


Multicenter Randomized Crossover Trial Evaluating the Provox Luna in Laryngectomized Subjects

Chathura B.B. Ratnayake, MBChB ; Renske Fles, PhD; I. Bing Tan, MD, PhD;
Laura W.J. Baijens, MD, PhD; Walmarie Pilz, PhD; Cees A. Meeuwis, MD, PhD;
Pauline H.E. Janssen-van Det; Rob van Son, PhD; Michiel W.M. Van den Brekel, MD, PhD

Objectives: The aim of this study was to compare the relative compliance and the dermatological and pulmonary outcomes when the Provox Luna system (Atos Medical, Malmö, Sweden) is added during the night to the usual tracheostoma care of laryngectomized subjects.

Methods: This was a multicenter randomized crossover trial conducted in the Netherlands Cancer Institute, Erasmus Medical Center, and Maastricht University Medical Center in The Netherlands. The study included 46 laryngectomized subjects with prior heat and moisture exchanger (HME) and adhesive experience.

Results: A significant improvement in the number of compliant individuals was found: Luna: $n = 43$ of 45 (96%); usual care: $n = 35$ of 46 (76%), $P = 0.02$. The Luna period was associated with longer intervals of daily HME use (Luna 23.2 hours [range: 15.6–24.0 hours], usual care [UC]: 21.5 hours [range: 6.0–24.0 hours], $P = 0.003$) and an increased frequency of skin improvement overnight (Luna 3.9 days [standard deviation (SD)]: 7.0 days), Usual Care: 8.1 days ([SD: 10.8 days], $P = 0.008$). Fifty-six percent ($n = 26$) of participants wanted to continue using the Provox Luna system at the conclusion of the study.

Conclusion: An improvement in compliance and skin recovery overnight was observed when the Provox Luna was added to the usual adhesive and HME use. Therefore, there is utility in supplementing the usual post-total laryngectomy care with the Provox Luna system at night, particularly in the setting of compliance concerns and in subjects who desire dermatological relief overnight.

Key Words: Heat and moisture exchanger, total laryngectomy, tracheostoma, Provox Luna, skin irritation, HME compliance, adhesives.

Level of Evidence: 1b

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INTRODUCTION

Anatomical changes that follow a total laryngectomy (TLE) alter the normal physiology of the upper respiratory tract.¹ Inspired air bypasses the upper airway due to the placement of a permanent tracheostoma at the base of the neck, impeding physiological upper airway conditioning (warming, filtration, and humidification).²

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From the University of Auckland, Auckland (C.B.B.R.), New Zealand; the Netherlands Cancer Institute (C.B.B.R., R.F., I.B.T., R.V.S., M.W.M.VdB.), Amsterdam; the Department of Otorhinolaryngology, Head and Neck Surgery (I.B.T., L.W.J.B., W.P.); the School for Oncology and Developmental Biology–GROW (L.W.J.B., W.P.), Maastricht University Medical Center, Maastricht; and the Erasmus Medical Center (C.A.M., P.H.E.J.-VD.), Rotterdam, The Netherlands.

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Send correspondence to Michiel van den Brekel, Professor of Head and Neck Surgery, The Netherlands Cancer Institute, Plesmanlaan 121, 1066CX, Amsterdam, the Netherlands. E-mail: m.vd.brekel@nki.nl

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Consequently, definitive open tracheostoma ventilation is associated with marked histological changes to the tracheal mucosa. This includes the loss of ciliated epithelial cells and goblet cell hyperplasia,^{3,4} which impairs mucociliary clearance.^{5,6}

The increased incidence of chronic airway inflammation and pulmonary infections are known long-term sequelae of prolonged impaired mucociliary clearance.^{7,8} Psychosocial complaints including reduced quality of life, and increased rates of anxiety and depression⁹ accompany these subject-reported symptoms. Heat and moisture exchangers (HMEs) are passive airway conditioning devices that are positioned at the opening of the tracheostoma. HMEs retain heat and moisture in the core media, thereby warming and humidifying inspired air.¹⁰ Compliant HME use is associated with reduced coughing, forced expectoration,^{11,12} external humidifier/vaporizer use, and lower healthcare costs.^{13,14} These findings have been attributed to an improved tracheal climate, particle filtering, and increased respiratory resistance.^{15,16}

