SUBSTITUTION VOICE REHABILITATION AFTER OPEN PARTIAL HORIZONTAL LARYNGECTOMY THROUGH THE PROPRIOECEPTIVE-ELASTIC METHOD (PROEL): A PRELIMINARY STUDY.

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Abstract

Objective. The aim was to investigate the efficacy of the Proprioceptive Elastic Method (PROEL) in the rehabilitation of the substitution voice after open partial horizontal laryngectomy (OPHL).

Study Design. Prospective outcome study.

Methods. 15 patients surgically treated by OPHL type II or type III for laryngeal cancer were recruited (experimental group). Each patient underwent a specific program of voice rehabilitation based on the PROEL method with the same speech and language pathologist. Acoustic-aerodynamic analysis: maximum phonation time (MPT); spectrographic classification (Titze’s modified classification), perceptual analysis (INFVo rating scale) and self assessments (SECEL questionnaire) were performed before the treatment (T0), after three months of rehabilitation (T1), and at the end of the 6-month rehabilitation program (T2).

A control sample of other 15 patients who underwent OPHL type II or type III and who underwent a standard peri-operative rehabilitation was randomly extracted from an historical database and compared to the experimental group.

Results. Significative voice improvements between T0-T1 and T2 were found for acoustic, aerodynamic, perceptual and self assessments analysis in the experimental group. Significative differences were found between the experimental group at T2 and the control sample for aerodynamic, self assessment and perceptual analysis.

Conclusions. The results of the present study support PROEL method as an effective approach for substitution voice rehabilitation after OPHL type II and III. Randomized-controlled trials on larger groups of patients are needed in future in order to compare PROEL with other rehabilitative approaches.
1 Introduction

Surgical and non-surgical treatments for laryngeal cancer can lead to voice impairment, with a severe impact on oral communication. This impairment can play a critical role affecting communication-related quality of life (QOL). People with verbal communication disabilities face demanding challenges in areas such as maintaining social roles, identity and accessing daily services [1].

Several treatment options are available today for the management of laryngeal cancer, including surgical and non-surgical approaches. Among these, surgical function-sparing approaches allow the preservation of the main laryngeal functions and avoid a permanent tracheostoma, which causes cosmetic disability and results in a decreased QOL [2-4].

Open Partial Horizontal Laryngectomies (OPHLs) represent a group of surgical procedures that have been recently classified with a systematic nomenclature by Succo et al. [5]. According to the OPHL classification system, three types of OPHLs can be described: Type I (formerly defined horizontal supraglottic laryngectomy), Type II (previously called supracricoid laryngectomy), and Type III (also named supratracheal laryngectomy). While type I OPHL spares the glottic plane and shows little impact on voice quality; type II and III OPHLs sacrifice both vocal folds, resulting in the creation of a neoglottis. Voice after type II and III OPHL is usually highly deteriorated, with a hoarse and breathy quality. A comparative outcome study by Schindler et al. showed similar results in functional outcomes after type II and type III OPHLs [6].

The Proprioceptive Elastic Method (PROEL) is a multidimensional approach to voice and dysphonia developed by Alfonso Borragan [7]. The method uses pressure, vibration, temperature, and stretching sensory stimuli in order to communicate with the phonatory organ in an intuitive and easy way. Proprioception and elasticity are obtained through voice hydration procedures, instable-balance postures, laryngeal manipulations and semi occluded vocal tract postures. Particular importance is given to the reduction of vocal risk factors such as vocal overload, inflammatory conditions (e.g. smoking and laryngopharyngeal reflux) and to vocal fold surface hydration procedures (nasal hydrotherapy). In order to eliminate tension, stress and muscular stiffness, body stretching maneuvers and facilitating instable postures are carried out (e.g. the so called leaning Pisa Tower
position, where the patient stands on tiptoe with his/her body leaning upwards while looking up at the ceiling). Laryngeal manipulations and semi occluded vocal tract exercises (e.g. semi-occluded ventilation mask postures) promote an easier and resonant phonation. Recently, the PROEL method showed efficacy in the treatment of a group of patients affected by functional dysphonia [8]. Because voice quality is one of the major critical points regarding functional results after type II and type III OPHLs, post surgical voice rehabilitation is crucial in order to reach a satisfying voice related QOL. Nevertheless, little information about voice rehabilitation programs and strategies after partial laryngectomies can be found in scientific literature [9-13]. The aim of the present study was to investigate the efficacy of the PROEL method in the rehabilitation of substitution voice after type II and type III OPHL.

