Multidisciplinary Research Journal of Health Sciences
Volume 10 Issue 4, October-December 2022
ISSN: 2995-4444
Impact Factor: 5.89
http://kloverjournals.org/journals/index.php/hs

REVITALIZING SMELL PERCEPTION: ADVANCED STRATEGIES FOR OLFACTORY RESTORATION IN TOTAL LARYNGECTOMY CASES

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Abstract: Laryngeal cancer, primarily afflicting male individuals, presents as a prevalent malignancy within the upper aerodigestive tract, predominantly as carcinomas. The treatment of laryngeal malignancies encompasses multiple therapeutic modalities, including radiation, chemotherapy, and surgery. While non-surgical approaches are often favored, laryngectomy, a surgical procedure, becomes necessary in cases where radiation and chemotherapy fail to produce satisfactory therapeutic outcomes. Partial laryngectomy, frequently combined with radiotherapy and/or chemotherapy, involves the removal of a portion of the larynx, enabling the unobstructed flow of air through the respiratory passages, from the nasal cavities to the lungs. For more advanced cases of laryngeal cancer, total laryngectomy (TL) is imperative. TL involves the complete excision of the entire larynx, including the hyoid bone, necessitating a surgical incision in the anterior neck. Various muscles, including hyoidean muscles and the lower pharyngeal constrictor muscle, are sectioned and subsequently sutured, preserving the communication between the hypopharynx and the esophagus.

Keywords: Laryngeal Cancer, Laryngectomy, Total Laryngectomy (TL), Partial Laryngectomy, Malignant Neoplasia

1. Introduction

Laryngeal cancer is one of the most common malignant neoplasias of the upper aerodigestive tract that affects mainly male subjects compared to female ones and consists prevalently in carcinomas (Boscolo-Rizzo et al., 2008). Laryngeal malignant neoplasiascan be treated by performing various therapeutic methods, i.e. radiation, chemotherapy and surgery (Zenga et al., 2018). Although non surgical therapies should be preferred, however the surgical practice of laryngectomy has to be performed if radiation and chemotherapy produced no good therapeutic effects (Woodard et al., 2007). In partial laryngectomy, that is often associated with radiotherapy and/or chemotherapy, only a portion of the larynx is removed, thus maintaining the normal airflow through the nasal cavities, pharynx, larynx, trachea and bronchi up to the lungs (Woodard et al., 2007; Boscolo-Rizzo et al., 2008). Total laryngectomy (TL) is required in the therapy of more advanced laryngeal cancer (Boscolo-Rizzo et al., 2008) and involves the complete removal of the whole larynx, as well as of the hyoid bone. In this condition a surgical incision is performed in the anterior part of the neck and various muscles, i.e. hyoidean muscles and lower pharyngeal constrictor muscle, are cut and finally they are stitched up maintaining only the communication between hypopharynx and oesophagus.

The upper respiratory way was separated from the lower one, thereforelaryngectomized patients can breathe through a tracheostomy opened in the neck (van Dam et al., 1999; Hilgers et al., 2000).

Although TL surely represent a life-saving therapeutic procedure, however total laryngectomized patients lose their natural voice, as well as nasal breathing, thus the airflow cannot passthrough the nasal cavities and this situation provokes hyposmia and anosmia (Moore-Gillon, 1985;van Dam et al.,

1999;Hilgers et al., 2000; Woodard et al., 2007; Boscolo-Rizzo et al., 2008;Manestar et al., 2012; Ionescu et al., 2015;Riva et al., 2017;Zenga et al., 2018):air cannot reach the olfactory mucosa and therefore it cannot stimulate the olfactory Schultz's neurons and, as a consequence, total laryngectomized patients could suffer from both physical and psychological repercussions, including throat dryness, as well as oral communication skill (Boscolo-Rizzo et al., 2008).As far as the rehabilitation of total laryngectomized patients was concerned, it was mainly focused on vocal and speech recovery, whereas less attention was turned to the loss of the specific sense of smell that causes a decrease of appetite and also of sexual activity, as well as the level of a good mood (Ionescu et al., 2015). Anosmia was always considered an inevitable consequence of TL and improvement in olfaction during the first six months after operation and successively the presence of a relatively normal smell in some larygectomizedsubjects was also reported (Hilgers et al., 2000). Van Dam et al. (1999) proposed that laryngectomized patients could be divided into two groups on the basis of an odor detection and/or an odor differentiation test, i.e. "smellers" and "nonsmellers" and showed that one third of the patients could be classified as smellers and they also maintained a better taste sensitivity and appetite.