HME benefits correlate with the duration of use.¹⁷ Although short intervals of nonuse (a few hours) have failed to demonstrate significant changes to HME efficacy,³ failure of compliant use of this device during both the day and night is attributed with poor pulmonary

outcomes.^{11,18,19} A large body of evidence showing a significant improvement in subject reported benefits resulting from compliant HME use exists; however, noncompliance ranges from 48% to 82% of subjects.^{11,20,21} Furthermore, approximately 20% of subjects report skin irritation at the adhesive site and further discomfort while sleeping with the HME device in place.^{17,22}

Conventional HME devices and peristomal adhesives contain inflexible synthetic materials that are thought to influence comfort, compliance, and skin irritation. Atos Medical (Malmö, Sweden) has developed the Provox Luna by designing a hydrogel-based soft adhesive with soft silicon housing in an effort to ameliorate these issues. Use of hydrogel-based adhesives is widely documented elsewhere in the body for wound management.^{23,24} These are glycerin- or water-based materials that are thought to reduce irritation at the site of contact to the skin via a cooling effect.^{23,24} Although hydrogel adhesion may be inferior adhesive properties to silicon glues, the Luna adhesive may be an alternative to improve comfort during the night and, consequently, compliance and pulmonary complaints following TLE.

The aim of this clinical trial is to assess subject preference and compare the relative compliance of HME use when the Provox Luna is added to a subject's usual care (UC) and to document the associated changes to subject-reported symptoms.

MATERIALS AND METHODS

Subjects

Subjects were recruited at The Netherlands Cancer Institute, the Erasmus Medical Center, and Maastricht University Medical Center in The Netherlands. The multicenter study protocol was approved by the Medical Research Ethics Committee of the Netherlands Cancer Institute and performed in compliance with ISO 14155: 2011 (E): Clinical Investigation of medical devices for human subjects—Good clinical practice and the regional and national regulations (The Netherlands Central Committee on Research Involving Human Subjects—*Centrale Commissie Mensgebonden Onderzoek*, case number: NL59449.031.16). Following the acquisition of informed consent, subjects were invited to participate if they fulfilled the following criteria were over 18 years old, at least 3 months post-TLE, at least 6 weeks postradiotherapy, and had experience with HME and adhesive use. Subjects were excluded on the basis of prior medical problems prohibiting HME or adhesive use, recurrent or metastatic disease, functional incapacity to insert and remove an HME or adhesive independently, inability to understand or provide informed consent, impaired cognitive ability, or regular use of a cannula (e.g., LaryTube; Atos Medical).

A total of 53 subjects were recruited from Erasmus Medical Center (n = 26), Maastricht University Medical Center (n = 15), and The Netherlands Cancer Institute (n = 12) into the study from January 2017 to October 2017. The mean subject age was 65 years (range: 54–80 years). Male-to-female ratio was 46:7. Thirty-two subjects received primary radiotherapy (RT) or chemoradiotherapy (CRT) and a salvage laryngectomy; 19 received postoperative RT or CRT; and two received no radiotherapy. Eight worked full time; four worked part time; 27 were retired; 11 received incapacity benefits; and three had other nonspecific working conditions. Types of voice prosthesis included Provox Vega (n = 18), Provox 2 (n = 19), Provox ActiValve (n = 13), and those without voice prosthesis (n = 3). HME use during the day at baseline was comprised of Provox XtraFlow (n = 31), Provox XtraMoist (n = 15), and Provox

FreeHands series (n = 6); and one subject used nothing. Forty-two subjects reported using an HME every night. Eleven used an HME infrequently and sometimes used a bib or cannula (e.g., LaryTube) during the night. Subjects were instructed to continue their baseline nighttime care routine during the UC period of the study and to use the Provox Luna system at night during the Luna period of the study. Further background clinical data of the initial 53 subjects recruited into the study is reported in Table I.

