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Research Article

Meta-Analysis of the Use of Botulinum Toxin in Surgery. A Benefit Without Precedents

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Abstract

Background: Botulinum toxin is produced by the bacterium Clostridium botulinum it has seven different serotypes (A-G). Botulinum toxin type A (BTX) since 1973, has been used clinically for a wide variety of medical-surgical disorders or pathologies such as muscle, tendon and nerve diseases. BTX has been approved for use in humans by the FDA in various diseases.

The objective of this study is to make a systematic review of the use of botulinum toxin in a pre-surgical way in muscle or tendon defects.

Material and methods: Search strategy: The collection was carried out in the database from 1999 to January 2016, in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PUBMED, OVID and EMBASE. The following terms were used in the search: botulinum toxin, botulinum toxin type A, botox, randomized clinical trials, preoperative, presurgical.

Results: The search database found 268 articles that could have been included in the meta-analysis. Based on the inclusion and exclusion criteria, 189 articles were excluded after reading the titles and abstracts of the articles. Four articles were not RCTs. In total, 13 articles reported corresponding data with RCTs comparing botulinum toxin type A with placebo.

Conclusion: The use of botulinum toxin type A, in a presurgical way in muscular or tendon defects, presents minimal adverse effects and great efficacy in adjuvant that comparatively yield better results with the surgical techniques called gold standards, in specific pathologies. It was verified in this meta-analysis that there is an equivalence in therapeutic effects as another option in the surgical arsenal in the diseases studied.

Keywords: *Botox; Botulinum Toxin; Botulinum Toxin Type A; Randomized Clinical Trials*

Introduction

Botulinum toxin is produced by the Clostridium botulinum bacteria in seven serotypes (A-G). Botulinum toxin type A (BTX) has been used clinically for a wide variety of muscle, tendon and nerve disorders since 1973 [1]. Botulinum toxin has been approved by the FDA for the following indications: blepharospasm, strabismus, primary axillary hyperhidrosis, spasticity of the upper extremities, chronic migraine, detrusor hyperactivity and bladder hyperactivity, as well as improvement in aesthetic appearance, in wrinkles [1-5].

In recent years, more evidence has been generated of how botulinum toxin stimulates the wound repair process, generating a decrease in muscle tension in a pre-surgical manner [6].

Objective of the Study

The objective of this study is to make a systematic review of the use of botulinum toxin in a presurgical way in muscle or tendon defects.

Material and Methods

Search strategy

We searched the database 1999 to January 2016, in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PUBMED, OVID and EMBASE. The following terms were used in the search: botulinum toxin, botulinum toxin type A, botox, randomized clinical trials, preoperative, presurgical.

Inclusion criteria and trial selection

Randomized Controlled Clinical Trials (RCTs), selected by two independent reviewers, were included.

Randomized controlled clinical trials that met the following criteria were included:

1. The study design included treatment with botulinum toxin type A.
2. The study provided accurate data that could be analyzed, including the total number of participants.
3. The full text of the study could be visualized. When the same study was published in several journals or different years, the most recent publication was used for meta-analysis.

Quality assessment

Data extraction

The following information was collected from each study:

1. The name of the RCT.
2. The study design and sample size.
3. The treatment that patients received.
4. The country where the study was conducted.

Results

Characteristics of individual studies

The search database found 268 articles that could have been included in the meta-analysis. Based on the inclusion and exclusion criteria, 189 articles were excluded after reading the titles and abstracts of the articles. Four articles were not RCTs. In total, 13 articles reported corresponding data with RCTs comparing botulinum toxin type A with placebo.

Quality of individual studies

Effectiveness

Hand surgery

In a prospective study with seven children under six years of age, in which they were injected with botulinum toxin (2.5 U/kg, 7 U/kg) during surgical repair of zone 2 of the flexor tendon, to induce muscle relaxation flexor, improving the postoperative outcome and the rehabilitation of patients. Patients also received a regime of controlled passive movement after surgery. The results were evaluated with a follow-up of 18 months based on the acquisition of muscle tone and active finger movements, the total range of movement of the affected joints, the postoperative grip strength, muscular atrophy and the length of the Phalanges involved (See figure 1). The study shows how the selective use of botulinum toxin type A generates a sufficient muscular reduction in the spontaneous activity of the fingers, allowing a better rehabilitation program [7].

