Optimal Duration for Voice Rest After Vocal Fold Surgery: Randomized Controlled Clinical Study

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Summary: Objectives. Voice rest is commonly recommended after phonomicrosurgery to prevent worsening of vocal fold injuries. However, the most effective duration of voice rest is unknown. Recently, early vocal stimulation was recommended as a means to improve wound healing. The purpose of this study is to examine the optimal duration of voice rest after phonomicrosurgery.

Study Design. Randomized controlled clinical study.

Methods. Patients undergoing phonomicrosurgery for leukoplakia, carcinoma *in situ*, vocal fold polyp, Reinke's edema, and cyst were chosen. Participants were randomly assigned to voice rest for 3 or 7 postoperative days. Voice therapy was administered to both groups after voice rest. Grade, roughness, breathiness, asthenia, and strain (GRBAS) scale, stroboscopic examination, aerodynamic assessment, acoustic analysis, and Voice Handicap Index-10 (VHI-10) were performed pre- and postoperatively at 1, 3, and 6 months. Stroboscopic examination evaluated normalized mucosal wave amplitude (NMWA). Parameters were compared between both groups.

Results. Thirty-one patients were analyzed (3-day group, n = 16; 7-day group, n = 15). Jitter, shimmer, and VHI-10 were significantly better in the 3-day group at 1 month post operation. GRBAS was significantly better in the 3-day group at 1 and 3 months post operation, and NMWA was significantly better in the 3-day group at 1, 3, and 6 months post operation compared to the 7-day group.

Conclusions. The data suggest that 3 days of voice rest followed by voice therapy may lead to better wound healing of the vocal fold compared to 7 days of voice rest. Appropriate mechanical stimulation during early stages of vocal fold wound healing may lead to favorable functional recovery.

Key Words: Voice rest–Stimulation–Phonomicrosurgery–Fibroblast–Voice therapy.

INTRODUCTION

Vocal fold scarring can occur following injury, inflammation, or surgical intervention. Vocal fold scarring leads to the disruption of the layered structure of the lamina propria.[1–3] Once the vocal fold is scarred, severe dysphonia can occur. Although many therapeutic strategies for vocal fold scarring have been evaluated, a consistent treatment has yet to be developed. Therefore, prevention of scarring is an important therapeutic target.[4]

Voice rest is commonly recommended after vocal fold surgery to prevent worsening of the injury and scarring of the vocal fold. Whether voice rest actually leads to better wound healing of the vocal fold, however, is unknown.[5] Recent literature reviews have shown the absence of an established standard protocol for voice rest, and the type and duration of voice rest vary among clinicians.[6,7] Cho et al[8] evaluated the effect of voice rest after vocal fold surgery in a canine model. Bilateral excision of the vocal fold mucosa was performed followed by simulated "voice rest" induced by resection of the left recurrent laryngeal nerve.[8] Cho et al concluded that voice rest precipitates the re-epithelialization process and recommended 2 weeks of voice rest and 8 weeks of vocal hygiene after phonosurgery. An American Academy of Otolaryngology survey indicates that most surgeons recommend 7 days of voice rest, but there is a lack of evidence supporting this duration.[7] Koufman and Blalock[6] performed a retrospective review of the patients who had undergone microlaryngeal surgery. They concluded that there were no standard protocols for the duration or type of voice rest recommended by the surgeons.[6] Typical voice rest periods are not based on mechanisms of the wound healing process. Moreover, there have been very few prospective randomized clinical studies comparing durations of voice rest based on the wound healing process. To date, there are no established protocols or duration for voice therapy as well.[5,6,9–14] Moreover, Rousseau et al[15] have described a relatively low self-reported "complete compliance" of 35% among patients who were prescribed voice rest.

The effect of rest versus exercise has been a controversial topic in orthopedic rehabilitation research for more than a century.[16] However, controlled remobilization during the early stages of healing leads to favorable functional recovery.[17–19] Long-term immobilization is even considered to be detrimental to the recovery; therefore, it is not generally recommended in orthopedic rehabilitation.[17,19–21] Such outcomes rely largely on the degree of connective tissue healing.