TABLE I.
Clinical Characteristic Data of All Subjects Who Were Initially Enrolled into the Study (n = 53).

Characteristic	
Randomization (n)	
Provox luna first	27
Usual care first	26
Age (years) at entry	
Mean/median (range)	65.3/64 (54–80)
Post-TL (months)	
Mean/median (range)	69.1/36 (4–294)
Gender (n)	
Male	46
Female	7
Primary tumor location (n)	
Larynx	46
Hypopharynx	6
Other	1
N status (n)	
N0	38
N1	10
N2	5
Neck dissection (n)	
Unilateral	8
Bilateral	26
None	19
Esophagectomy (n)	
Conducted	4
None	49
Pharyngectomy (n)	
Total	6
Partial	4
None	43
Reconstruction (n)	
Jejunum	6
Pectoralis major	11
None	36
Chemoradiotherapy (n)	
Preoperative RT	27
Preoperative CRT	5
Postoperative RT	18
Postoperative CRT	1
None	2

Provox Luna: Atos Medical, Malmö, Sweden.
CRT = chemoradiotherapy; N = node; RT = radiotherapy, TL = total laryngectomy.

Methods

The study was a multicenter randomized crossover trial in design whereby subjects acted as their own control in order to limit bias and provide a valid control interval. Subjects were randomized into two groups using a variable block randomization method (Castor EDC [electronic data capture]; Amsterdam, The Netherlands)²⁵ beginning with the use of Provox Luna system during the night or with their usual care for 28 days. The subjects were then crossed over for a second period of 28 days. Formal evaluations took place at the commencement, midpoint (at 28 days), and end of the study. Study coordinators were in contact with subjects by phone every week to ensure they were recording daily observation in their diaries and to address any problems that had arisen. Standardized questionnaires were employed in the form of a case report form (CRF) to obtain general clinical data and baseline HME/adhesive use at the onset, subject experiences at the midway point, and comparisons and final thoughts in the final evaluation. All subjects were also given a diary and instructed to record the hours of daily HME use, type of HME or alternative used during the night, the number of episodes of disrupted sleep due to coughing every night, the presence of skin irritation in the evening, and any skin improvement overnight. Subjects were also supplied with Luna HMEs, a supply of Luna adhesives, a shower cap, and additional protective adhesive strips.

The primary outcome measure in this study was the overall compliance of HME use. Compliant HME use was defined as HME use for at least 20 hours of every day in at least 24 days out of 28 days. Secondary outcomes included pulmonary and dermatological effects, subject satisfaction, sleeping, and general quality of life. The structured questionnaire CRF aimed to provide some further insight into subject experiences and factors that may influence future HME use. The EuroQol five-dimensions five-level (EQ-5D-5 L) questionnaire was also employed to compare quality-of-life outcomes. This validated tool scores on five domains (mobility, self-care, daily activities, pain/discomfort, and anguish/depression) in a balanced health state index. The EQ visual analogue scale (VAS) records the patient's self-rated health on an analogue visual scale. EQ-5D-5 L scores and VAS were recorded at the start of the study, after 4 weeks of usual care, and after 4 weeks of Provox Luna HME use.

Of the initial 53 subjects enrolled in the study, 26 subjects were randomized to begin with the use of Provox Luna system during the night, and 27 subjects began with UC, both for 28 days. There were four dropouts (7.5%): two were due to recurrent metastatic disease, and two were due to subjects' revoked initial agreement to participate in the second week of study. Among the remaining 49 subjects, one had failed to record diary data, and two subjects were later found to have never used an HME prior to the study and thus failed to comply with the inclusion criteria. One Luna period diary was lost during follow-up; thus, following exclusion of these subjects, the final analysis was comprised of 46 UC period diaries (87%) and 45 Luna period diaries (85%) (Fig. 1).

