Medical devices for airway patient

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Medical devices for airway patients

A clinical evaluation of new products and techniques

Bertram J. de Kleijn

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A clinical evaluation of new products and techniques

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Content

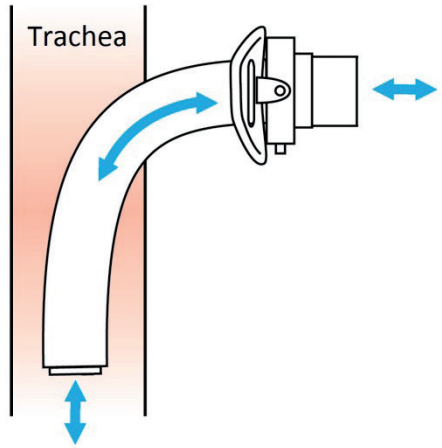
General Introduction

A medical device is any instrument or device, any substance or any other article intended by the manufacturer to be used in or on humans to detect, treat, or alleviate diseases or disabilities, or to prevent disease, and which does not achieve any of its primary intended purposes through chemical action within or on the body.[1]
As becomes clear from the definition of medical devices stated above, a medical device can be a lot of things. An intravenous catheter, ECG machine, limb prosthesis, cochlear implant, adhesive or tracheal cannula are just some examples. In this thesis several relatively new medical devices used for airway management in ear, nose, throat (ENT) patients are tested. Two speaking valves are tested in different studies, one for patients after tracheotomy (ProTrach® DualCare™) and one for laryngectomized patients (Provox® FreeHands FlexiVoice™). In the third study a peristomal adhesive, the Provox® StabiliBase OptiDerm™ for laryngectomized patients is tested. The forth study shows the use of 3D techniques to design custom-made airway cannulas for patients with aberrant anatomy. The fifth study compares two methods to perform a tracheotomy: surgery or by using a medical device. The sixth and final chapter describes the process, pitfalls and lessons learned after conducting a multicenter study of the ProTrach® DualCare™.

1. ProTrach® DualCare™

A tracheotomy is a procedure to create an opening in the trachea. It can be performed for different reasons, i.e. benign or malignant upper airway obstruction or in case of need for mechanical ventilation for more than 10-14 days.[2] After a tracheotomy, an airway cannula is placed to keep the tracheostoma open. An airway cannula provides a safe and well-tolerated airway, giving access for bronchial lavages, facilitating faster weaning from the ventilator and decreasing the risk of pneumonia caused by long term ventilation.[3]
After a tracheotomy the patient loses his or her upper airway function and the ability of normal speech because the airflow passes through the cannula directly into and out of the trachea (figure 1). The upper airway consists of the nose, mouth and pharynx. When a person breathes through his or her nose, resistance of the nares and the inside of the nose will cause turbulence of the airflow. The air swirls past the mucosa, humidifying, warming and filtering the inhaled air. When a tracheotomy is performed and a patient breathes through the tracheostomy, the function of the upper airway is lost. To compensate for this loss, a Heat and Moisture Exchanger (HME) has been created. An HME is basically a coated sponge, it can be placed in front of the tracheostomy opening and is designed to substitute the loss of the upper airway function. When air is exhaled, it is moist and warm from mucosal contact in de lungs. The HME can preserve some of this heat and moist for the next inhalation, so that the inhaled air is warmed, humidified and filtered.[4-6] The use of an HME reduces coughing, mucus production, forced expectoration and respiratory infections.[7-10]

Figure 1: Airflow after tracheotomy, direction of the air is shown by the blue arrows.