2 Materials and Methods
This prospective outcome study was carried out according to the Declaration of Helsinki. All subjects enrolled in the study gave their informed consent; experimental data concerning the PROEL-based rehabilitation program were collected prospectively; a final comparison with an historical control sample was carried out in order to compare the results obtained with the PROEL method to the results historically obtained with a standard rehabilitative approach.

2.1 Population
Fifteen patients (12 males and 3 females) who underwent type II or type III OPHL at the Head and Neck Department of the FPO-IRCCS Candiolo Institute, at San Luigi Gonzaga Hospital and at Martini Hospital (Italy) were recruited during the last two years and enrolled in the experimental group. Inclusion criteria were: OPHL type II or type III, no evidence of disease at the last follow-up, preservation of respiration, speech and oral feeding (absence of percutaneous endoscopic gastrostomy or naso-gastric tube), absence of the tracheostoma, no salvage total laryngectomy performed, and >6 months after surgery. Each patient underwent standard rehabilitation of voice and speech during hospitalization and no further rehabilitation after discharge. The standard voice and speech rehabilitation program consists of a supraglottic voice training aiming at a basic
understanding and activation of the neoglottis. It focuses on apnea training; push-pull exercises and short vocalizations with hard onsets. The mean age of subjects recruited was 63.09 ± 9.92 years. According to the modern nomenclature [5], 3 patients underwent type IIa OPHL (20%); 5 patients underwent type IIa + ARY OPHL (33.33%); 2 patients underwent type IIb OPHL + ARY (13.33%); 3 patients underwent type IIIa OPHL (20%), and 2 patients underwent type IIIa OPHL + CAU (13.33%). Mean distance from surgery was 33.55 ± 40.83 months (6-98 months).

A control sample composed of other fifteen patients (13 males and 2 females) who underwent type II or type III OPHL at the Head and Neck Department of the FPO-IRCCS Candiolo Institute, at San Luigi Gonzaga Hospital and at Martini Hospital in the last 10 years was randomly extracted through a random number generator from an historical database of more than 500 patients. All the patients included in the historical database satisfied the same inclusion criteria cited for the experimental sample. Functional outcomes were previously collected following the same procedure used for the experimental sample, at least 6 months after surgery. Each patient underwent a standard rehabilitation of voice and speech during hospitalization and no further rehabilitation after discharge. The mean age of the patients of the control sample was 65 ± 7.49 years. 2 patients underwent type IIa OPHL (13.3%); 5 patients underwent type IIa + ARY OPHL (33.3%); 1 patient underwent a type IIb OPHL (6.7%); 4 patients underwent type IIIa OPHL (26.7%), and 3 patients underwent type IIIa OPHL + CAU (20%). Mean distance from surgery was 35.86 ± 27.12 months (6-75 months).

Sociodemographic and clinical features of the two groups of patients are shown in table 1.

2.2. Procedures

Each patient of the experimental group underwent a rehabilitation program following the standard principles of the PROEL method as described by Alfonso Borragan [7; 8]: 1. Control of vocal risk factors; 2. Vocal proprioceptive awareness; 3. Elimination of the mechanisms of stress, tension, and muscular stiffness; 4. Projection and resonance of the voice; 5. Research into the feeling of freedom and well-being. Each patient underwent a 45-60 min PROEL session per week for the first three months. After each session, the therapist gave the patient concrete instructions to carry out a series
of exercises for 5 minutes twice a day. For the last three months the sessions took place every two weeks, with the aim of consolidating the results. All the therapeutic program was conducted by the same experienced speech language pathologist (SLP).