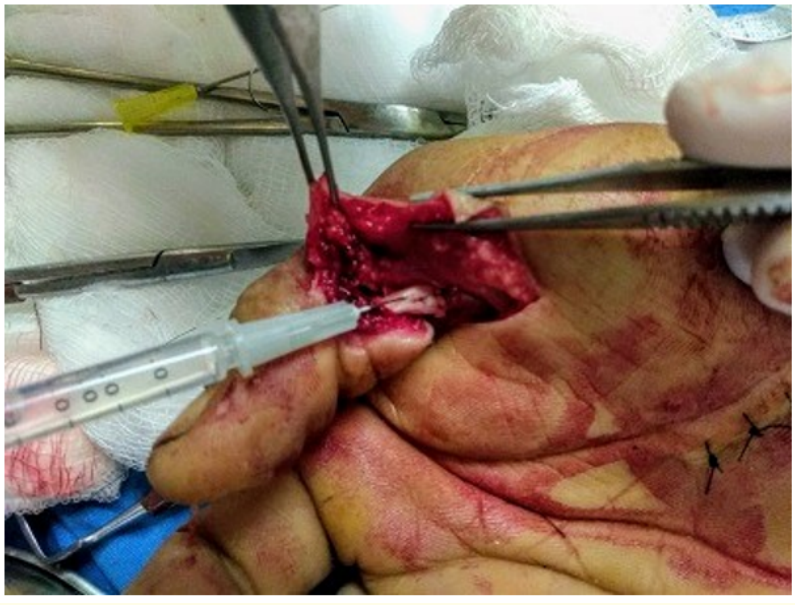

Figure 1: *Application of intraoperative botulinum toxin in the tendon flexor repair of the hand.*

In another study represented by thirty-nine children with cerebral palsy of the upper extremities, with a range of four to sixteen years of age and surgical candidates for the transfer of the ulnar flexor of the carpus to the short radial extensor of the carpus, release of the round pronator and deviation of the long extensor of the thumb with the release of the adductor of the thumb, were distributed randomly (twenty-nine patients) or by family preference (ten patients), to one of three treatment groups: surgical treatment group 1; botulinum toxin group 2 injection; or regular therapy group 3. Thirty-four patients (twenty-five randomized and nine of family preference) were evaluated twelve months after treatment, based on the range of active movement, pressure and strength of grip and stereognosis. A better result was observed in group 1 than in the other two groups ($p < 0.001$), improving supination and wrist extension during activities after surgery. However, both groups 1 and 3 showed greater improvement in clamp strength than group 2. The result suggests that surgical treatment in patients with cerebral palsy of upper extremities candidates for standard tendon transfer shows greater improvement of modest magnitude, than botulinum toxin injection or regular therapy in the active range of motion [8].

Breast reconstruction

Two RCTs talk about botulinum toxin infiltration for pain control, in breast reconstruction with tissue expanders. In the study, forty-eight patients were divided into two groups with a two-year follow-up. In twenty-two, 100 IU of diluted botulinum toxin was injected into the pectoralis major muscles, anterior serratus and abdominal rectum insertion; while in twenty-six patients it was dispensed with. The botulinum toxin group was significantly better with pain after the operation (score of 3 +/- 1 versus 7 +/- 2; $p < 0.0001$), during the initial period (score of 2 +/- 2 versus 6 +/- 3; $P = 1.6 \times 10 (-6)$) and the final expansion (1 +/- 1 versus 3 +/- 2; $P = 0.009$). The volume of expansion per session was greater, as well as the required expansion sessions were smaller in the botulinum toxin group (5 +/- 1 versus 7 +/- 3; $P = 0.025$). There was a significant increase in the use of narcotics in the patients of control in the first 24 hours (17 +/- 10 mg versus 3 +/- 3 mg; $P < 0.0001$), in the initial period, as well as in the periods of final expansion ($P = 0.0123$ and 0.0367, respectively). An expander in the botulinum toxin group versus 5 in the control group required removal ($P = 0.13$). This study shows how muscle infiltration of botulinum toxin for mastectomy and placement of the tissue expander significantly reduces postoperative pain and uncomfortable discomfort for patients resulting in prolonged inhibition of muscle spasms, facilitating reconstruction with expander of tissue [9].