Although some factors, such as atrophy of the Schultz's neuron in the olfactory mucosa, eventually in addition with atrophy of the olfactory bulb, may also play a pivotal role in the olfactory problems in patientsafter TL, restoring nasal airflow is a necessary prerequisite for rehabilitation of olfactory acuity in such patients. The socalled "smellers" of the above mentioned study (van Dam et al., 1999) had developed a particular own technique to improve smell by moving the jaw and the muscles of the mouth floor, as well as the masticatory ones. Hilgers et al. (2000) reported an intervention study by employing the Nasal Airflow-Inducing Maneuver (NAIM) in which a repeated extended yawning movement is performed, lowering the jaw, the mouth floor, the tongue body and base and the soft palate, while keeping the lips securely closed. It is a method similar to yawning with the closed mouth, i.e. "polite yawning". NAIM provokes a negative pressure in both the oral cavity and the oropharynx and it induces a nasal airflow that enables odorous substances to reach the olfactory epithelium.

In the present work we would describe a study on the effects of the olfactory rehabilitation in twelve laryngectomized patients by applying the above proposed NAIM technique - with minimal adjustments - to assess whether such patients can acquire this olfactory rehabilitation technique and whether NAIM can improve olfactory acuity that we evaluated at the beginning, during and at the end of the smell rehabilitation cycle, as well as twelve months later to verify the maintenance of the recovered smell functions.

2.0 Materials and Methods

Twelve male patients (aged between 58 and 76 years, mean age 66,08 □6,17, median age 66) were proposed to undergo a smell rehabilitation cycle (Table 1).

PATIENTS	AGE	ALARYNGEAL SPEECH TECHNIQUE
1	59	VOICE PROSTHESIS
2	66	VOICE PROSTHESIS
3	64	OESOPHAGEAL VOICE
4	72	VOICE PROSTHESIS

5	69	OESOPHAGEAL VOICE	
6	67	VOICE PROSTHESIS	
7	67	VOICE PROSTHESIS	
8	76	OESOPHAGEAL VOICE	
9	75	VOICE PROSTHESIS	
10	58	OESOPHAGEAL VOICE	
11	59	LARYNGOPHONE	
12	61	LARYNGOPHONE	
MEAN AGE	66,08□ 6,17	MEDIAN AGE	66
MAXIMUM	76	MINIMUM	58

Table 1. Age and alaryngeal speech technique of each laryngectomized patients

All of them underwent TL in different periods for laryngeal cancer and none of them underwent either chemotherapy or radiotherapy after surgery and had at least a 2-year follow up period to evaluate stabilized late adverse effects.All patients already underwent voice rehabilitation and they were using different alaryngealspeech techniques: two of the laryngectomized subjects were using a laryngophone, six were using a voice prosthesis and four of them were employing the oesophageal voice. All patients were free from both nasal and pharyngeal concurrent pathologies as shown by a preliminarfibre-optic rhinoscopy with light localanaesthesia (10% lidocaine spray).

2.1 Olfactory rehabilitation technique.

Sessions (each 45 min long) of the olfactory rehabilitation cycle started at the end of preventive clinical examinations and were performed three times a week for four weeks. Patients were trained to the NAIM technique (Hilgers et al., 2000)to enable odorous substances to reach again the olfactory mucosa. NAIM exercises have to be repeated several times and patients were stimulated to actively use the NAIM as often as possible, in particular after the end of the 4-week smell rehabilitation cycle.

2.2 Analysis of olfactory functions

2.2.1. Olfactory perception.

Tests of olfactory perception were performed at three time intervals, i.e. before the beginning of the smell rehabilitative cycle, after the third rehabilitation session (i.e., at the end of the first rehabilitation week) and at the end of the olfactory rehabilitative intervention (day 28). A solution (4%) of 1-butanol in di-propylene glycol was employed to detect the olfactory perception of each patient. Patients were asked to vote the detected smell intensity by means of a numeric score between 0 (no olfactory perception) and 10 (maximum of olfactory perception). Mean values (□ standard deviation) of the voted smell intensity at each considered period were calculated. Statistical analyses were performed by considering the Student's t-test with significant differences between two groups verified when $p < 0,01$.

