Correlation of self-assessment with expert rating and acoustic analysis for spasmodic dysphonia treatment with botulinum neurotoxin A

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A B S T R A C T
Objectives: Objective and subjective evaluation of botulinum neurotoxin A (BoNTA) treatment for adductor type spasmodic dysphonia is presented. Therefore, a combinatorial approach based on patients’ and speech experts’ assessment of voice impairment, as well as on the acoustic analysis of spoken standardized text was performed.
Study design: Prospective clinical study.
Materials and methods: For 17 patients, the voice quality prior to and 4–8 weeks after BoNTA injection (9 transoral, 8 transcutaneous) was investigated. Voice Handicap Index-12 (VHI-12) questionnaires as well as ratings of the GRB (grade, roughness, breathiness) scale were analyzed. Moreover, objective parameters such as pure speech duration, local jitter, local shimmer and voice breaks were evaluated.
Results: The pre-post analysis of all patients revealed a significant reduction of the VHI-12 score, the jitter values and the number of voice breaks. Changes in speech duration and breathiness differed significantly for transoral vs. transcutaneous BoNTA injection.
Conclusions: We were able to correlate the questionnaire-based self-assessment with external evaluation of the speech roughness and with acoustic signal analysis parameters, in particular for the jitter. Our data indicated beneficial effects for transoral BoNTA application.

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Introduction
Spasmodic dysphonia is an action-triggered focal dystonia characterized by involuntary contractions of laryngeal muscles [1]. Patients present with a hoarse voice and iterative voice breaks, which compromise the intelligibility of speech and often result in a major burden for the patients [2]. Based on the results of a class I study conducted by Troung et al. in 1991 [3,4], laryngeal injections of botulinum neurotoxin type A (BoNTA) are currently accepted as a standard for therapy [5,6]. It was observed that paralysis of dystonic laryngeal muscle groups may alleviate typical symptoms especially in the adductor form of the disease (ADSD) [7]. Supportively, several large retrospective clinical studies and meta-analyses reported a high clinical efficacy [8–11], but an objective verification of the beneficial effects of BoNTA remained a challenge so far. This includes the evaluation of the injection technique, as administration of BoNTA can be performed either endoscopically or transcutaneously with passage of the cricothyroid ligament. Consequently, titration of dosage and testing of different BoNTA formulas is required for optimized therapy results. Previous investigations employed the standardized assessment of patients’ self-perception (Voice Handicap Index, Voice Related Quality of Life, etc.) [12–14] or ratings of speech experts (e.g. the Grade, Roughness, Breathiness (GRB)-scale or the Clinician’s Perceptual Judgment of Voice Impairment tool) [15,16]. Moreover, evaluations of acoustic criteria such as jitter, shimmer, number of voice breaks, fundamental frequency as well as its standard deviation were performed [17,18]. According to the variability of the results, none of these parameters was suited to represent the whole spectrum of the disorder on its own. Therefore, some research groups combined the aforementioned three dimensions of evaluation [15,19], but further validation of such promising approach is required and its extension to the comparison of different injection techniques is pending. With the present study, we deliver a contribution to improved objective and subjective elucidation of ADSD treatment based on patients’ and speech experts’ assessment of voice impairment as well as on the acoustic analysis of spoken standardized text.

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Table 1
13 females (F) and 4 males (M) participated in this study. The probands’ median age was 68 years. In 53% of the investigations, BoNTA was applied via a transoral (to) approach. The remaining patients were transcutanously (tc) treated. The median interval between injections and follow-up assessment was 40 days. MU refers to mouse units. D to DYSPORT® and B to BOTOX®. Description of patient and treatment details.

<table>
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<td>Dosage [MU]</td>
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<td>5.3</td>
<td>2.5</td>
<td>6.7</td>
<td>12.5</td>
<td>13</td>
<td>9.5</td>
<td>5.3</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>3.5</td>
<td>7.5</td>
<td>5.3</td>
<td>10</td>
</tr>
</tbody>
</table>

Materials and methods

Patient selection and ethical approval

The voice quality of 17 patients with ADSD (13 females, median age 68 years) was investigated before and after laryngeal injection of BoNTA. All patients, whose diagnosis was confirmed by an experienced phoniatrist, gave informed consent for participation. The study was approved by the ethics-committee of the University of Duesseldorf (file number 3842). Detailed information about the participants is listed in Table 1. Two groups of patients were recruited: 9 were subject to individually optimized dosage and preparation during previous BoNTA treatments. 8 patients just started therapy with varying BoNTA amounts and formulas as well as different injection techniques to avoid pre-determination of therapeutic parameters.

Voice analysis by acoustic and self-assessment criteria

As 9 patients were regularly treated within a 3–4 months interval, their voice status was assessed directly prior to BoNTA injection to prevent any interference with preceding treatment procedures. 4–8 weeks after injection, the patients underwent a second examination to determine the clinical effects of the current BoNTA therapy session.