The general wound healing process is divided into three phases: inflammation, proliferation, and maturation. The inflammatory phase consists of the 3 days after injury, during which hemostasis and inflammatory responses occur.[5,9] The proliferative phase extends from day 3 to 1 month post injury, during which angiogenesis and epithelialization occur. Fibroblasts migrate into the wound area between 48 and 72 hours after injury,[22] and play an important role by producing large amounts of extracellular matrix

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including collagen, elastin, proteoglycan, and glycosaminoglycan.[23] The maturation phase lasts for 1 year or longer, during which remodeling of the wound occurs.[24] Kishimoto et al[25] investigated the clinical maturation process of human vocal folds scarred by type I–III cordectomy, and they reported that vibratory function appeared to stabilize about 6 months after the procedure.

Reactive oxygen species (ROS) are another important factor that determines the fate of wound healing.[26–28] Several studies demonstrated that ROS have a positive role in the healing process as a defense against invading microorganisms or mediators of intracellular signaling,[29,30] but overexposure to ROS is harmful to wound healing.[30,31] The correct balance between oxidative and antioxidative forces is needed for favorable wound healing. Mizuta et al[32] suggested that a large amount of ROS is produced during the early phase of vocal fold wound healing, until postinjury day 3,[26] and this period may be crucial for regulating ROS levels. Therefore, rest of injury should be required for a certain period particularly during the inflammatory phase to avoid additional tissue damage caused by ROS. But it is not known if we should require the voice rest after postinjury day 4. Also, the effect of early mobilization on vocal fold tissue is unknown.

Empirical data from well-designed clinical voice studies are an essential component of evidence-based medicine. Such data are needed to know the common use of postoperative voice rest. Based on the basic and clinical perspectives mentioned above, we hypothesized that voice rest should be necessary during the inflammatory phase (3 days), but early initiation of phonatory stimulation may lead to better wound healing. The purpose of the present study is to examine the optimal duration of voice rest and the effect of early initiation of voice therapy on vocal fold wound healing. All procedures were approved by the institutional review boards at Kyoto University. The experiment employed a prospective randomized controlled design.

METHODS

Subjects

Patients more than 20 years old who underwent phonomicrosurgery for leukoplakia, carcinoma *in situ* (CIS), polyp, Reinke's edema (RE), or cyst were enrolled. A microflap technique was used for the removal of benign lesions. The epithelium was also resected in cases of leukoplakia and CIS, but the superficial layer of the lamina propria was preserved intact. Leukoplakia and CIS were included, although voice rest after epithelial excisions for CIS/leukoplakia varies due to institutions. Many institutions in Japan adopt voice rest, and Koufman and Blalock[6] also performed a retrospective review of the patients who had undergone microlaryngeal surgery for the same lesions with postoperative voice rest. Another reason is that leukoplakia and CIS are thought to be a good model to know about the wound healing mechanism after shallow resection of the vocal fold mucosa. Patients with a history of radiation therapy for the larynx were excluded.

Procedures

Participants were randomly assigned to two groups according to the absolute voice rest period, either 3 or 7 days. Both groups received voice therapy for 6 weeks following the voice rest periods. The 6-week period of voice therapy was designed to span the entire proliferative phase of wound healing. This period was also selected based on a report indicating that dropout from voice therapy increases after 6 weeks.[33] Vocal function was evaluated prior to surgery and at 1, 3, and 6 months post operation.

Voice therapy consisted of vocal hygiene and tube phonation. All participants were counseled on the aspects of voice hygiene including education about the anatomy and physiology of voice, hydration, laryngopharyngeal reflux diet modification, environmental modification, and stretches and relaxation.[34] Regarding tube phonation, the subjects were instructed to phonate sustained vowel-like sounds through a tube (21 cm in length and 10 mm in inner diameter) as follows: (1) sustain the musical note middle C for 5 seconds using /o:/; (2) repeat this note 12 times; (3) sustain the musical notes middle C, D, E, F, and G using /o:/ for 5 seconds, respectively; then (4) repeat these notes four times. The subjects were encouraged to produce all tones softly, with frontal focus, and to complete these tube phonations twice a day.