However, in the other study twenty-three patients were enrolled between October 2009 and February 2012, where the effects of the intraoperative injection of 100 IU of botulinum toxin in the pectoral muscle of one side versus placebo in the contralateral side were evaluated during immediate reconstruction with tissue expander after bilateral mastectomy (See figure 2). There was no statistically significant difference in preoperative and postoperative changes in pain scores on the side of botulinum toxin compared to the control side at any point after postoperatively In addition, all pain scores showed a tendency to zero over time. Therefore, the study shows that intraoperative injection of the pectoral muscle with botulinum toxin is not effective in improving pain control in tissue expander reconstruction in mastectomized patients [10].

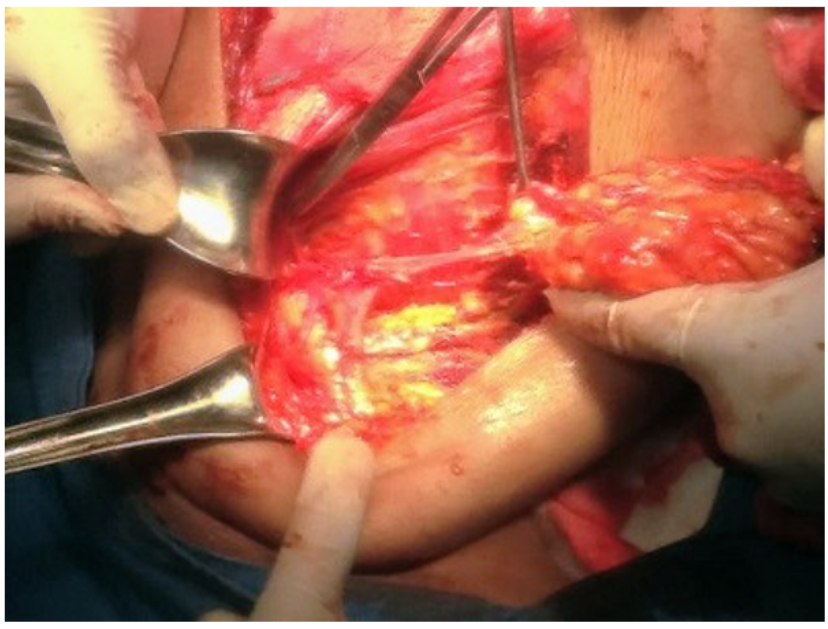

Figure 2: *Breast reconstruction, after modified radical mastectomy.*

Cheiloplasty

In this double-blind study, sixty patients underwent a review of a cleft lip scar between July 2010 and March 2012, where they were randomized to receive botulinum toxin type A (n = 30) or saline-control solution (n = 30) by injections into the underlying orbicularis muscle of the lips, immediately after wound closure. A 6-month follow-up was carried out where fifty-eight patients completed the study; Two patients in the control group did not return to the evaluations. Scars were independently assessed by analog visual scale and photographic measurements plus ultrasound, the widths of the scars. The visual analog scale in the botulinum toxin group was significantly better than in the control group (7.47 +/- 0.64 versus 6.10 +/- 1.06; p = 0.001). According to the photographic measurements, the scar was significantly narrower in the botulinum toxin group, at the first measurement point (0.62 +/- 0.18 mm versus 0.95 +/- 0.31 mm; p = 0.001) and in the second point (0.63 +/- 0.18 mm versus 0.92 +/- 0.36 mm; p = 0.001). In the case of ultrasonographic measurements, they were also better in the botulinum toxin group (0.72 +/- 0.25 mm versus 1.03 +/- 0.42 mm; p = 0.001). The study shows how the quality of the surgical scars of the upper lip, which are oriented perpendicularly to the direction of the traction exerted by the underlying orbicularis muscle of the lips, are significantly better due to their temporary paralysis, reducing the tension of the wound during healing [11].