Statistical Analysis

Statistical analysis was performed using the IBM SPSS PC + 22.0 (SPSS Inc., Armonk, NY) statistical package. Where applicable, collected data was presented with mean and median calculations accompanied by associated standard deviations (SD) and ranges. Collected data was assessed for normality with the Kolmogorov Smirnov test. All categorical data was then analyzed with a McNemar test (combined with a binomial test), and the remaining data was analyzed using the paired Wilcoxon signed ranks (WMPSR) or the Mann-Whitney test. Multiple comparisons of ordinal or interval data were made with the Kruskal-Wallis test. Trends were analyzed with Pearson correlation (CC) over the two HME periods. All statistical tests were two-tailed

and were evaluated with a 5% level of significance. The statistical protocol for the study was approved by The Netherlands Cancer Center Medical Ethical Board.

RESULTS

Compliance

The number of compliant users differed significantly between the two periods (Luna: $n = 43$ of 45 [96%], UC: $n = 35$ of 46 [76%], $P = 0.02$ McNemar test). A significant improvement in the hours of HME use per day (Luna mean: 23.3 [SD: 1.4], median: 23.9 [range: 15.6–24.0] hours, UC mean: 21.6 [SD: 4.3], median: 23.3 [range: 6.0–24.0] hours, $P = 0.003$ WMPSR) and the number of compliant days overall (Luna mean: 27 [SD: 4.3], median: 28 [range: 0–28] days, UC mean: 22.5 [SD: 10.1], median: 28 [range: 0–28] days, $P = 0.002$ WMPSR) was observed during the interval of Provox Luna use (Table II). All eight subjects who had reported not using an HME every night at baseline were noncompliant during the UC period (out of 11 noncompliant subjects). Two of them were the non-compliant subjects during the Luna period. Nine of the 11 subjects who were noncompliant HME users during the UC period had compliant HME use during the Luna period. In the Luna interval, 19 subjects reported longer use of an HME during the day by a mean of 4.3 hours, and nine subjects had shorter use by a mean of 0.6 hours.

No difference in the weekly mean hours of HME use per day was established between separate weeks within the Luna ($P = 0.32$, Friedman test) or UC period ($P = 0.16$, Friedman test). Subjects who were randomized to begin with Provox Luna use or UC versus those who ended with Provox Luna use or UC, respectively, has statistically similar outcomes in all domains; hence, the order of product use did not appear to impact outcomes.

Coughing

The overall mean number of disturbed sleep episodes due to coughing per night did not differ between the UC (mean: 0.50 [SD: 0.75, range: 0–2.6] episodes) and Luna (mean: 0.49 [SD: 0.75, range: 0–2.6] episodes, $P = 0.537$ WMPSR) periods (Table II). Correlated against the day number in each period (1–28), the fraction of subjects who woke up due to coughing decreased during the Luna period ($P = 0.001$, $R = -0.57$ Pearson CC) and increased during the UC period ($P = 0.003$, $R = +0.55$ Pearson CC). This effect was seen for Luna and UC in both group A and group B (see Fig. 2) ($P = 0.17$ for Luna in group A, $P < 0.05$ for all other curves).

The overall mean number of days in which subjects reported at least one episode of disturbed sleep due to coughing overnight did not differ between the UC and Luna periods (UC: mean 8.3; median 2 [SD 10.7, range 0–28], Luna: mean 7.2; median 3 [SD 9.4 range 0–28], $P = 0.10$).

Skin Irritation and Skin Improvement

Skin irritation was reported by 26 subjects at baseline, 21 subjects during the UC, and 19 subjects during

