Randomized study comparing onabotulinum toxin diluted in lidocaine and epinephrine versus saline solution for the treatment of periocular lines

Estudo randomizado comparando toxina onabotulínica diluída em lidocaína e epinefrina versus solução salina para o tratamento das linhas perioculares

ABSTRACT

Introduction: Standard dilution of botulinum toxin is performed with 0.9% saline solution. Some studies show that when diluted in lidocaine and epinephrine, the toxin preserves its function without compromising effectiveness or safety.

Objective: To establish whether the paralyzing effect of ona-toxin type A reconstituted in anesthetic (2% lidocaine) and vasoconstrictor agent (1:50,000 epinephrine) is as effective as that of the same toxin reconstituted in saline solution, at 48 hours, 1 week, 2, 4, 12 and 24 weeks, for the treatment of periocular lines. To compare the tolerance to pain between the two reconstitution alternatives.

Methods: Fifteen patients with periocular wrinkles were randomized to receive onabotulinum toxin diluted in lidocaine with epinephrine or in saline. Re-evaluations were carried out in 48 hours, 1 week, 2, 4, 12 and 24 weeks.

Results: The data indicate that there was no difference in the symmetry and durability of the botulinum toxin, nor in the pain during the application.

Conclusions: There was no statistically significant difference in the frequency of lateral periocular muscle paralysis and symmetry resulting from the applications of onabotulinum toxin reconstituted in lidocaine with epinephrine or in saline solution. This outcome is consistent with those of previous studies.

Keywords: botulinum toxins, type A; dilution; lidocaine

RESUMO

Introdução: A diluição-padrão da toxina botulínica é feita com solução salina 0,9%. Alguns estudos mostram que diluída em lidocaína e epinefrina a toxina mantém sua função sem comprometer a eficácia ou segurança.

Objetivo: Estabelecer se o efeito paralisante da toxina onabotulínica tipo A reconstituída em anestésico (lidocaína a 2%) e agente vasoconstritor (epinefrina 1:50.000) é tão efetivo quanto o da mesma toxina reconstituída em solução salina em 48 horas, uma semana, duas, quatro, 12 e 24 semanas para o tratamento de linhas perioculares e comparar a tolerância à dor de uma e outra possibilidade.

Métodos: 15 pacientes com rugas perioculares foram randomizados para receber toxina onabotulinum diluída em lidocaína com adrenalina ou diluída em solução salina e foram reavaliadas em 48 horas, uma semana, duas, quatro, 12 e 24 semanas.

Resultados: Os dados indicam que não houve diferença na simetria e na durabilidade da toxina botulínica, nem tampouco na dor durante a aplicação.

Conclusões: Não houve diferença estatisticamente significativa na frequência de paralisia muscular periocular lateral e na simetria decorrente das aplicações de toxina botulínica reconstituída em lidocaína com epinefrina ou em solução salina, resultado consistente com estudos prévios.

Palavras-chave: toxinas botulinícas tipo A; diluição; lidocaína
INTRODUCTION

The injection of botulinum toxin (BT) aimed at treating facial wrinkles is one of the most widely performed procedures worldwide. Botulinum toxins are powerful neurotoxins derived from the bacterium Clostridium botulinum that acts on the neuromuscular junction by inhibiting the release of acetylcholine, causing a temporary neuromuscular blockade. The bacterium produces several BT serotypes – namely A, B, Ca, Cb, D, E, F, G – of which the strongest is serotype A, which is most commonly used for cosmetic treatments. Serotype A BT cleaves Snap-25 (25KDa synaptosome-associated protein), from the Snare complex (soluble NSF attachment receptor). The effects of BT on the target muscles decrease over time as Snap-25 protein regenerates and muscle contractility is restored.

Botulinum toxin was approved by the US’ FDA (Food and Drug Administration) for cosmetic use in 2002 regarding the treatment of the glabellar complex muscles, and in 2013 for periocular lines. It is used off-label for all other facial cosmetic indications. There are currently 3 types of A toxins approved by the FDA for cosmetic use in the glabellar lines: onabotulinum toxin A, abobotulinum toxin A and incobotulinum toxin A. The standard dilution of BT is carried out with 0.9% saline. Some studies show that when diluted in 1% lidocaine and 1:100,000 epinephrine, BT keeps its function without compromising effectiveness or safety. The advantage of reconstituting it in lidocaine and epinephrine is that there is an increase in its short-term efficacy, accelerating the onset of the effect and reducing the discomfort associated with injections. In most patients, the full effect of botulinum toxin-induced paralysis is imperceptible before 48 to 72 hours after application, and the effect lasts for 3 to 4 months.

The present study was carried out to establish whether the paralyzing effect of the onabotulinum toxin type A reconstituted in anesthetic (2% lidocaine) and vasoconstricting agent (1:50,000 epinephrine) is as effective as that of the same toxin reconstituted in saline solution after 48 hours, 1 week, 2 weeks, 4 weeks, 12 weeks and 24 weeks after. Questionnaires aimed at assessing satisfaction, adverse effects, pain, and treatment durability were answered by the patients throughout the study. Following the procedure, an evaluator blinded to the difference in dilutions between the treated sides (standard solution and experimental dilution) analyzed the photographs, videos and answers to the questionnaires at each step.

RESULTS

Data were collected from 15 female patients. The mean age was 39.1 years (SD = 7.9, min = 25, max = 52). Regarding previous treatments, 9 (60%) patients had never undergone the procedure before, 2 (13.3%) had undergone it once, 1 (6.7%)...
had undergone it twice, 2 (13.3%) had undergone it five times and one (6.7%), six times.