In another double-blind study, sixty patients, with unilateral cleft lip and subjected to primary cheilopasties between August 2011 and June 2102, were randomized to receive injections of botulinum toxin type A or the vehicle in the underlying orbicularis muscle of the lips, immediately after wound closure. The scars were evaluated after a six-month follow-up, where fifty-nine patients completed the trial, by the analog visual photographic scale and the photographic measurement of the width of the scar. Measurements of the width of the scar at two defined points revealed significantly better results of the analogous visual scale and narrower scars in the botulinum toxin group. The study shows that the injection of botulinum toxin into the underlying orbicularis muscle of the lips produces scars after cheiloplasty with better appearance and narrower but did not provide additional benefits in terms of scar pigmentation, vascularization, flexibility or height of the same [12].

Blepharospasm

In this study, one hundred and two patients completed a double-blind study ≤ 20 weeks, entering an open extension period ≤ 69 weeks and receiving ≤ 5 additional treatments of botulinum toxin type A; at flexible doses (≤ 50 U per eye) and at flexible injection intervals (minimum six weeks). Disability rates of blepharospasm and adverse effects were measured during the trial, in which eighty-two patients completed the study; Fifty-six received a maximum of five injections of botulinum toxin. For each injection, there was a control visit six weeks later. The rates of disability of blepharospasm qualified by the patients themselves improved significantly for all ($p \leq 0.001$). All scores improved significantly at the end of the trial, compared to the first injection ($p < 0.05$). The most frequent adverse effects were palpebral ptosis in 31.4% and dry eye symptoms in 17.6%. The study shows how repeated injections of botulinum toxin type A, administered at flexible doses at intervals of six to twenty weeks, according to the needs of the patient, provide sustained efficacy in the treatment of blepharospasm without new or unexpected safety risks [2].

Diabetic foot

In a double-blind study seventeen patients with diabetes mellitus, diabetic neuropathy and a plantar ulcer of the forefoot were randomly distributed to one of three groups, receiving injections into the twin - soleus muscle affected with; 1) saline solution (n = 5, weight = 99 ± 21 kg), 2) 200 units of botulinum toxin (n = 7, weight = 101 ± 5 kg), or 3) 300 units of botulinum toxin (n = 5, weight = 129 ± 22 kg). The peak torsion stress of the plantar flexor and the plantar peak pressure of the forefoot were measured before and two weeks after the injection. The plantar peak torsion effort in the affected limb increased in placebo and in the group of 300 units of botulinum toxin (3 ± 4 Nm and 6 ± 10 Nm, respectively) and decreased -8 ± 11 Nm in the group of 200 units of botulinum toxin. The forefoot plantar pressure peak did not change in the placebo group and in the group of 300 units of botulinum toxin (0 ± 0 and 11 ± 5 N/cm^2 respectively) and decreased -4 ± 16 N/cm^2 (4%) in the group of 200 units. This study could not determine the dose necessary to consistently reduce plantar flexor strength and plantar forefoot pressure (See figure 3) [13].