The patients’ voices were assessed by a trained speech and language pathologist before the PROEL-based voice therapy (T0), after three months of rehabilitation (T1) and at the end (6 months) of the speech therapy program (T2). Concerning self-assessments, each participant completed the Italian version of the Self-Evaluation of Communication Experiences after Laryngeal Cancer (I-SECEL) [14;15]. The I-SECEL questionnaire specifically assesses communication dysfunction after laryngectomy and their effects on patients’ daily living activities. The questionnaire is composed of 34 items divided into 3 subscales: General (5 items), Environmental (14 items), and Attitudinal (15 items). Total scores range from 0 to 102, the general subscale from 0 to 15, the environmental subscale from 0 to 42 and the attitudinal subscale from 0 to 45. The higher the score, the greater the perception of communication dysfunction. The maximum phonation time (MPT) was measured through window selection on the production of 3 sustained /a/; the longest phonation time was recorded. Perceptual evaluation was carried out with the INFVo rating scale, a perceptual scale specifically developed for substitution voice, assessing overall quality impression and intelligibility (I), additive and unnecessary noise (N), speech fluency (F), and presence of voiced segments (Vo). Each parameter is scored on a visual analog scale from 0 (minimally deviant) to 10 (maximally deviant substitution voicing) and then is reported to a 4 categories ordinal scale [16]. The perceptual evaluation was performed by listening to a recorded 56-word and 99-syllable passage. A spectrography of the sustained vowel /a/ was performed. Patients’ voices were classified into 4 categories on the basis of the spectrogram analysis, according to the proposed modified Titze’s classification [17]. The following categories were used: 1. Type 1 voices, periodic without strong modulations or subharmonics; 2. Type 2 voices, with strong modulations, bifurcations, or subharmonics; 3. Type 3 voices, smearing of energy across harmonics with visible fundamental frequency and 1 or 2 harmonics; 4. Type 4 voices, aperiodic. Voices were recorded with a microphone Samson Meteor Mic (Samson Technologies, Hauppauge, NY) placed at a distance of
30 cm from the mouth of the patient, connected via USB to a MacBook Pro computer (Apple, Cupertino, CA) running PRAAT software (Version 5.3.57 for Mac, Boersma & Weenick, University of Amsterdam, Amsterdam, The Netherlands). The audio signals were digitized on 16 bit at sampling frequency of 48 kHz.

Voice recordings were assessed randomly and independently by 2 raters blinded to session assignment, speech and language pathologists, who underwent specific training. Both SLPs had at least 2 years of experience with perceptual assessment of substitution voice. In case of disagreement between the raters, they jointly reassessed the parameter until a consensus was reached.

Multiparametric voice assessments of the experimental group at T2 were then compared with the acoustic, aerodynamic, perceptual and self-assessment outcomes of the control sample.

2.3 Statistical analysis
Statistical analysis was carried out with GraphPad Prism software (Version 7.0, Apple, Cupertino, CA, USA). Means and standard deviations (SDs) for acoustic, aerodynamic, self-assessment and perceptual analysis were calculated. The normality of the distributions was assessed with the Kolmogorov-Smirnov test. Friedman tests with Dunn’s post-hoc corrections for multiple comparisons and ANOVA tests with Tukey's post-hoc corrections for multiple comparisons were used to detect statistical differences between the variables measured at T0, T1, and T2, as appropriate. Unpaired t-tests and Mann-Whitney tests were used to compare the outcomes of the experimental group and the control sample, as appropriate. An alpha of 0.05 was considered for the statistical procedures.

3 Results
No significant differences were found concerning age, gender distribution, type of surgery and months from surgery distribution between the experimental group and the control sample, as shown in table 1.
3.1 Acoustic-aerodynamic analysis

Means and SDs for MPT in the experimental group were $6.67 \pm 3.05$ sec at T0; $8.72 \pm 2.76$ sec at T1 and $9.98 \pm 3.2$ sec at T0, as shown in figure 1. Means and SDs for Titze’s modified spectrographic class were $3.91 \pm 0.30$ at T0; $3.64 \pm 0.50$ at T1 and $3.09 \pm 0.83$ at T2, as shown in figure 2. For MPT, significant differences were found between T0-T1 ($p=0.022$); T1-T2 (0.03) and T0-T2 ($p=0.011$). Concerning Titze’s modified spectrographic class, significant differences were found between T0-T2 ($p=0.015$).