The majority of patients had paralysis within 48 hours (Table 1), and both paralysis and symmetry within 2 weeks (Table 2). The sides applied with lidocaine and saline solution were compared at each experimental timepoint of the evaluation (Graph 1). There was no statistically significant difference between the sides in any of the evaluated timepoints.

Ten (66.7%) patients reported pain. Three (20.0%) patients reported pain regarding the side treated with lidocaine, while 8 (53.3%) reported pain in the side diluted with saline. There was no statistically significant difference ($P = 0.180$).

Whitening effect was observed in 6 (40.0%) patients, all on the side treated with lidocaine. It is important to note that it was not possible to compute the statistical significance, since no patient showed whitening on the side treated with saline solution.

**DISCUSSION**

The present study’s main objective was to establish whether the paralyzing effect of onabotulinum toxin A reconstituted with anesthetic (2% lidocaine) and vasoconstrictor agent (1:50,000 epinephrine) is as effective as that of the same toxin reconstituted with saline solution at 48 hours, 1 week, 2 weeks, 4 weeks, 12 weeks and 24 weeks, for the treatment of periocular lines. This study found no statistically significant difference in the paralyzing effect in any of the experimental timepoints in which the patients in both groups (lidocaine and saline solution) were evaluated and compared with the assistance of photographs and videos. Other authors have reported symmetry when comparing the two types of dilution 1 week after the application.$^{12,16}$

The present study also assessed the tolerance to pain, evidencing that there was no decrease in pain on the side treated with saline when compared to the side treated with lidocaine. Lidocaine tends to be painful due to its acid pH, which does not seem to offer an advantage regarding the minimization of pain during the application of BT.$^{17}$ Gassner et al. studied 10 volunteers, reporting an immediate and statistically significant paralyzing effect when BT was diluted in 1% lidocaine and 1:100,000 epinephrine.$^{12}$ Kim et al. investigated the satisfaction of 181 patients who received BT type A reconstituted in 1% lidocaine with 1:100,000 epinephrine, describing the immediate paralytic effect caused by the anesthetic as positive.$^{18}$ In addition, epinephrine is mentioned in some articles as beneficial for minimizing the diffusion of BT.$^{12,13,19}$

The present study’s results are limited due to the small sample size. In this manner, a non-significant value allowed to state that there was no difference between the different types of dilutions or, alternatively, the sample was too small to allow detection of any difference. The present study used 2% lidocaine and 1:50,000 epinephrine, while other studies found in the literature employed 1% lidocaine and 1:100,000 epinephrine. The study did not propose to evaluate the doses necessary to achieve better clinical outcomes in the periocular region, since it used similar doses in all patients, aiming at verifying the paralysis and symmetry effects related to the two different types of dilution. Finally, the blinded evaluator carried out a subjective assessment of the photographs and videos due to the fact that there was no objective scale of measurement.

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**Table 1: Presence of Paralysis and Symmetry at the Different Experimental Timepoints**

<table>
<thead>
<tr>
<th>Time</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 HOURS</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>1 WEEKS</td>
<td>3 (20)</td>
</tr>
<tr>
<td>2 WEEKS</td>
<td>9 (60)</td>
</tr>
<tr>
<td>4 WEEKS</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>12 WEEKS</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>6 MONTHS</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2: Presence of Paralysis at the Different Experimental Timepoints**

<table>
<thead>
<tr>
<th>Time</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 HOURS</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>1 WEEKS</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>2 WEEKS</td>
<td>12 (80)</td>
</tr>
<tr>
<td>4 WEEKS</td>
<td>12 (80)</td>
</tr>
<tr>
<td>12 WEEKS</td>
<td>12 (80)</td>
</tr>
<tr>
<td>6 MONTHS</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 3: Comparison of the Presence of Paralysis between Sides Treated Either with Lidocaine and Saline Solution, at Different Experimental Timepoints**

<table>
<thead>
<tr>
<th>Time</th>
<th>Lidocaine</th>
<th>Saline</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 HOURS</td>
<td>2 (13.3)</td>
<td>7 (46.7)</td>
<td>0.125</td>
</tr>
<tr>
<td>1 WEEKS</td>
<td>6 (40)</td>
<td>8 (53.3)</td>
<td>0.727</td>
</tr>
<tr>
<td>2 WEEKS</td>
<td>9 (60)</td>
<td>12 (80)</td>
<td>0.250</td>
</tr>
<tr>
<td>4 WEEKS</td>
<td>10 (66.7)</td>
<td>12 (80.0)</td>
<td>0.500</td>
</tr>
<tr>
<td>12 WEEKS</td>
<td>10 (66.7)</td>
<td>12 (80.0)</td>
<td>0.500</td>
</tr>
<tr>
<td>6 MONTHS</td>
<td>-</td>
<td>-</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*This content is a direct transcription of the provided text and has been formatted for clarity and readability.*
CONCLUSION

In line with the literature, the present study did not evidence statistically significant difference in the frequency of lateral periocular muscle paralysis and symmetry in the application of BT reconstituted with lidocaine and epinephrine as compared with that reconstituted only with saline solution. The data suggest that the effects durability was similar in both groups. Also, the pain sensation during the application was not inferior to that in the lidocaine group.

REFERENCES


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DECLARATION OF PARTICIPATION:

Mauricio de Quadros: Bibliographic survey, project design, botulinum toxin application, preparation of the discussion and conclusion sections, and final editing of the paper.

Ana Lupe Webber: Bibliographic survey, structuring of the study project, photographic and video based evaluation of outcomes.

Mariana Silveira Ferreira: Bibliographic survey, structuring of the study project, patient randomization and selection, preparation of photographs and videos, photographic and video based reassessment of patients.

Ana Paula Schwarzbach: Bibliographic survey, structuring of the study project, patient randomization and selection, photographs and videos, preparation of photographs and videos, photographic and video based reassessment of patients.