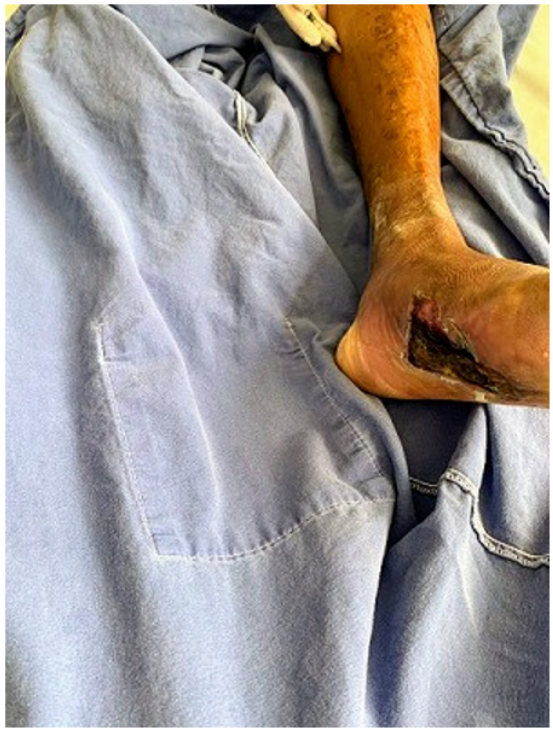

Figure 3: *Application of botulinum toxin in the gastrocnemius muscle with plantar ulcer.*

Abdominal wall

In a prospective study of patients with abdominal wall hernia after treatment of open abdomen were taken between September 2007 and January 2009. Botulinum toxin was applied bilaterally under electromyographic guidance on the abdominal wall. The measurement of the abdominal transverse wall defect was performed at weekly intervals: clinically, in the first two patients and with computed tomography in the next ten patients. Surgical closure was scheduled if no further reduction in the hernia defect was observed. The monthly hospital visits were followed up. In the first two patients, there was a reduction in the hernia defect of 50 and 47.2% respectively, documented after the third week of application of botulinum toxin, without further reduction. In the ten whose measurement of the hernia defect was performed by computed tomography, the transverse defect was compared at the beginning and 4 weeks after the application of botulinum toxin (13.85 +/- 1.49 cm versus 8.6 +/- 2.07 cm), a mean reduction of 5.25 +/- 2.32 cm was observed ($p < 0.001$; 95% confidence interval, 3.59 - 6.91). The hernia repair was carried out without recurrences in a mean follow-up of 9.08 months. The study shows how botulinum toxin application before abdominal wall hernia repair seems to be useful. The achieved paralysis of the lateral muscles and the reduction of the transverse hernia defect allows a closure at minimal tension in the patients [14].

Chronic anal fissure

In a prospective study twenty-one patients with persistent symptoms of chronic anal fissure after receiving treatment with 1% isosorbide dinitrate, applied 6 times a day for 8 weeks, followed by 2% diltiazem ointment, applied 2 times a day for 8 weeks and injections of botulinum toxin type A in the internal anal sphincter, they underwent fisurectomy in combination with the application of botulinum toxin type A (80 U) under regional anesthesia. After twelve weeks, nineteen patients (90%) with chronic anal fissure had healed. The median

follow-up was 16 months, with no recurrences. The study shows how fisurectomy in combination with the injection of botulinum toxin type A into the internal anal sphincter is an effective treatment for patients with chronic anal fissure resistant to medical treatment [15].

In another prospective study, twenty one patients with subsequent chronic anal fissure were treated with botulinum toxin injection (n = 10) or internal lateral sphincterotomy (n = 11). Follow-up was carried out for fourteen months where the maximum resting pressure and the maximum compression pressure were evaluated, making measurements before, finding similar anal pressures in both groups and two weeks after the treatment by anal manometry. After treatment, the maximum resting pressures were reduced from 104 +/- 22 mmHg to 86 +/- 15 mmHg in the surgical group ($p < 0.05$) and from 101 +/- 23 mmHg to 83 +/- 24 mmHg in the botulinum toxin group ($p < 0.05$). Maximum compression pressures were reduced from 70 +/- 27 mmHg to 61 +/- 32 mmHg ($p > 0.05$) in the surgery group and from 117 +/- 62 mmHg to 76 +/- 34 ($p < 0.01$) in the botulinum toxin group. The fissures were cured in 70 percent of the patients in the botulinum toxin group and 82 percent in the surgery group ($p > 0.05$). During the 14-month follow-up, no relapses were recorded. The study shows how internal lateral sphincterotomy and botulinum toxin injection treatment appear to be equally effective in the treatment of chronic anal fissure by reducing anal sphincter pressure [16].