The patients received one session (40 minutes) of this tube phonation therapy preoperatively. It has been reported that during tube phonation, the larynx is lowered and mean glottal flow is modified, which facilitates vocal fold vibration. This method was reported to attenuate acute vocal fold inflammation.[35–37] Also, *in vitro* and human studies gave us the possibilities that tube phonation with alternative pitches and current time course seems to be appropriate as stimulus to the vocal fold during wound healing.[38,39]

The patients were also instructed to fill in daily records of their postoperative voice rest, phonation, and voice therapy for 6 weeks. They sent it to us by mail, and we confirmed their postoperative compliance of the voice therapy and vocal situation. All voice therapy was performed by a single trained speech language pathologist (MK).

Table 1 shows the background data for each group. The 3-day group included 16 subjects who underwent analysis. Their lesions

TABLE 1.
Demographic Data for Each Group

	3-Day Group	7-Day Group
Subject	16	15
Pathology	3 leukoplakias	2 leukoplakias
		1 CIS
	2 cysts	1 cyst
	10 polyps	9 polyps
	1 RE	2 REs
Mean age (years)	54	53
Age range (years)		
20–29	1	0
30–39	3	2
40–49	3	5
50–59	2	4
60–69	3	2
70–79	4	2
Gender	12M, 4F	7M, 8F
Smoker	1	2

Abbreviations: CIS, carcinoma *in situ*; F, female; M, male; RE, Reinke's edema.

TABLE 2.
Preoperative Baseline of Each Parameter (Mean Value + SD)

	3-Day Group Mean (±SD)	7-Day Group Mean (±SD)	Significance (*P* Value)
Preoperative baseline			
GRBAS (%)	9.5 (±2.34)	9.53 (±2.56)	0.9681
VHI-10 (%)	18.19 (±8.86)	17 (±9.81)	0.7259
Jitter (%)	1.1 (±0.87)	1.62 (±2.63)	0.4593
Shimmer (%)	4.06 (±3.37)	4.21 (±5.93)	0.9307
MPT (%)	12 (±4.76)	12.8 (±7.49)	0.7233
Preoperative baseline in males			
GRBAS (%)	9.83 (±2.59)	10 (±2.45)	0.8919
VHI-10 (%)	15.92 (±7.8)	16.14 (±12.7)	0.9619
Jitter (%)	1.25 (±0.93)	0.95 (±0.65)	0.4525
Shimmer (%)	4.66 (±3.72)	2.98 (±1.66)	0.2783
MPT (%)	13.5 (±4.56)	14.71 (±9.55)	0.7100
Preoperative baseline in females			
GRBAS (%)	8.5 (±1.0)	9.12 (±2.15)	0.5993
VHI-10 (%)	25 (±9.35)	17.75 (±7.31)	0.1683
Jitter (%)	0.65 (±0.5)	2.22 (±3.55)	0.4116
Shimmer (%)	2.27 (±0.53)	5.29 (±8.07)	0.4828
MPT (%)	7.5 (±1.00)	11.125 (±5.19)	0.2100

Abbreviations: GRBAS, grade, roughness, breathiness, asthenia, strain; MPT, maximum phonation time; SD, standard deviation; VHI-10, Voice Handicap Index-10.

included leukoplakia in 3 patients, cyst in 2 patients, polyp in 10 cases, and RE in 1 case. The 7-day group consisted of 15 subjects. Their lesions included leukoplakia in 2 cases, CIS in 1 case, cyst in 1 case, polyp in 9 cases, and RE in 2 cases. The distribution of age, gender, and smoking habits showed no significant differences between groups. Also, there were no significant differences in the patient characteristics (Table 2).