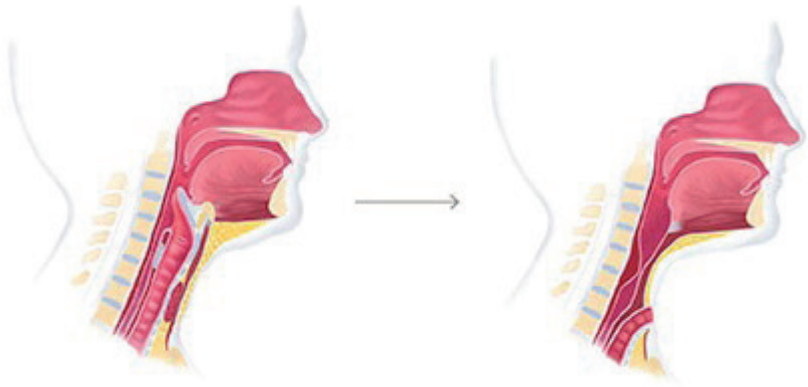
Besides the loss of upper airway function, normal use of the vocal cords is lost after a tracheotomy. As a tracheostomy opening is positioned below the larynx, the vocal cords are bypassed. To be able to speak, a patient needs to occlude the cannula while exhaling. This redirects the air through the vocal cords. The cannula can be occluded by obstructing the airflow with a finger or by pressing on an HME. To aid patients, hands-free speaking valves have been developed. These open when a patient inhales, providing a free airway, and close when a patient exhales, redirecting the air through the vocal cords.
The ProTrach® DualCare™ is a device combining a hands-free speaking valve and a functional HME, it was developed by Atos Medical (Hörby, Sweden). As the function of the HME is dependent on exhaled air it is not conditioned when a speaking valve blocks the exhaled air. The DualCare™ is unique as it is currently the only device implementing a fully functional HME (in HME mode) and speaking valve (in speaking mode) in one device.

2. Provox® FreeHands FlexiVoice™

A total laryngectomy is a procedure performed for advanced or recurrent laryngeal and hypopharyngeal malignancies. During this procedure the larynx is removed, an airway stoma is created in the neck and the alimentary tract is separated from the respiratory tract (figure 2).[11] Comparable with the situation after a tracheotomy, patients lose the upper airway function and ability to speak. Different from a tracheotomy the larynx and thus the vocal cords are removed, thereby permanently separating the upper and lower airways. To facilitate speaking, a tracheoesophageal puncture is performed after which a voice prosthesis can be placed. This prosthesis prevents food or liquids to pass to the trachea but allows air to flow from the lungs to the esophagus, facilitating pulmonary-driven speech.[12] After the placement of a voice prosthesis,

air can be redirected to the esophagus by occluding the stoma with a finger or HME. Mucosal vibrations produce a sound which can be used for speech. An airtight occlusion of the stoma is needed to have the best possible quality of pulmonary-driven speech. Specialized HMEs make the occlusion easier, improving speech quality and thus compliance rate with an HME.[13] Comparable with tracheotomized patients, a speaking valve can also be used to redirect the air. Different from the speaking valves used for tracheotomized patients, these devices use a flexible membrane that stays open during normal breathing. When a patients wants to speak, the natural increase in air pressure will close the valve.[14,15] Speaking valves for laryngectomized patients have been around for decades.[15-17]

Figure 2: Anatomy before and after laryngectomy (Courtesy Atos Medical)



Before total laryngectomy.

After total laryngectomy.

Similar to tracheotomized patients the loss of upper airway can be compensated by continuously using an HME, preventing pulmonary problems.[18-20] In 2003 the Provox® FreeHands HME™ (Atos Medical, Hörby, Sweden) was introduced. Similar to the ProTrach® DualCare™ it was the first automatic speaking valve with an integrated HME.[14]

The FreeHands HME™ had a low compliance rate (19% of patients used it on a daily basis and 57% only on special occasions) due to unpredictable fixation of the adhesive to the peristomal skin.[21] This is a problem for all automatic speaking valves connected to a peristomal adhesive. It is problematic to have a long-lasting seal of the adhesive while using an automatic speaking valve because the air pressure needed to speak pushes the adhesive loose from the skin. [21]

To improve compliance and user friendliness, a new automatic speaking valve, the Provox® FreeHands FlexiVoice™ (Atos Medical AB, Hörby, Sweden), was designed. Similar to the ProTrach® DualCare™ the FreeHands FlexiVoice™ has two modes: a speaking mode and an HME mode. In the Flexivoice™ these modes reduce the air pressure needed to close the membrane by using

more flexible membranes compared to other speaking valves. To prevent the membrane from closing while breathing, the membrane can be fixated in HME mode. To increase the durability of the adhesive more there is also an option to occlude the FlexiVoice™ manually, providing a relieve of pressure on the adhesive. These unique features are expected to improve patient satisfaction, compliance with an HME and adhesive device life.