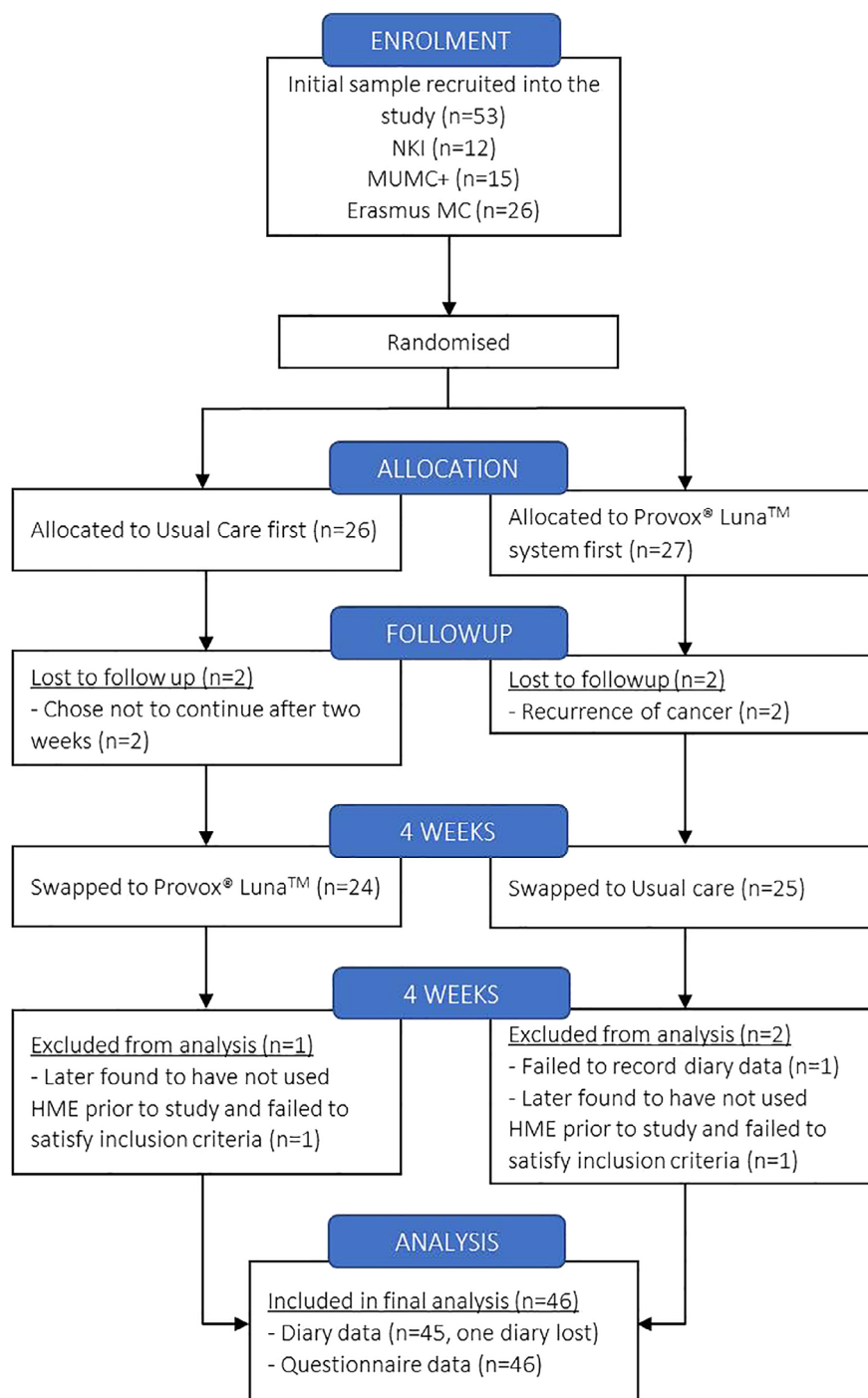


Fig. 1. Breakdown of the recruitment of subjects and the number of subjects who were included in the final analysis. Erasmus MC = Erasmus Medical Center; MUMC = Maastricht University Medical Center; NKI = National Cancer Institute. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

the Luna period. During the study, 12 subjects reported skin irritation at multiple days per week (both UC and Luna periods). The mean number of days when subjects documented skin irritation in the evening did not differ between the UC (mean: 6.6 [SD: 10.4], median: 0 [range: 0–28] days) and Luna (mean: 5.1 [SD: 7.9], median: 1 [range: 0–28] days, $P = 0.338$) periods. However, skin improvement overnight was observed in a greater frequency of nights

during the Luna interval (Luna 29 subjects, mean: 8.1 [SD: 10.8], median: 2, range: [0–28] days, UC 17 subjects, mean: 3.9 [SD: 7.0], median: 0, range: [0–28] days, $P = 0.012$). Only one of the 11 noncompliant subjects during the Luna period did not report skin improvement overnight at least once. Both noncompliant subjects during the Luna period reported skin improvement overnight. Of the eight subjects who reported not using an HME every night at baseline, six

reported skin improvement overnight at least once during the Luna period and seven during the UC period.