Assessment

Vocal outcomes were evaluated preoperatively, and at 1, 3, and 6 months postoperatively. The following assessments were performed: grade, roughness, breathiness, asthenia, and strain (GRBAS) scale, aerodynamic assessment, acoustic analysis, stroboscopic examinations, and the Voice Handicap Index-10 (VHI-10). Stroboscopic examination was performed using a digital video stroboscopy system with a 70° rigid endoscope, Model 9295 (KayPENTAX, Lincoln Park, NJ). Aerodynamic assessment, which included the maximum phonation time (MPT), was examined with a phonation analyzer (PA-500; Nagashima Co., Osaka, Japan). Acoustic analyses evaluated jitter and shimmer using the *Multidimensional Voice Program* (Model 5105, KayPENTAX).

GRBAS is an anchored perceptual analysis. The GRBAS scale was independently evaluated by two trained raters including a laryngologist and a speech language pathologist. This scale was first developed by the Japanese Society of Logopedics and Phoniatrics and has become popular worldwide.[40] The GRBAS scale is scored from 0 to 3 in which 0 = within normal limits, 1 = slight, 2 = moderate, and 3 = severe. The ratings of the five subscales (G, R, B, A, S) were summed, and the mean rating score between two raters was calculated. Inter-rater reliability was evaluated using Spearman's rank correlation coefficient, and the result showed significant correlation, with a correlation coefficient of $r = 0.8$ ($P < 0.001$).

NMWA was used as a parameter for vocal fold vibratory function.[41–45] It was measured by analyzing stroboscopic images during vibration. Vocal fold vibration during phonation of a sustained vowel /i:/ at the patient's normal pitch and loudness was recorded through a 70° endoscope. Normalized mucosal wave amplitude (NMWA) was calculated using *ImageJ* software (National Institutes of Health, Bethesda, MD). To calculate NMWA, the distance ($d1$) from the midline of the glottis to the free edge of the vocal fold was measured at the anteroposterior middle portion of the vocal fold during the closed phase. The closed phase was determined by the motion of the upper and lower lips of the vocal folds. The same distance ($d2$) was measured at the maximum open phase. The mucosal wave amplitude was defined by subtracting $d1$ from $d2$ and was normalized by dividing this value by the membranous vocal fold length (L). Therefore, NMWA = $(d2 - d1)/L \times 100$ (arbitrary units)[41–45] (Figure 1), and it was measured at the affected side and assessed postoperatively.

The primary endpoint was set at the degree of improvement (improvement rate) in each parameter after 6 months in the 3- and 7-day groups. The improvement rate was calculated by the formula: |postoperative value − preoperative value|/preoperative value × 100 (%). The secondary endpoint was the improvement rate for each parameter at each time point in the 3- and 7-day groups.

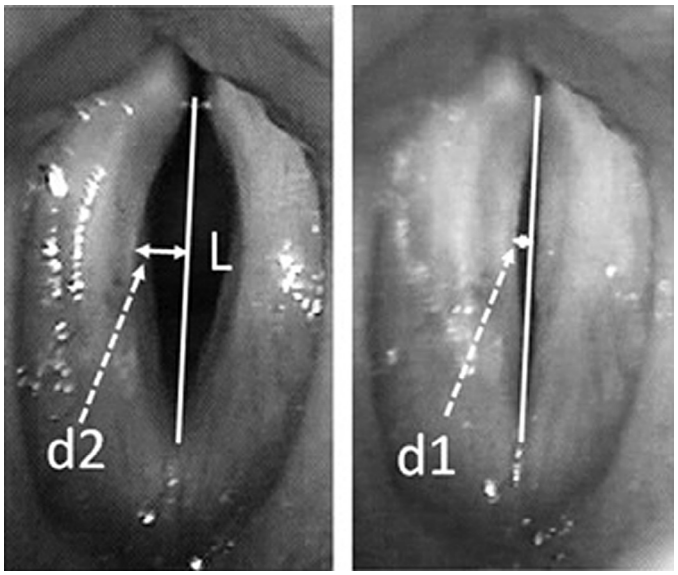

FIGURE 1. Image analysis of stroboscopic findings. Measurement of normalized mucosal wave amplitude (NMWA). NMWA = (d2 – d1)/L × 100 (units). d1, distance from the midline of the glottis to the free edge of the vocal fold during the closed phase; d2, the same distance at maximum open phase; L, membranous vocal fold length.[45]