3. Provox® StabiliBase OptiDerm™

As discussed above, the peristomal adhesive is an important aid for laryngectomized patients. It is one of the most commonly used devices to provide a placeholder for an HME or a speaking valve in front of the stoma. As every tracheostoma has a different shape, there is a wide variety of peristomal adhesives available.[22-24]

The Provox® StabiliBase™ (Atos Medical AB, Hörby, Sweden) is an adhesive that provides an anatomically shaped conical base with high stability. A study by Hilgers et al. showed patients prefer the StabiliBase™ over their normal adhesive and the StabiliBase™ had a significantly higher device life. Especially patients with a deep tracheostoma found the StabiliBase™ more comfortable.[23]

Some patients experience skin irritation with the standard adhesive material of the StabiliBase™. Therefore, the design of the StabiliBase™ was combined with the more skin-friendly hydrocolloid adhesive used in the Provox® OptiDerm™. This new product is called the Provox® StabiliBase OptiDerm™. It is designed to provide patients with the high stability of the StabiliBase™ while reducing skin irritation.

4. Using 3D techniques to design custom-made airway cannulas

After a tracheotomy, an airway cannula is placed to keep the tracheostoma open. Usually this is a standard, commercially available cannula with fixed curvature, radius, size and diameter. In most cases, these cannulas are sufficient. However, in patients with aberrant anatomy, normal commercially available cannula can cause discomfort. Over time, suboptimal placement may lead to inflammation of the tracheal mucosa, granulation tissue formation, airway obstruction and even fatal complications.[25]

Normally the choice of the cannula is based on availability and expertise of the surgeon. In case of an aberrant anatomy, this process is difficult. In these cases the positioning of the cannula tip can be checked by using an endoscope, but the outcome of this assessment is subjective and dependent on the expertise of the surgeon. To aid the process of optimal cannula placement, pre-operative visualization and 3D reconstruction of the upper airway could hypothetically aid in the

surgical planning of the tracheotomy site and choice of cannula post operatively. Furthermore, 3D techniques can be used to design custom-made cannula to guarantee an optimal fit and reduce complications.

5. Surgical versus percutaneous dilatation tracheotomy

As stated before, a tracheotomy is a surgical procedure to create an opening to the trachea. A tracheotomy is traditionally created surgically. In 1969 a Seldinger or 'over the wire' technique was developed to create a tracheostoma by percutaneous dilatation.[26] This technique is used on Intensive Care Units all over the world. It is a safe technique for stable patients without anatomical abnormalities and, as it is a bedside procedure, it implies lower cost and a quicker procedure compared to surgery.[27,28]

There is a disagreement in literature about short term complications of Percutaneous Dilatation Tracheotomy (PDT), showing lower, higher or the same rate of short term complications.[29-32] After tracheotomy, a possible long term complication is tracheal stenosis. This is a serious complication that can lead to discomfort and possible need for re-surgery. Only few articles have compared long term complications of PDT compared to surgical tracheotomy.[33-35] During a PDT, pressure is needed to dilate the trachea. There is an assumed higher risk of fracturing a tracheal ring, potentially leading to tracheal stenosis.[36,37] A comparative study is presented to determine if there is a higher short term and long term complication rate in PDT.

6. Multicenter study ProTrach® DualCare™

The ProTrach® DualCare™ presented in chapter 1 was tested in a multicenter study. The aim of the study was to determine patient preference compared to the device patients normally used. The DualCare™ is the only speaking valve for tracheotomy patients implementing a fully functional HME (in HME mode) and speaking valve (in speaking mode) in one device. It is expected to give a higher quality of life and thus have a higher patient preference. Chapter 6 describes the pitfalls of conducting a multicenter study and lessons learned.