Mean values for MPT and Titze’s modified spectrographic class for the control sample were $6.60 \pm 3.16$ seconds and $3.2 \pm 0.67$ as shown in figure 1 and 2, respectively. Significant differences between experimental T2 mean values and control mean values were found for MPT ($p=0.012$).

3.2 Perceptual analysis

Mean and SD for the INFVo rating scale in the experimental group are shown in table 2. The INFVo perceptual rating scale showed significant differences in all the subscales. In particular, post hoc tests showed significant differences between T0 - T2 for the subscales I ($p=0.0001$), N ($p=0.0001$), F ($p=0.0004$), Vo ($p=0.0002$); between T0 - T1 for the subscales F ($p=0.0017$), Vo ($p=0.0426$) and between T1 - T2 for the subscale F ($p=0.0084$).

Means and SD for the INFVo rating scale of the control sample were I = $2.06 \pm 0.53$; N = $2.32 \pm 0.48$; F = $1.94 \pm 0.37$; Vo = $2.34 \pm 0.58$. Significant differences between the experimental group at T2 and the control sample were found for the subscales I ($p=0.0489$); N ($p=0.0078$); F ($p=0.0004$); Vo ($p=0.0001$). Graphical results as shown in figure 3.

3.3 Self-assessments

Means and SDs for the SECEL questionnaire are shown in table 3. Significant differences were found for all the subscales. In particular, post hoc tests showed significant differences between T0-T2 for the subscales T ($p=0.0400$), G ($p=0.0290$); between T0-T1 for the subscales T ($p=0.0013$), E ($p=0.0040$) and A ($p=0.0218$).
Means and SDs for the SECEL questionnaire in the control sample were T: 35.33±11.92; G: 9.93±2.37; E: 17.53±6.95; A: 7.87±5.67. A significant difference between the experimental group at T2 and the control sample were found for the subscale G (p=0.0001). Graphical results are shown in figure 4.

4 Discussion
The current study investigated voice quality and voice related QOL improvements after a specific voice rehabilitation program based on the PROEL method in patients who underwent type II and type III OPHLs. Multiparametric voice assessments showed significant improvements regarding acoustic-aerodynamic analysis, perceptual evaluations and self-assessments after the rehabilitation program. One of the strengths of the study is the multiparametric voice assessment showing similar trends in voice improvement in aerodynamic, acoustic and perceptual analysis at T0, T1 and T2. Self-assessments on the contrary improved at T1 compared to T0 but did not improve further at T2 for some subscales.

MPT significantly improved between T0-T1 and T0-T2, suggesting an increased valving activity of the neoglottis, while the significant reduction of mean Titze’s spectrographic class suggested an improvement of the mean acoustic quality of the substitution voice produced by the neoglottis. Perceptually, the patient’s voices improved significantly for all the INFVo subscales: overall quality impression and intelligibility (I), additive and unnecessary noise (N), speech fluency (F), and presence of voiced segments (Vo). A significant reduction in SECEL questionnaire scores was detected too, suggesting an improvement in voice related QOL.

The comparison between the experimental group after a PROEL-based voice rehabilitation and the control sample (with no further rehabilitation after hospitalization) showed overall better results for the experimental group and some significative differences concerning aerodynamic measures (MPT), self-assessments and perceptual analysis, suggesting the efficacy of a PROEL-based rehabilitation program after hospitalization for the vocal function of patients who underwent type II and III OPHLs.
Looking individually at the results of the experimental group, the overall impression of the authors is that patients who underwent an OPHL procedure longer ago are likely to have little improvement compared to the ones who underwent surgery more recently. Nonetheless, the small size of the sample and the lack of a multivariate analysis doesn’t allow to generalize such statement at the moment.