Statistical test

Statistical analysis was performed using commercially available software (*Excel Statistics 2012*; Social Survey Research Information Co., Ltd., Tokyo, Japan). For the preoperative baseline of each parameter, unpaired *t*-test was performed (Table 2). Statistical tests using data for each time point and parameter were completed. Two-way factorial analysis of variance followed by a Scheffe post hoc test was performed between the 3- and 7-day groups (Table 3). Significant differences were reported at the alpha level of 0.05. All reported *P* values were two sided. A *P* value of less than 0.05 was considered significant.

RESULTS

Figures 2 and 3 and Table 3 show the mean value with standard deviation of each parameter prior to and at 1, 3, and 6 months postoperatively for each group.

Results of the primary endpoint

MPT, jitter, shimmer, VHI-10 and GRBAS did not show statistical differences between the groups at 6 months postoperative. Figure 2 shows that NMWA was significantly better in the 3 day group than the 7 day group at 6 months postoperative (P = 0.0003).

TABLE 3.
Phonatory Outcome (Mean Value + SD)

	3-Day Group		7-Day Group		
	Mean (±SD)	95% CI	Mean (±SD)	95% CI	Significance (*P* Value)
GRBAS (%)					
po1m	58.8 (±88.75)	36.86 to 17.35	39.65 (±73.23)	29.25 to 3.35	0.023*
po3m	72.82 (±88.82)	43.8 to 22.64	42.96 (±72.77)	32.87 to 6.98	0.006**
po6m	62.21 (±86.41)	43.62 to 27.68	43.34 (±87.5)	39.2 to 17.15	0.28
VHI-10 (%)					
po1m	46.79 (±72.88)	82.5 to 11.07	15.02 (±117.35)	74.4 to –44.36	0.037*
po3m	76.07 (±726.82)	89.21 to 62.93	50.59 (±87.42)	94.83 to 6.35	0.09
po6m	83.45 (±23.6)	95.01 to 71.89	65.32 (±57.48)	94.4 to 36.23	0.23
Jitter (%)					
po1m	–12.03 (±144.69)	58.87 to –82.92	–136.27 (±608.99)	171.92 to –444.45	0.023*
po3m	38.53 (±42.29)	59.25 to 17.8	10.24 (±123.32)	72.64 to –52.17	0.6
po6m	30.24 (±39.69)	49.69 to 10.79	26.05 (±59.59)	56.2 to –4.1	0.94
Shimmer (%)					
po1m	23.76 (±49.24)	47.88 to –24.13	-39.37 (±251.36)	87.84 to –127.2	0.015*
po3m	23.21 (±48.54)	46.99 to –23.78	-2.34 (±115.25)	55.99 to –58.32	0.31
po6m	35.36 (±35.1)	52.56 to –17.2	0.39 (±84.09)	42.94 to –42.55	0.17
MPT (%)					
po1m	58.8 (±88.75)	108.10 to 21.12	39.65 (±73.24)	79.04 to 4.92	0.28
po3m	72.82 (±88.82)	116.34 to 29.3	42.96 (±72.77)	79.78 to 6.13	0.09
po6m	62.21 (±86.41)	104.56 to 19.87	43.34 (±87.45)	87.62 to –0.94	0.28
NMWA (%)					
po1m	8.23 (±3.36)	10.06 to 6.41	5.22 (±3.13)	6.99 to 3.45	0.0006**
po3m	10.29 (±3.47)	12.18 to 8.41	6.08 (±3.82)	8.24 to 3.91	0.0000**
po6m	12.3 (±3.24)	14.06 to 10.54	5.99 (±4.06)	8.29 to 3.69	0.0000**

*$P < 0.05$; **$P < 0.01$

Abbreviations: CI, confidence interval; GRBAS, grade, roughness, breathiness, asthenia, strain; MPT, maximum phonation time; NMWA, normalized mucosal wave amplitude; SD, standard deviation; VHI-10, Voice Handicap Index-10.