Scope of this thesis

The objective of this thesis is to analyze medical devices used for airway patients. Main outcome measures are patient satisfaction, patient preference and/or complication rate. It gives insight in the usability, safety and feasibility of several new and older medical devices.

In this thesis, several new medical devices developed by Atos Medical (Hörby Sweden) are studied. In **chapter one** a single center prospective feasibility study to determine quality of life, pulmonary rehabilitation and patient satisfaction of the DualCare™ is presented. **Chapter two** shows a multicenter prospective study to evaluate the feasibility of the FlexiVoice™. In **chapter three** of this thesis the Provox® StabiliBase OptiDerm™was tested in a 2 × 2 crossover prospective multicenter clinical trial.

The **fourth chapter** in this thesis shows a three-step study to analyze the added value of pre- and post-operative visualization and 3D techniques for planning of the tracheotomy and developing a custom designed cannula. The **fifth chapter** of this thesis shows a single center retrospective comparative study of PDT versus surgical tracheotomies comparing short term and long term complications. In **chapter six** the process of conducting a multicenter follow up study of the DualCare™ is presented.

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Chapter 1

Clinical feasibility study of a new Speaking Valve with heat and moisture exchanger for tracheotomized patients (ProTrach® DualCare™)

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Abstract

Objective: The aim of this study was to evaluate the clinical feasibility of the ProTrach® DualCare™ (Atos Medical, Hörby, Sweden), a device combining a hands free speaking valve and a Heat and Moisture Exchanger (HME) for tracheotomized patients.

Study Design: A non-randomized, prospective single center feasibility study.

Methods: 16 adult tracheotomized patients were included. Participants were asked to test the DualCare™ for two weeks, while continuing their normal activities. After these two weeks, participants could choose whether or not to take part in the long-term evaluation. The EuroQOL-5D, Borg scale and questionnaires on speaking, pulmonary function and patient preference were used. During the long term evaluation, a minor redesign was implemented and all participants were asked to test the new device again for one week, with a potential long term evaluation. Eleven decided to participate.

Results: The device was well-tolerated. Speaking noise was reduced (p=0.020) and speech was considered to sound more natural compared to previously used devices according to the users (p=0.020). Overall 11 participants preferred the DualCare™ to their standard device. No serious adverse events were reported.

Conclusion: Overall 11 of 16 participants preferred the DualCare™ to their standard speaking valve or HME. Users of the DualCare™ were able to use hands free speech with the benefits of an HME and the device was considered clinically feasible and has the potential to improved quality of life of tracheotomized patients.

Key Words: ProTrach® DualCare™, Speaking valve, HME, hands free, tracheotomized

Level of Evidence: 2b

Introduction

The upper airways humidify, warm and filter inhaled air. When a tracheostoma is created, upper airways are bypassed. A Heat and Moisture Exchanger (HME) substitutes the loss of the upper airway function by conditioning incoming air with the moist and heat of expiratory air.[1-3] The use of an HME is known to reduce mucus production, coughing, shortness of breath, forced expectoration, stoma cleaning and respiratory infections.[4-7]