During the Luna period and the UC period, there was a difference between compliant versus noncompliant subjects with regard to skin irritation (Luna: $P = 0.03$, UC: $P < 0.001$, Wilcoxon two-sample test). Also, during the UC period skin improvement overnight differed between compliant and noncompliant subjects (Luna: $P = 0.13$, UC: $P < 0.001$, Wilcoxon two-sample test). Here, patients who were noncompliant reported less skin irritation. The number of nights during the Luna period when

TABLE II.
Comparison of Compliance, Coughing at Night, Skin Irritation, and Skin Improvement Between UC and Luna Periods.

Outcome Measure	Usual Care (n = 46)	Luna HME (n = 45)	P Value
Compliance			
Overall number of compliant individuals (n)	35	43	0.065
Mean (SD) hours of HME use per day [range]	21.6 (4.3) [6.0–24.0]	23.3 (1.4) [15.6–24.0]	0.003
Mean (SD) number of compliant days [range]	22.5 (10.1) [0–28]	27.0 (4.3) [0–28]	0.025
Weekly mean (SD) hours of HME use per day [range]			
Week 1	21.6 (4.2) [0.9–24.0]	23.3 (1.4) [15.3–24.0]	0.011
Week 2	21.8 (3.9) [8.4–24.0]	23.0 (2.0) [14.9–24.0]	0.011
Week 3	21.4 (4.6) [4.9–24.0]	23.3 (1.5) [15.8–24.0]	0.001
Week 4	21.3 (4.1) [5.6–24.0]	23.3 (1.5) [16.3–24.0]	0.001
P value	0.994	0.902	
Overall mean number (SD) of nights without HME use [range]			
Bib use	2.5 (7.2) [0–28.0]	0.1 (0.5) [0–3.0]	0.013
Exposed tracheostoma	2.2 (7.1) [0–28.0]	0.1 (0.4) [0–2.0]	0.058
Coughing at Night			
Mean (SD) number of episodes of disturbed sleep due to coughing per night [range]	0.50 (0.75) [0–2.6]	0.49 (0.75) [0–2.6]	0.537
Mean number (SD) of days with at least one episode of disturbed sleep due to coughing at night [range]	8.3 (10.7) [0–28]	7.2 (9.4) [0–28]	0.10
Skin Irritation			
Overall mean (SD) number of days with skin irritation in the evening [range]	6.6 (10.4) [0–28]	5.1 (7.9) [0–28]	0.347
Skin Improvement			
Overall mean (SD) number of days with skin improvement overnight [range]	3.9 (7.0) [0–28]	8.1 (10.8) [0–28]	0.008

Luna HME: Atos Medical, Malmö, Sweden.
HME = heat and moisture exchanger; SD = standard deviation; UC = usual care.