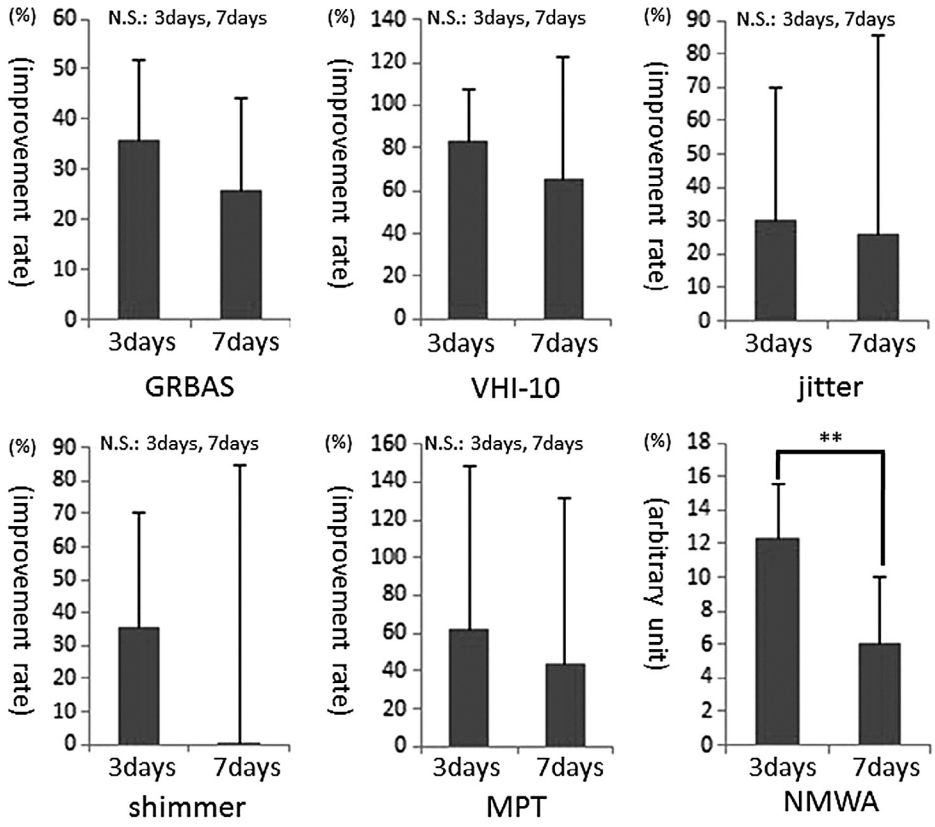

FIGURE 2. Phonatory outcomes between the 3- and 7-day groups 6 months post operation. NMWA was significantly better in the 3-day group than the 7-day group ($P = 0.0003$). There were no statistically significant changes in MPT, jitter, shimmer, VHI-10, or GRBAS. $^{**}P < 0.01$. GRBAS, grade, roughness, breathiness, asthenia, strain; MPT, maximum phonation time; NMWA, normalized mucosal wave amplitude; N.S., not significant; VHI-10, Voice Handicap Index-10.

Results of the secondary endpoint

The MPT did not show statistical differences between the 3- and 7-day groups at any time point. Jitter, shimmer, and VHI-10 were significantly better in the 3-day group than in the 7-day group at 1 month post operation ($P = 0.023$, 0.015, and 0.037, respectively). There were no statistically significant changes in either group at 3 or 6 months. NMWA was significantly better in the 3-day group than in the 7-day group at 1, 3, and 6 months ($P = 0.0006$, 0.0000, and 0.0000, respectively). GRBAS was significantly better in the 3-day group than in the 7-day group at 1 and 3 months ($P = 0.023$ and 0.006, respectively) (Figure 3).