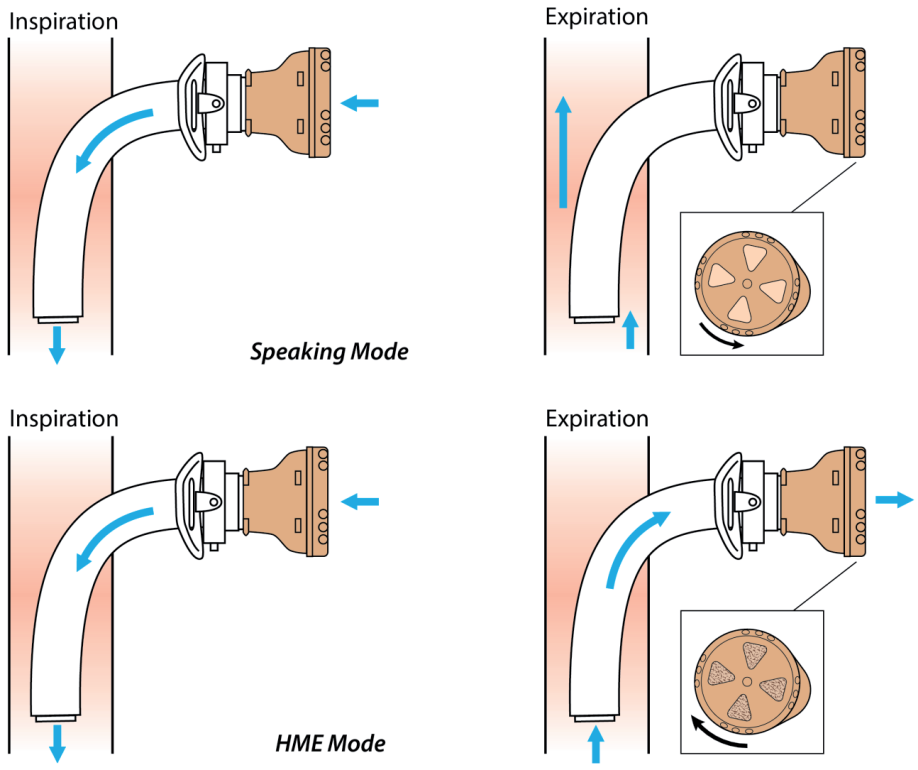
To speak, a tracheotomized patient needs to redirect the air through the vocal cords by occluding the tracheostomy tube. This can be done by occluding the opening of the tube with a finger or by pressing on an HME. A hands-free speaking valve can also be used to enable hands free speech. Being able to speak hands free is important as it facilitates non-verbal communication and the use of both hands simultaneously with speaking. Also, patients do not emphasize their handicap by pointing at the stoma as is done when using a finger to occlude the stoma. A hands free speaking valve can also reduce secretions and improve olfaction.[8] Some studies reported reduced aspiration as well.[9-12] Others didn't find reduced aspiration.[13,14]

To compensate for the loss of upper airway function and the loss of normal voice in tracheotomized patients, the ProTrach® DualCare™ was developed, a device combining a hands-free speaking valve and an HME. Before the development of the DualCare™, patients had to choose between using an HME or a hands-free speaking valve. There are other speaking valves with an incorporated HME.[15] However in these devices there is no bi-directional flow and thus the HME is not conditioned.[15] The DualCare™ combines a speaking valve and a fully functional HME in one device using two modes; the speaking mode and the HME mode. The airflow in both modes is shown in figure 1. In speaking mode the membrane functions as a bias-closed speaking valve. This means the membrane is closed and opens only during inhalation. The HME is not conditioned in this mode, comparable with the other devices. When the HME-mode is activated by turning the lid of the DualCare™ (figure 3), the membrane is slid away from the openings. Air can flow in and out through the cannula, conditioning the HME with the exhaled air.

Van den Boer et al compared several speaking valves with integrated HME in an ex vivo study. They concluded no speaking valve offers humidification function in speaking mode. The ProTrach® DualCare™ is the only speaking valve offering an HME mode, enabling a significant increase in humidification.[15]

Combining both features in one device is expected to improve compliance with an HME (in hands free speaking valve users) and thereby enhancing quality of life by improving pulmonary rehabilitation, and patient satisfaction by using a hands-free speaking valve (in HME users). This study was conducted to determine the clinical feasibility of the ProTrach® DualCare™, leading to a re-design in the process.

Figure 1: DualCare™ in speaking mode and HME mode (courtesy Atos Medical)