A translated and shortened version of the widely used original Voice Handicap Index (VHI), the VHI-12, was employed for a subjective self-assessment of the patients (supplementary material). It can be up-scaled to the original VHI [20] and offers a standardized tool for the comparison of VHI-based studies performed in different languages.

The participants’ voices were recorded during readings of the German version of the Aesopian fable “The North Wind and the Sun”. For analysis, the data were pseudonymised to blind the investigators for specific patient-related information. All silent sequences between the words were removed to exclusively investigate voiced speech. Subsequently, the program PRAAT was applied to assess the total duration of these text passages as well as local jitter, local shimmer, and amount of voice breaks [21]. The acoustic evaluation was performed by forward cross-correlation pitch extraction. Local jitter values were calculated as percentages of the mean period length, whereas the shimmer was determined based on the mean period amplitude. Additionally, unprocessed pseudonymised recordings were rated by 6 speech therapists applying the German equivalent of the GRB scale [22].

Techniques used for laryngeal BoNTA injection

Onabotulinum neurotoxin (BOTOX®; Allergan, Inc., Irvine, CA, USA) and abobotulinum neurotoxin (DYSPORT®; Ipsen Biopharmaceuticals, Inc., NJ, USA) were used for ADSD therapy. For comparability, the applied DYSPORT® amount was multiplied by 0.33 and thereby converted into its equivalent dosage of BOTOX® [23]. 2.5–15 mouse units were injected into the M. vocalis/thyroarythenoideus complex. Transoral access was achieved using a rigid endoscope with magnifying lens for visual control. For transcutanous application, the injection needle was forwarded through the cricothyroid ligament with a slight craniolateral angulation to target the vocalis/thyroarytenoid muscle complex. Electromyographic guidance ensured a correct placement of the injection needle [24].

Statistical analysis

Wilcoxon’s signed rank test was used for paired comparison of the assessments before (t1) and after BoNTA treatment (t2). For GRB rating, the average value of 6 different ratings per patient was determined. Changes (post injection vs. pre injection) in the VHI-12 rating score, in voice characteristics, and in the GRB rating were correlated according to Spearman’s Rho. The Mann–Whitney-U-test was applied for comparison of the two injection techniques. A p-value of less than 0.1 was considered as a trend, of less than 0.05 as statistically significant.

Results

The patients’ VHI-12 score changed significantly after BoNTA injection (median dropped from 23 to 14; p = 0.034; Fig. 1A). Similar applied to the parameters jitter (medians: 3.89% vs. 3.55%; p = 0.001; Fig. 1C) and the number of voice breaks (medians: 184 vs. 156; p = 0.029; Fig. 1D). The median roughness significantly declined (from 2.00 to 1.83; p = 0.041; Fig. 1B), as well. The evaluation of shimmer, pure speech duration, breathiness, and grade did not reveal any significant changes (data not shown).

A significant correlation between changes of roughness and the VHI-12 score (r = 0.494, p = 0.044) and a trend between changes of jitter and VHI-12 score (r = 0.434, p = 0.082) was observed. The comparison between the transoral and transcutanous injection techniques is summarized in Table 2. Significant post-pre differences of breathiness and speech duration were detected (Fig. 2).

Discussion

The findings obtained in our study revealed a significant reduction of the VHI-12 score. Translated to the original voice handicap index, this means a total decline from 57.5 to 35 points. It can be consequently rated as clinically relevant, as it refers to a category change in rating, for example from “highly compromised” to “average compromised” [20,25]. Most patients expressed a clear reduction of the ADSD symptom severity. It confirms that the questionnaire-based self-assessment can be recommended as an adequate tool to indicate therapeutic success [12]. Complementary to previous studies, this was comprehensible by external auditors as well, because the roughness significantly improved in correlation to the VHI-12 results [15]. Such roughness change has been
assigned to a reduced laryngeal hyperadduction during phonation [26]. It means that beneficial effects of BoNTA treatment became audible in the physiology of speech. As the patients were aware of their treatment, psychological effects may have contributed, but a placebo effect with exclusive impact on the cognitive domain instead of the speech level can be excluded. Moreover, these findings were objectified by acoustic signal analysis. The number of voice breaks, which was identified as pathognomonic for ADSD, significantly decreased. Aperiodicity during phonation reflected by jitter changes significantly improved. Because such aperiodicity can be referred to laryngeal vibration characteristics, the results suggest beneficial therapeutic effects at the local origin of disease manifestation – the laryngeal muscle apparatus. Perception of roughness is in line with jitter changes and seems to be associated with the patients' subjective self-assessment. With a modulus of not more than 9%, a jitter reduction was verifiable for almost 90% of the patients. Compared to detected amount of voice break changes, it reflects a more homogeneous distribution, which implies that jitter may have been an underestimated parameter so far to monitor BoNTA effects on ADSD symptoms. Amplitude variability

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**Table 2**

Development of VHI-12 scores, GRB rating, and acoustic voice analysis after BoNTA treatment for the transorally and transcutaneously injected patient groups. Maximum and minimum values as well as the 25%, 50% (median), and the 75% quartiles are presented. Changes of breathiness (p=0.035) and speech duration (p=0.036) differed significantly (indicated by asterisk). MWU = Mann–Whitney-U-Test. Comparison of transoral injection technique with transcutaneous injections using subjective and objective criteria.