DISCUSSION

The present study evaluated the optimal duration of voice rest and the effects of early initiation of therapeutic phonatory stimulation on vocal fold wound healing after phonomicrosurgery.

A number of studies on other tissues have demonstrated that application of mechanical stimulation influences wound healing. Repetitive loading of mechanical stimulation affects cell shape, proliferation, and differentiation,[46–48] and continuous movement minimizes scar formation of joints of the extremities. For example, Woo et al[20] demonstrated that early initiation of mechanical stimulation promoted collagen synthesis and improved stress–strain values in a canine knee ligament injury model. Mechanical stimulation also reduced dermal wound size in mice.[49]

Regarding the vocal fold wound healing, it has been reported that mechanical stimulation to human vocal fold fibroblasts causes increased expression levels of proteoglycans and hyaluronic acid.[38] Another report indicated that mechanical stimulation promoted fibroblast proliferation and migration in the rabbit vocal fold.[50] Therefore, early vocal stimulation during the proliferative phase may enhance the wound healing process in the vocal fold. Indeed, several studies have described the effectiveness of postoperative voice therapy in phonomicrosurgery patients. These studies reported that postoperative voice therapy decreased the risk of recurrent dysphonia, although they did not describe the details of the procedures nor the amount of voice therapy.[10,12,13]

The current study set up 2 groups according to the voice rest period based on both the wound healing mechanism and effects of mechanical stimulation on the wound: in the 3-day group, voice rest was limited just during the inflammatory phase and early stimulation was applied, while in the 7-day group, the voice rest was extended to the proliferative phase, and vocal stimulation was delayed as compared to the 3-day group. The results indicated that NMWA was significantly better in the 3-day group than in the 7-day group at 1, 3, and 6 months, whereas jitter and shimmer were significantly better in the 3-day group than in the 7-day group only at 1 month post operation. As NMWA was measured at the affected side, improvement of NMWA represents the functional recovery of the mucosa. But regarding jitter and