2.2.2. Olfactory discrimination

Patients underwent olfactory discrimination tests at three different time intervals, i.e. before beginning the smell rehabilitation cycle, at the end of the olfactory rehabilitation period (day 28) and finally after

twelve months. The olfactory discrimination test consisted in bottles each containing a specific odorant. Each patient was presented with 26 bottles and everyone had to choose the correct answer among four choices and write it in a questionary. prevent the visual detection of the target sticks, subjects were blindfolded with a sleeping mask.

Presentation of each bottle was separated by at least 30 seconds. Mean values (☐ standard deviation) of the correctly identified substances were calculated. Statistical analyses were performed by considering the Student's ttest with significant differences between two groups verified when $p < 0,01$.

3.0 Results

3.1 Olfactory rehabilitation technique

The first step to recover the olfactory sensitivity was to teach the patients the NAIM technique. Most patients learned it already during the first unit of the smell rehabilitation cycle, however a minority of patients found particular difficulties in performing the NAIM exercises, therefore they were suggested by speech therapists to provide some minimal modifications to the original NAIM technique: in particular, patients speaking with the oesophageal voice were suggested to reproduce the same action they performed for the oesophageal speech. **3.2. Analysis of olfactory functions**

3.2.1. Olfactory perception

Data of this experimental phase are reported in Table 2 and graphically presented in Fig. 1.Before beginning the olfactory rehabilitation cycle, the mean value of the olfactory perception was 3,58 ☐ 1,73in a score between a minimum of 1 and a maximum of 6 (median value 4). After the third rehabilitation unit, the mean value of the olfactory perception was 5,75 ☐ 1,22, in a score between 4 and 7 (median value 6).

OLFACTORY PERCEPTION LEVELS (QUANTITATIVE INDIVIDUAL SCORE BETWEEN 0 AND 10)			
PATIENTS	OLFACTORY PERCEPTION LEVEL WITHOUT SMELL REHABILITATION	OLFACTORY PERCEPTION LEVEL AFTER THE THIRD REHABILITATION UNIT (DAY 7)	OLFACTORY PERCEPTION LEVEL AT THE END OF REHABILITATION CYCLE (DAY 28)
1	2	4	7
2	3	5	8
3	1	5	7
4	4	6	8

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5	4	7	8
6	5	7	9
7	3	5	8
8	1	4	9
9	6	7	9
10	5	7	8
11	6	7	7
12	3	5	7
MEAN VALUES	3,58 ☐ 1,73	5,75 ☐ 1,22	7,92 ☐ 0,79
MEDIAN VALUES	4	6	8

Table 2. Olfactory perception levels of each laryngectomized patient at three different time intervals

Finally, at the end of the rehabilitation cycle (day 28), the mean value of the olfactory perception increased up to 7,92 ☐ 0,79, in a score between 7 to 9 (median value 8).

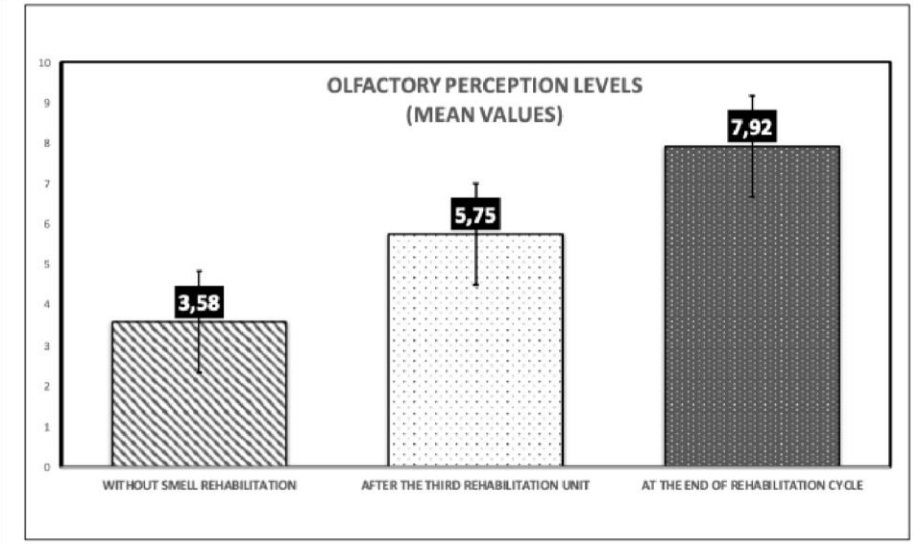

Fig. 1. Graphic presentation of olfactory perception levels at three different times

By performing the paired Student's t-test, the significance of the differences between the mean values of the olfactory perception without any rehabilitative intervention and those after the third rehabilitative session, as well as between this one and the olfactory sensitivity at the end of the

rehabilitative intervention (day 28), were evidenced for a level of p<0,01 and it was considered as statistically significant.