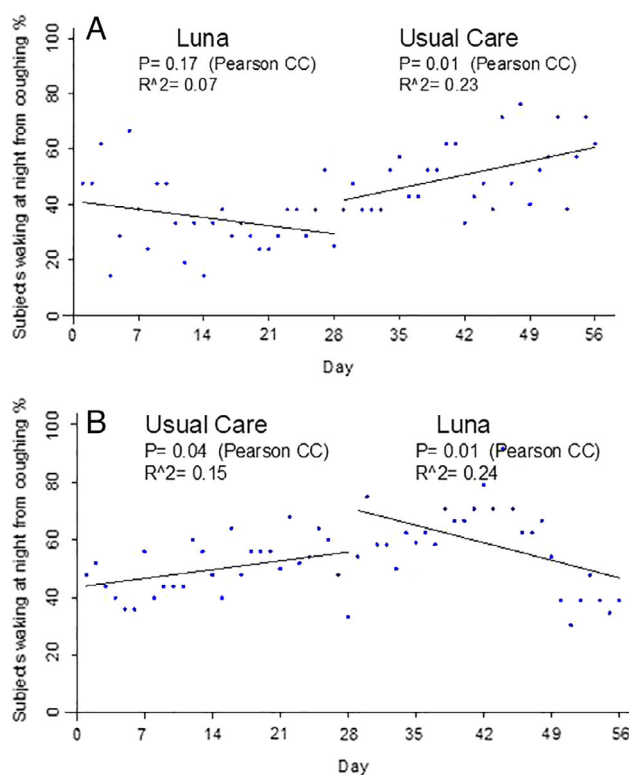


Fig. 2. Percentage of subjects with at least one episode of disturbed sleep due to coughing for each day throughout the study period. (A) Subjects randomized to Provox Luna (Atos Medical, Malmö, Sweden) first (n = 23) and (B) subjects randomized to Usual Care first (n = 23). Pearson CC = Pearson correlation. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

there was no skin irritation during the day and an improvement of the skin overnight (189 nights in n = 18 subjects) outnumbered those during the UC period (51 nights in n = 7 subjects, $P = 0.001$ WMPSR).

Overall Subject Experience

At the final evaluation, all 46 subjects were asked to compare the Provox Luna system to that of their usual care using a standardized questionnaire. Table III shows the number of subjects who reported their comparative experience with the Luna system under various outcome categories. Significantly improved subjective dermatological experiences were observed, including 30% less episodes of skin irritation ($P = 0.03$), 22% less severity of skin irritation ($P > 0.05$), and 33% shorter duration of skin irritation ($P = 0.05$) with 28% better skin recovery ($P = 0.008$) with Provox Luna system. Similarly, 35% of subjects reported a more comfortable sleeping experience with the Provox Luna system compared to their UC. However, no reported difference was recorded for questions regarding patient-reported differences in breathing and coughing.

The mean subject reported satisfaction score regarding use of the Luna system (from 1–5) was 3.7 ± 1.2 . Twenty-six (57%) subjects concluded they would continue using the Provox Luna following the study: every night (n = 19), 5 to 6 nights per week (n = 2), 3 to 4 nights per

TABLE III.
Subject Reported Overall Experience at Final Follow-up Visit Comparative Questionnaire in All Subjects Who Successfully Completed the Study (n = 46).

Comparative Experience	Easier/Lower/ Less/Better	Same	Harder/Higher/ More/Worse	Not Available
Compared to my usual nighttime HME, breathing with Luna HME was:	9	24	7	6
Compared to my usual nighttime HME, breathing resistance of Luna HME was:	8	26	6	6
Coughing off the HME with Luna, compared to my usual nighttime HME was:	1	13	2	30
Coughing during the night with Luna, compared to my usual nighttime HME was:	5	26	1	14
Mucus production during the night with Luna, compared to my usual nighttime HME was:	7	29	1	9
Forced expectorations during the night with Luna, compared to my usual nighttime HME was:	2	14	–	30
How did you sleep during the period of using Provox Luna, compared to my usual HME was:	5	33	2	6
Comfort of sleep during night with Luna HME, compared to my usual nighttime HME was:	14	21	5	6
Comfort of sleep during night with Luna Adhesive, compared to my usual nighttime adhesive was:	14	19	6	7
The number of episodes of skin irritation during the period using Provox Luna, compared to my usual care was:	14	28	4	–
The severity of the skin irritation during the period using Provox Luna, compared to my usual care was:	10	32	4	–
Recovering of the skin during the period using Provox Luna, compared to my usual care was:	15	28	3	–
The duration of the skin irritation during the period using Provox Luna, compared to my usual care was:	13	28	4	1

Luna Adhesive: Atos Medical, Malmö, Sweden; Luna HME: Atos Medical, Malmö, Sweden; Provox Luna: Atos Medical, Malmö, Sweden.
HME = heat and moisture exchanger.

week (n = 3), and 1 to 2 nights per week (n = 2). Twenty subjects (43%) did not wish to continue using the adhesive due to lack of advantages (n = 7), having to change adhesive more often (n = 6), adhesive not sticky enough (n = 3) or too small (n = 1), expense (n = 1), and burning feeling of the adhesive (n = 1).