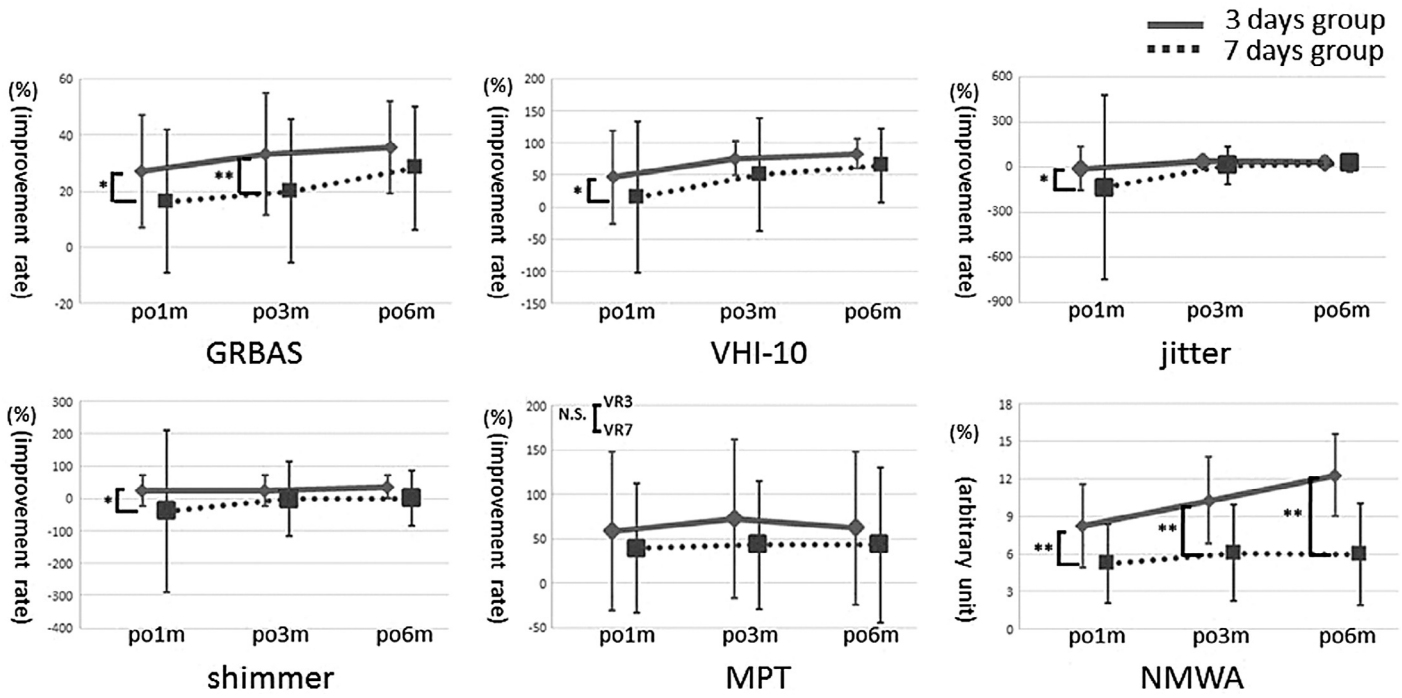

FIGURE 3. Phonatory outcomes between the 3- and 7-day groups at each time point. Jitter, shimmer, and VHI-10 were significantly better in the 3-day group at 1 month post operation ($P = 0.023$, 0.015, and 0.037, respectively). GRBAS was significantly better in the 3-day group at the 1- and 3-month time points ($P = 0.023$ and 0.006, respectively), and NMWA was significantly better in the 3-day group at each time point (1, 3, and 6 months) compared to the 7-day group ($P = 0.0006$, 0.0000, and 0.0000, respectively). *$P < 0.05$, **$P < 0.01$. GRBAS, grade, roughness, breathiness, asthenia, strain; MPT, maximum phonation time; NMWA, normalized mucosal wave amplitude; VHI-10, Voice Handicap Index-10.

shimmer, they are the products by both vocal fold vibration, and thus discrepancy can occur between NMWA and jitter, shimmer. The results indicated early recovery of vocal mucosal function and better vibratory property in a long-term period in the 3-day group. Although the long-term final phonatory function was the same regardless of the voice rest period, early voice improvement should be important to stimulate the patient's motivation. This early motivation might eventually lead to stable changes in voice for the long term for as long as 2–5 years. Conversely, initial voice improvement can also reduce the patient's sense of urgency in complying with voice therapy. Therefore, these initial changes is thought be quite useful and important for the rehabilitation of voice following surgery. The results also indicate that there was some physiological evidence that stroboscopic parameters based on NMWA were better in the 3-day voice rest, although this did not correlate with either perception or handicap. We believe that it should be worthy to preserve the tissue property as much as possible.

The remaining question is what the most "appropriate" voice therapy is. It should be noted that if the early therapeutic phonatory stimulation is properly performed postoperatively, that stimulation may promote fibroblast activities, and optimal tissue restoration is expected. However, if the stimulation is excessive, vocal fold scarring may occur, leading to increased stiffness and decreased elasticity.[5] The current study used tube phonation as a possible "appropriate" stimulation, and the results seem to be positive. However, it may be necessary to explore an ideal voice therapy program as postoperative vocal stimulation.

A limitation of the present study is the small sample size, which weakens the randomized status. As this is an exploratory study, the sample size was relatively small, but we believe that the current study is the first study to examine the effects of voice rest period in a randomized setup. A larger study with more statistical power should be warranted in the future.

CONCLUSION

Voice rest for 3 days with early initiation of voice therapy led to better recovery of the vocal fold property than 7 days of voice rest. This suggests that early initiation of voice therapy with appropriate mechanical stimulation may improve vocal fold wound healing. Thus, 3 days of voice rest followed by the appropriate therapeutic vocal stimulation may be recommended for patients after phonomicrosurgery.

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