<table>
<thead>
<tr>
<th></th>
<th>Transoral injection</th>
<th>Transcutaneous injection</th>
<th>MWU</th>
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<tbody>
<tr>
<td></td>
<td>Min 25% 50% 75% Max</td>
<td>Min 25% 50% 75% Max</td>
<td>p</td>
</tr>
<tr>
<td>VHI-12 [pts.]</td>
<td>–34 –10.5 –6 –0.5 8</td>
<td>–15 –10.3 –5 –0.5 28</td>
<td>0.832</td>
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<tr>
<td>Grade [pts.]</td>
<td>–0.50 –0.42 0.00 0.25 0.50</td>
<td>–0.34 –0.17 0.08 0.00 0.50</td>
<td>0.978</td>
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<tr>
<td>Roughness [pts.]</td>
<td>–1.17 –0.84 –0.17 0.00 0.50</td>
<td>–0.59 –0.34 –0.09 0.00 0.33</td>
<td>0.514</td>
</tr>
<tr>
<td>Breathness [pts.]</td>
<td>–0.316 0.00 0.33 0.59 1.00</td>
<td>–0.67 –0.62 –0.25 0.25 0.50</td>
<td>0.035*</td>
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<tr>
<td>Duration [s]</td>
<td>–9.18 –8.46 –3.03 –1.65 0.49</td>
<td>–9.19 –3.04 2.34 3.49 5.13</td>
<td>0.036*</td>
</tr>
<tr>
<td>Voice break count</td>
<td>–48 –33 –20 –4 13</td>
<td>–145 –32 –6.5 11.5 61</td>
<td>0.495</td>
</tr>
<tr>
<td>Local jitter [%]</td>
<td>–1.16 –0.71 –0.18 –0.06 0.61</td>
<td>–1.49 –0.81 –0.39 –0.07 –0.04</td>
<td>0.673</td>
</tr>
<tr>
<td>Local shimmer [%]</td>
<td>–1.85 –0.66 0.86 2.11 3.62</td>
<td>–4.42 –3.27 –0.71 0.89 2.34</td>
<td>0.167</td>
</tr>
</tbody>
</table>

**Fig. 1** Evaluation of voice quality after treatment with BoNTA. The boxplots represent maximum and minimum values as well as the 25%, 50% (median), and the 75% quartile. (A) Median VHI-12 total score changes before treatment (t1) and after treatment (t2). 13 patients reported an improvement. (B) Roughness changes based on median score. The scorings revealed a reduction for 10 patients and identical t1 and t2 values for 5 patients. An interrater-reliability of 0.792 (intraclass correlation coefficient) was achieved. (C) Jitter changes based on median score. A decline of jitter was observed for 16 patients. (D) Voice break changes based on median score. A lower voice break number after BoNTA treatment (t2) was detected for 11 patients.
of voiced speech does not seem to provide a significant contribution in the present case, because shimmer values did not show any change.

Similar considerations apply to the comparison of two pre-determined groups of patients that were either transorally or transcannately treated. Locally defined and therefore narrow injection areas, a higher percentage (67%) of therapy experienced subjects and the application of BOTOX® were characteristic for the first group. Compared to DYSPORT®, such BoNTA formula is currently controversially discussed to exhibit lower diffusion characteristics and more stationary effects [27]. In turn, transcannately injected patients predominantly received DYSPORT® and a larger number of 63% was naive to therapy. These de novo-patients were injected cautiously, since the mean dose in the transcannately group (7 MU) was lower than in the transoral group (9 MU). The finding of slightly increased breathiness in the transoral group is assigned to a more intense BoNTA effect, as it can be associated with glottis closure insufficiency due to laryngeal muscle dysfunction. Consequently, it may be regarded as an indirect marker for treatment effectiveness [8].

Conclusion

Transoral, endoscopically guided application may require anesthesia and sedation, but it can also warrant preferential benefits compared to the option of transcannately injection. Thus our findings are in line with a previous report based on an unblinded, subjective evaluation of retrospective data which suggested certain superiority for transoral application, as well [28]. Conclusively, the conduct of larger clinical trials for the comparison of the two injection techniques is recommended as a next step to tap the full potential of the optimization options explored in the present study. Moreover, a quantitative analysis of covariates such as BoNTA formula and the patients’ treatment experience on the observed effects will be promising.

Financial disclosure

V.H., C.J.H., and W.A. declare no financial disclosure.

H.H. took part in studies supported by Allergan, Merz and Ipsen, received honoraria for presentations at meetings and for the participation in Advisory Boards of these companies. However, the present study was neither initiated nor supported by Allergan, Merz or Ipsen. Therefore H.H. declares no financial conflict of interest in connection with the present study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.baga.2013.08.002.

References


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