The EQ-5D-5 L scores at baseline and after the UC period improved significantly ($P = 0.017$). However, improvement after the Luna period was (just) not significant ($P = 0.061$) and no difference was found between EQ-5D-5 L scores were found after either the UC versus the Luna period ($P = 0.443$).

DISCUSSION

This multicenter randomized crossover trial compared compliance, dermatological, and pulmonary outcomes when the Provox Luna system during the night was added to the UC in laryngectomized subjects. Analysis of the dataset revealed a significant improvement in compliance, mean hours of daily use, and a greater frequency of days when subjects reported skin improvement overnight during the Luna period. From the results of this study, it emerges that skin irritation is an important determinant of compliant HME use overnight.

Although our results suggest that coughing might reduce over time when the Luna HME and adhesive are used, the increase in reported coughing observed over

time during the UC period indicates that there are other study-specific factors involved. There is currently no satisfactory explanation for these observed trends, but compliant HME use might be a factor.

Compliance has been defined in this study based on HME use described previously.¹² Some of the subjects in this study used a bib at baseline and occasionally during the test period. Bibs may be used by laryngectomies because of the limited availability or insufficient reimbursement of HMEs. However, the HME properties of bibs crucially depend on their proper use because air leaks diminish their efficacy.^{18,26}

At the conclusion of the study, 57% (n = 26) indicated to continue using the Provox Luna system. The 43% (n = 20) who were indicated not to further use it mentioned that they perceived no advantages or that they disliked changing the adhesive more often. Difficulty in and issues with frequency of replacement have been described in several other HME studies.^{20,27}

Although previous works have indeed correlated improvements in pulmonary outcomes to categorical improvements in duration of HME use,^{11,20} this study is novel in that it evaluated the specific duration of HME use per day in hours. This allowed for better characterization of compliance outcomes. Historically, there has been variability in the definition of compliant or adherent use.^{11,27} This may have contributed to large range of reported non-compliance rates in using HMEs from 48% to 82% of

subjects.^{11,20,21} This clinical investigation employed compliant use as defined by ≥ 20 hours per day in ≥ 24 days in the 28-day period as previously described.^{12,13} This was determined as an acceptable and achievable duration of daily use after compensating for daily/weekly activities that may commonly limit compliance.

Owing to the randomized crossover trial design of the study, the subjects were their own controls, thus allowing for meaningful comparison of compliance and preferences of the subjects between the two periods. Subsequent analysis of the order of randomization revealed no significant impact on all observable outcomes, suggesting that the study design was appropriate for the comparative assessment of HME use. Furthermore, long-term conclusions are difficult to draw from the short follow-up interval.

By comparing compliance in the two arms of the study in which one arm testing a new product during the night, the compliance in patients usually not wearing an HME during the night automatically increases. This might be a flaw in the design. Also, receiving weekly follow-up and stressing the compliant use creates a situation with an artificially increased compliance. The compliance reported at baseline, observed during the usual care period of 76%, is higher than previously reported in the literature.^{11,20,21} This may have resulted from the increased subject education in the participating centers where the importance of HME use is stressed. HME use during a subject's UC period in this study may not reflect their baseline, and reporting bias may be present. Results on compliance of this study must therefore be interpreted with caution.

CONCLUSION

This multicenter randomized crossover trial compared compliance and the dermatological and pulmonary outcomes of adding the Provox Luna system during the night to UC in laryngectomized subjects. Significant improvements in compliance, hours of HME use per day, and skin improvement overnight were observed with the Luna. More than half of the patients wanted to continue using the Luna. The Provox Luna system is a viable additive to a subject's UC, especially in the setting of compliance concerns and in subjects who desire dermatological relief overnight.

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