3.2.2. Olfactory discrimination

Data of this experimental phase are reported in Table 3 and graphically presented in Fig. 2. The first olfactory discrimination test was performed before any rehabilitative intervention and after the first olfactory perception test.

OLFACTORY DISCRIMINATION OF 26 ODOROUS SUBSTANCES (QUANTITATIVE SCORE BETWEEN 0 AND 26)			
PATIENTS	WITHOUT OLFACTORY REHABILITATION	28 DAYS AFTER OLFACTORY REHABILITATION	12 MONTHS AFTER OLFACTORY REHABILITATION
1	5	13	12
2	4	10	11
3	7	15	13
4	4	9	11
5	6	13	13
6	6	14	12
7	5	10	12
8	7	13	11
9	5	12	10
10	7	11	13
11	4	10	8
12	5	10	7
MEAN VALUES	5,42□1,16	11,67□1,92	11,08□1,93
MEDIAN VALUES	5	11	11

Table 3. Olfactory discrimination of each laryngectomizedpatient at three different time intervals

The first olfactory discrimination analysis revealed a mean value of 5,42 □ 1,16 of correctly identified substances among a total of 26 ones. At the end of the smell rehabilitation period (day 28), the mean value of correctly identified substances was 11,67□1,92, with a relevant increase (115,31%) compared to the olfactory discrimination before rehabilitation.

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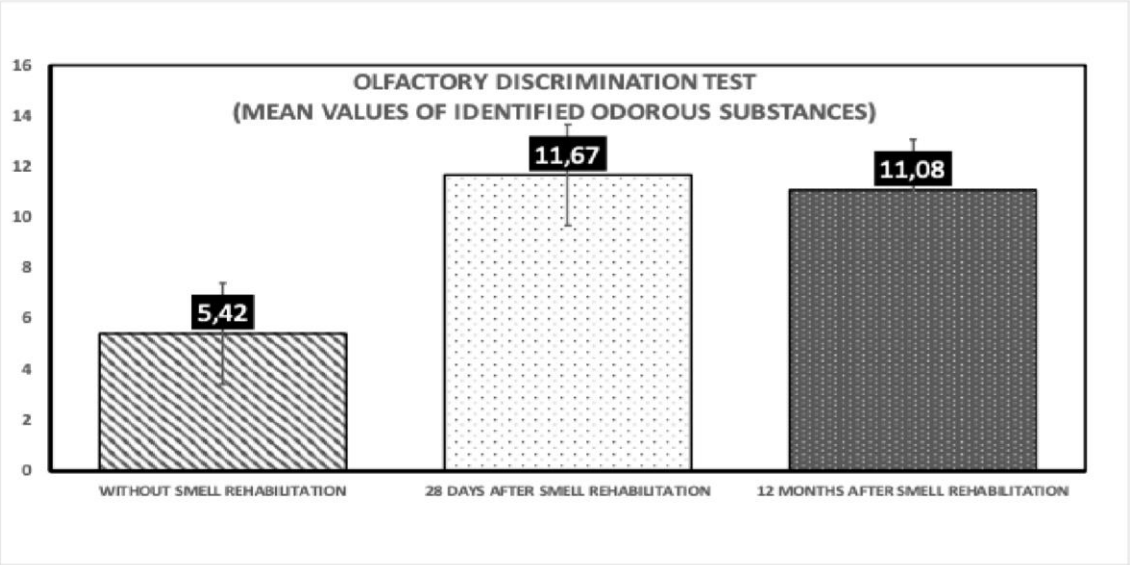

Fig. 2. Graphic presentation of olfactory discrimination at three different time intervals

A third olfactory discrimination test was performed twelve months after the end of the smell rehabilitation cycle: the mean value of the correctly identified substances was 11,08 □ 1,93, with a negative difference of 5,33% in comparison with the mean value at the end of the rehabilitative intervention (day 28). However a relevant increase (104,43%) was always detected in comparison to the mean value of correctly identified substances without any olfactory rehabilitation cycle.