Achalasia

In a double-blind study, eighty newly diagnosed patients with achalasia were randomized receiving botulinum toxin injection (n = 40) or laparoscopic myotomy (Nissen fundoplication or Dor anterior partial (n = 40)). Six months were followed up evaluating symptoms; resting pressures of the lower esophageal sphincter, measured by manometry; Barium swallow was used to evaluate the esophageal diameter pre- and post-treatment. Eight to one hundred units of botulinum toxin were injected twice, one month apart, into the esophagogastric junction. After six months of follow-up, symptom scores improved more in surgical patients (82% CI 76 - 89 versus 66% CI 57 - 75, $p < 0.05$). The lower esophageal sphincter pressure decrease was similar in both groups; esophageal diameter reduction was greater after surgery (19% CI 13 - 26 versus 5% CI 2-11, $p < 0.05$). Later, symptoms recurred in 65% of patients treated with botulinum toxin and the probability of being symptom free at 2 years was 87.5% after surgery and 34% after botulinum toxin ($p < 0.05$). The study shows that laparoscopic myotomy is as safe as botulinum toxin treatment. Botulinum toxin should be reserved for patients who are not fit for surgery or as a bridge to the most effective therapies, such as surgery or endoscopic dilation [17].

In another prospective study, one hundred and eighteen patients with achalasia were randomized to receive one of three doses of botulinum toxin in a single injection: 50 U (n = 40), 100 U (n = 38) and 200 U (n = 40). Of the patients who received 100 U, those who responded were reinjected with an identical dose after 30 days. Clinical and manometric evaluations were performed at the beginning, 30 days after the initial botulinum toxin injection and at the end of the follow-up (mean of 12 months, range of 7-24 months). Thirty days after the initial injection, 82% of patients were considered responders without a clear dose-related effect. At the end of the follow-up, however, the recurrence of symptoms was evident in 19% of the patients who received two injections of 100 U compared to 47% and 43% in the 50 U group and the 200 U group respectively. Patients in the 100 x 2U group were more likely to remain in remission at any time ($p < 0.04$), with 68% (95% CI 59 - 83) still at 24 months. The study shows how two injections of 100 U of botulinum toxin 30 days apart seem to be the most effective therapeutic scheme and how the main determinant of the response to botulinum toxin is the presence of vigorous achalasia [18].

Discussion

This research was designed in order to evaluate the use of botulinum toxin in a pre-surgical manner in muscle or tendon defects.

Comparison between studies

In the case of studies in hand surgery there were differences in the use of botulinum toxin compared to surgical treatment, on the one hand there was a muscular reduction in the spontaneous activity of the fingers, allowing a better postoperative result and a better rehabilitation after surgical repair of zone 2 of the flexor tendon at eighteen months follow-up. However, the other study shows how tendon

transfer surgery in patients with cerebral palsy discreetly improved the active range of movements compared to botulinum toxin injection at 12-month follow-up. Not showing adverse effects in both studies [7,8].

In the treatment with muscle infiltration of the botulinum toxin for pain control in breast reconstruction with tissue expanders after mastectomy made differences in the studies. On the one hand the use of botulinum toxin improved postoperative pain, requiring less use of narcotics both at the beginning and in the final expansion of the tissue; requiring smaller expansion sessions and improving the volume of expansion per session through prolonged inhibition of muscle spasms in a two-year follow-up. Removal of one tissue expander in the botulinum toxin group was required. While in the other study the intraoperative injection of botulinum toxin in tissue expander reconstruction in mastectomized patients there were no significant changes in pre and postoperative pain scores with the control group, without presenting adverse effects during the study [9,10].