Concerning PROEL application to voice rehabilitation, a previous study by Lucchini et al. suggested the method’s efficacy in the treatment of functional dysphonia [8]. No experience about the application of the PROEL method for substitution voice rehabilitation after OPHL has been described so far. Long-term functional outcomes after OPHLs – in particular, type II OPHLs – have been investigated widely. In this surgery, both vocal folds are sacrificed and the voice is produced by the vibration of the arytenoid mucosa against the epiglottis/tongue base. The site of the mucosal wave is normally observed between the anterior part of the body of one or both arytenoids and the tongue base or epiglottis [18]. Thus, the vocal signal after type II OPHL shows substantially poor volitionally induced valving activity and resistance to airflow during voicing [19-22], resulting in a strained, deep and asexuated voice (difficult to modulate and to raise) and speech that is composed of reduced phrase groups, because the patients rapidly become short of breath [5; 23-25]. Functional results of type III OPHLs have recently been analyzed [26], showing similar outcomes to type II OPHLs [6], with severe voice impairment but well preserved oral communication, and with almost all patients showing a good attitude towards their communication dysfunction. Concerning technological communication systems, a recent study by Crosetti et al. [27] investigated telephonic voice intelligibility after various laryngeal cancer treatment options. Type II and III OPHLs showed the poorest intelligibility rates comparing to transoral laser microsurgery procedures, radiotherapy and type I OPHL. Concerning voice related QOL, most authors have reported a moderate reduction in voice related QOL after type II and III OPHL; however, the reports are somewhat contradictory [18; 21; 24; 25; 28].

Regarding substitution voice rehabilitation strategies after open partial laryngectomy, a recent study by Palmer et al. [13] tested the Expiratory Muscle Strength Training (EMST) after supracricoid laryngectomy, obtaining some interesting results on some objective and subjective respiratory
parameters like the peak cough flow and the dyspnea index. The improvement of respiratory parameters could have a positive impact on some vocal aerodynamic parameters like the MPT, thus representing an interesting goal for rehabilitation after OPHL. Anyway, the study has some considerable limitations, like the very small sample size and the lack of a control group. In the present study, the significant improvement of MPT registered after the PROEL-based rehabilitation approach could be likely related to the effect of respiratory muscles training obtained through instable balance postures and water resistance therapy [7; 8].

Other studies investigated the efficacy of some semi-occluded vocal tract postures on voice rehabilitation after OPHL. Fouquet et al. [12] found an efficacy of the hand-over-mouth exercise on voice perceptual quality and neoglottis closure and vibratory patterns after 2 minutes of training. Silveira et al. [11] tested a bilabial fricative exercise combined with the vowel /e/. The authors found a vocal improvement concerning both perceptual and endoscopic findings after 4 minutes spent performing the proposed exercise. Even if the described studies have great limitations represented by the small sample sizes, they both suggest a possible positive effect of semi-occluded vocal tract postures on substitution voice quality. This aspect has to be taken into account, since one of the basic principles of the PROEL method, represented by the proprioception of the vocal tract, is reached through the use of semi occluded vocal tract exercises performed through semi occluded ventilation masks [29;30].

Another aspect that is worth of consideration is represented by the great attention given by the PROEL method to vocal folds hydration and lubrication. As shown by a recent systematic review by Alves et al. [31] most of the recent literature about voice hydration is of good quality evidence and suggests that both systemic and surface hydration procedures should be encouraged in voice hygiene programs. Even if OPHLs require the removal of the true vocal folds, the vibrating residual mucosa presumably benefits from a condition of optimal hydration and lubrication.

The main limitations of the present study were the small number of recruited patients and the lack of a randomized controlled trial study design, even if a random selection of the control patients from an historical database was performed in order to reduce the selection bias. Future research should include larger number of patients and should focus on the various components of the PROEL method.
in order to investigate their effectiveness separately and to determine the weight of their contribution to the final functional result. Future studies should also aim at comparing the PROEL method to other rehabilitative approaches with randomized clinical trials.