4. Discussion

After TL, trachea and lungs are completely disconnected from pharynx, mouth and nasal cavities and respiratory airflow takes place directly through a tracheostomy above the suprasternal notch. Therefore, loss of olfactory acuity is a very disturbing side effect of this debilitating surgical procedure and the majority of total laryngectomized patients reveal a complete loss of the sense of smell (Hilgers et al., 2000). Van Dam et al. (1999) reported that 32% of laryngectomized patients were still able to smell, whereas 68% of them were unable to detect or to differentiate any of the submitted odorous substances. However, after TL major attention is turned to speech restoration, whereas smell recovery is really less attentioned (Boscolo-Rizzo et al., 2008; Ionescu et al., 2015). In addition to these problems, also the global quality of life should be considered after TL, including physical, emotional, mental, social and behavioral situations (van Dam et al., 1999;Woodard et al., 2007; BoscoloRizzo et al., 2008;Ionescu et al., 2015;Riva et al., 2017; Zenga et al., 2018). By considering all these factor, we proposed twelve laryngectomized patients to undergo a trial of smell rehabilitation in addition to classic speech rehabilitative cycles.

For this aim, we considered to apply the NAIM technique, known also as “Polite Yawning”, i.e. yawning with closed lips. By considering the experience in this olfactory smell rehabilitative intervention, we observed that most patients learned the NAIM already after the first rehabilitative session, however those speaking with the oesophageal voice (four subjects) showed some difficulties to acquire the NAIM, therefore they were suggested to inhale some air in the same way to produce their oesophageal voice. Thus, all patients were able to acquire a correct NAIM technique either by applying the original method (Hilgers et al., 2000)or by using the above mentioned modified method. We observed a

significant amelioration of the olfactory perception already after the third rehabilitative unit, with a statistically significant difference calculated by performing the Student's t-test ($p< 0,01$). In the subsequent rehabilitative period, some difficulties were encountered in the discrimination of specific odorous substances: although most substances were already well known by the laryngectomized subjects, however there were also other substances that were not recognized by the patients. It seems interesting to observe the very high increase (115,31%) of correctly identified substances at the end of the rehabilitation period in comparison to the beginning of the rehabilitative trial, therefore confirming the relevance of this post-operative recovery practice. Patients were also stimulated to perform constant NAIM exercises to preserve the recovered smell ability, therefore we would compare the olfactory discrimination ability after twelve months to the same one at the end of the olfactory rehabilitative cycle (day 28) and we found a decrease in the ability of identifying odorous substances, but it was not statistically significant at the Student's t-test ($p >0,01$).

However, it is evident that a continuous rehabilitative practice should be done by laryngectomized patients after the institutional rehabilitation cycle and periodic controls should be performed by speech therapists. The recovery of smell functions greatly ameliorated the quality of life of laryngectomized subjects, not only for the specific sensorial function, but also for the strictly correlated taste perception. Moreover, recovered smell perceptions could also enhance other life situation, i.e the relationships with other persons.

Some considerations should be done about the techniques performed in the detection of olfactory abilities. They were based on the so named "Connecticut Test" consisting in both a "Olfactory Thresold Test" - to the detect the minimal olfactory stimulation for every examined subject - and an "Identification Test" - performed to identify specific odorous substances (Cain et al., 1988).Other investigators proposed other methods, i.e. the "Q-stick Test" (Sorokowska et al., 2019), smell diskettes (Briner & Simmen, 1999), as well as the "Sniffin' Stick Test" (Hummel et al., 1997, 2007; Oleszkiewicz et al., 2019). In the present work we would perform a faster method to detect the olfactory perception by using only a dilution (4%)of 1-butanol in di-propylene glycol, since all enrolled patients referred no olfactory perception after the surgical intervention of TL and therefore we considered that is should not be necessary to test other 1-butanol dilutions. As far as the olfactory discrimination test was concerned, we employed a more complicated test than those reported by other investigators (Cain et al., 1988;Briner & Simmen, 1999;Hummel et al., 1997, 2007;Sorokowska et al., 2019; Oleskiewicz et al., 2019); however, we observed a relevant amelioration of the olfactory discrimination ability after the smell rehabilitation cycle.

In conclusion, although TL should be necessary in the treatment of advanced laryngeal cancer, however it is necessary to consider not only the classic speech rehabilitation, but also the not less important smell rehabilitation to recovery the capability to recognize odorous substances. Smell restoration is able to enhance also the recovery of taste sensitivity and therefore contribute to ameliorate the global quality of life in laryngectomized patients.

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