In the case of the treatment of cheilopasty in patients with cleft lip the results of the studies were similar. In both, botulinum toxin type A was injected into the underlying orbicularis muscle of the lips, immediately after wound closure, six months follow-up in both and showing significantly better results of the analog visual scale and narrower scars with photographic measurements in the botulinum toxin group, due to temporary muscle paralysis and reducing the tension of the wound during healing. However, the studies did not provide additional benefits in terms of scar pigmentation, vascularization, flexibility or height. There were no adverse effects in both studies [11,12].

In the case of blepharospasm, repeated injections of botulinum toxin type A, administered at flexible doses at intervals of six to twenty weeks, significantly improved disability rates in patients, providing sustained efficacy without new or unexpected safety risks. However, during the study there was palpebral ptosis in 31.4% of patients and symptoms of dry eye in 17.6% [2].

In the case of patients with diabetic foot and plantar ulcer of the forefoot, botulinum toxin was injected into the twin - soleus muscle, decreasing the peak torsion of the plantar flexor and the plantar pressure peak in advance with the application of 200 units and increasing the effort of torsion peak of the plantar flexor with the application of 300 units; at two weeks after the injection. Therefore, the study could not determine the dose necessary to reduce plantar flexor strength and plantar forefoot pressure, so additional research is needed to know the specific physiological changes in patients with diabetes mellitus and the impact on effectiveness of botulinum toxin in order to guide the appropriate dosage [13].

In the case of abdominal wall defects, botulinum toxin was injected before hernia repair showing a significant reduction in hernia defect through lateral muscle paralysis and reduction of the transverse hernia defect, allowing a closure at minimum tension in a follow-up at 9.08 months; showing no recurrences or adverse effects during the study [14].

In the case of patients with chronic anal fissure, studies show similar results. On the one hand, the injection of botulinum toxin type A in the internal anal sphincter in combination with fisurectomy, showed healing in 90% of patients with chronic anal fissure resistant to medical treatment with a median follow-up of 16 months and no recurrences were observed in that study. However, the other study shows how botulinum toxin has a cure of 70% of patients versus 82% in patients with internal lateral sphincterotomy, at a follow-up at 14 months and without recurrence. Thus, the study shows how botulinum toxin injection treatment is equally effective as internal lateral sphincterotomy in patients with chronic anal fissure by reducing the maximum resting pressure and the maximum compression pressure in the anal sphincter [15,16].

In the case of patients with achalasia the studies showed differences. In one of them recently diagnosed patients, botulinum toxin was injected in two doses one month apart and compared with laparoscopic myotomy, following up to six months in both studies. There was greater improvement of symptoms and greater reduction of esophageal diameter in surgical patients. The lower esophageal sphincter

pressure decrease was similar in both groups. The study shows that laparoscopic myotomy is as safe as botulinum toxin injection, the second being reserved in patients not surgically fit or as a bridge to more effective therapies. The probability of being disease-free at 2 years was 87.5% after surgical treatment and 34% in the case of botulinum toxin application. The other study shows how the injection of two doses of 100 U of botulinum toxin with a period of thirty days apart is an effective therapeutic scheme, with 68% of patients remaining in remission even after 24 months of follow-up [17,18].

Limitations of the Study

In the study, muscle or tendon defects could not be compared in the various pathologies treated by showing heterogeneity in established surgical treatments, only items with the same pathology and the efficacy of botulinum toxin injection as a preoperative treatment could be compared.

Strengths of the Study

The study included Randomized Controlled Clinical Trials (RCTs), performing a search in the database 1999 to January 2016, in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PUBMED, OVID and EMBASE.

Conclusion

The use of botulinum toxin type A, in a presurgical way in muscular or tendon defects, presents minimal adverse effects and great efficacy in adjuvant that comparatively yield better results with the surgical techniques called gold standards, in specific pathologies. It was verified in this meta-analysis that there is an equivalence in therapeutic effects as another option in the surgical arsenal in the diseases studied.

This work exposes a comparative diversity on the use of botulinum toxin type A, in its wide spectrum of applications of the various specific pathologies with good results it becomes a watershed for new protocols.

Disclosure

We declare that there are no conflicting interests and that we do not receive any kind of financing.

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