5 Conclusions

Because voice and oral communication can be severely deteriorated after oncologic laryngeal surgery, it is very important for clinicians to guide patients through effective and rewarding rehabilitative programs. The results of the present study seem promising, as they outline some significant positive changes in patients’ voices after a PROEL-based rehabilitation program, suggesting PROEL as a likely effective approach for voice rehabilitation after OPHL.
References


TABLES

**TABLE 1**

Sociodemographic and clinical factors in the two samples of patients

<table>
<thead>
<tr>
<th></th>
<th>Experimental group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. patients</td>
<td>15</td>
<td>15</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.09 ± 9.92</td>
<td>65 ± 7.49</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (n. and %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (80%)</td>
<td>13 (86.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>3 (20%)</td>
<td>2 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Distance from surgery (months)</td>
<td>33.55 ± 40.83</td>
<td>35.86 ± 27.12</td>
<td>ns</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPHL IIa</td>
<td>3 (20%)</td>
<td>2 (13.33%)</td>
<td></td>
</tr>
<tr>
<td>OPHL IIa + ARY</td>
<td>5 (33.33%)</td>
<td>5 (33.33%)</td>
<td></td>
</tr>
<tr>
<td>OPHL IIb</td>
<td>1 (6.7%)</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>OPHL IIb + ARY</td>
<td>2 (13.33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPHL IIIa</td>
<td>3 (20%)</td>
<td>4 (26.7%)</td>
<td></td>
</tr>
<tr>
<td>OPHL IIIb</td>
<td>2 (13.33%)</td>
<td>3 (20%)</td>
<td></td>
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</table>

**TABLE 2**

Mean values, standard deviations, test and p-value of INFVo subscales at T0, T1, and T2.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>T0 (mean and SD)</th>
<th>T1 (mean and SD)</th>
<th>T2 (mean and SD)</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.20 ± 0.65</td>
<td>1.58 ± 0.64</td>
<td>1.25 ± 0.61</td>
<td>Friedman test +</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>N</td>
<td>2.07 ± 0.63</td>
<td>1.69 ± 0.61</td>
<td>1.33 ± 0.64</td>
<td>Dunn’s multiple</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>1.96 ± 0.49</td>
<td>1.55 ± 0.44</td>
<td>1.22 ± 0.51</td>
<td>comparisons test</td>
<td></td>
</tr>
<tr>
<td>Vo</td>
<td>1.52 ± 1.22</td>
<td>0.73 ± 0.95</td>
<td>0.43 ± 0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3

Mean values and standard deviations, test and p-value of I-SECEL subscales at T0, T1, and T2.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>T0 (mean and SD)</th>
<th>T1 (mean and SD)</th>
<th>T2 (mean and SD)</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>39.36 ± 12.81</td>
<td>23.72 ± 8.32</td>
<td>28.09 ± 13.56</td>
<td>RM one way ANOVA + Tukey's multiple</td>
<td>p=0.0012</td>
</tr>
<tr>
<td>G</td>
<td>5.63 ± 2.69</td>
<td>4.27 ± 2.28</td>
<td>3.36 ± 1.96</td>
<td></td>
<td>p=0.0165</td>
</tr>
<tr>
<td>E</td>
<td>21.63 ± 7.59</td>
<td>14.63 ± 6.5</td>
<td>18.00 ± 7.94</td>
<td>comparisons test</td>
<td>p=0.0210</td>
</tr>
<tr>
<td>A</td>
<td>12.09 ± 7.07</td>
<td>4.81 ± 3.19</td>
<td>6.73 ± 5.20</td>
<td></td>
<td>p=0.0089</td>
</tr>
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FIGURES:

FIGURE 1: MTP mean values and SD in the experimental group at T0, T1, T2 and in the control group.

FIGURE 2: Titze’s modified spectrographic class mean values and SD in the experimental group at T0, T1, T2 and in the control group.

FIGURE 3: INFVo rating scale mean values and SD in the experimental group at T0, T1, T2 and in the control group.

FIGURE 4: SECEL questionnaire mean values and SD in the experimental group at T0, T1, T2 and in the control group.
Maximum Phonation Time (MPT)

Seconds

T0  |  T1  |  T2  |  Control
--- | ---  | ---  | ---