications authorized by the FDA in Colombia at present[5].

## CONCLUSIONS

The use of botulinum toxin type A has been used mainly for the control of spasticity or dystonia; in our environment it is approved for a wide range of conditions including the management of headache and other types of pain. With the present study, and based on the review that supports the mechanism of action of this molecule for pain control, it is determined that Botulinum toxin type A has a significantly positive effect for pain management identified with the FLACC scale in children with spastic cerebral palsy, allowing the use of this scale as routine in the examination of the patient with limited communication abilities and consider the use of this molecule for the control of pain in case of identifying activities that indicate discomfort in this, and other groups of patients.

## RECOMMENDATIONS

With the results of the present study it is recommended the use of a scale for an objective assessment of pain in patients with limitations in their communication, regardless of the diagnosis they have but with special reference to patients with spastic cerebral palsy, also, taking into account the values ??of these, and ideally reinforced by other studies, the resulting scores can be considered for the administration of botulinum toxin type A aiming to improve the signs and painful symptoms of the patient even if the indication for application of myorelaxant material for spasticity are not fulfilled.

It is hoped that this study will serve as a support to extend the use of scales for pain assessment in the pediatric patient's examination or those with communicative limitations.

However, it should be noted that during the period of data collection, patients who met the inclusion criteria showed very high extremes of values such as age (2 years and 18 years), which can disperse the findings in these variables, however, this can be considered as positive since,

as mentioned in the analysis of results, these were significant, evidencing that it is possible that regardless of the age ranges, the evaluation of pain with these scales allow to identify the degree of pain present at the moment and their response with the administration of botulinum toxin type A.

More studies, including experimental ones, are required in which the application of Botulinum Toxin type A may be considered in patients who show pain but do not have a strong indication of its administration for spasticity to determine its response over time.

### *Ethical disclosures Protection of human and animal subjects*

The authors declare that no experiments were performed on humans or animals for this study.

### *Confidentiality of data*

The authors declare that they have followed the protocols of their work center on the publication of patient data.

### *Right to privacy and informed consent*

The authors declare that no patient data appear in this article.

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