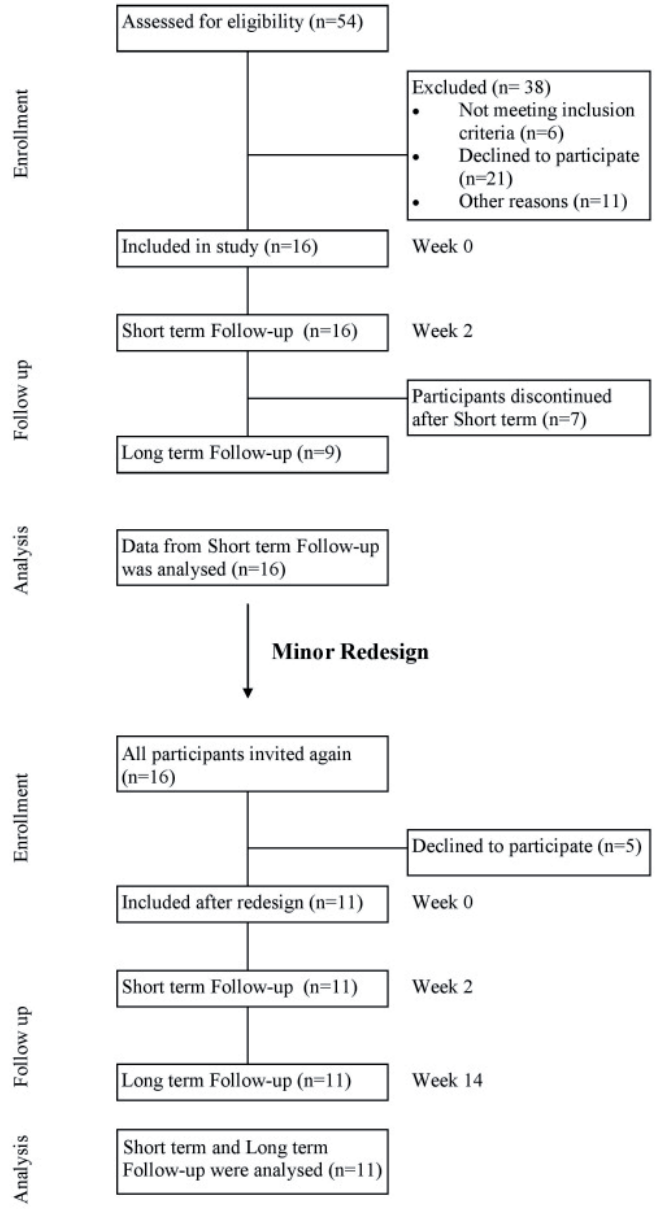


Materials and methods

Participants

This study was performed at the University Medical Center Groningen. Inclusion criteria were: at least 18 years old, tracheotomized, spontaneously breathing and able to use a speaking valve. Exclusion criteria were: inability to operate and remove the device, mechanical ventilation, severe aspiration, tidal volume of less than 100ml, laryngectomized patients, severe upper airway obstruction, or thick and copious mucus production. The inclusion process is shown in figure 2. The study took place from September 2013 to April 2014.

Figure 2: Inclusion process



Investigational product

The ProTrach® DualCare™ (ATOS Medical, Hörby, Sweden) consists of two parts. A re-usable speaking valve and a disposable HME (figure 3).

Figure 3: From top to bottom: Assembled DualCare™, Twisting function of DualCare™, 22mm and 15mm HME

The DualCare™ Speaking Valve must be assembled to the HME Cassette. The HME is available for 22 mm and 15 mm diameter connectors. The humidification properties and air pressure drops are the same for both HME sizes.

Ethical considerations

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen. Signed informed consent was obtained from all participants. The study was monitored for patient safety and data validation.

Methods

The ProTrach® DualCare™ was compared to the pre-study device(s) (speaking valves and/or HMEs) used by the participants. Structured, study-specific questionnaires were completed by the participants at the start of the study and after two weeks of using the new device with the 15 and/or 22mm HME, and after the optional long-term evaluation of 3 months. The period of 3 month was chosen as earlier reports have shown significant changes in airway function are seen from the use of an HME after this period of time.[16]

During the long-term evaluation, it was discovered that some patients had issues with stickiness of the valve (n=4). This was successfully addressed by a slight redesign.

At the time of the redesign, nine out of sixteen patients were still included in the long-term part of the study. All sixteen participants were asked if they were interested in trying the redesigned valve. The

nine patients still in the study and two patients that had discontinued after the short-term evaluation agreed to do so. With these eleven patients, the study was started again, with a one week short-term follow-up, and an optional long-term evaluation of 3 months. After the first week, data that could potentially have been influenced by the new design were collected again and replaced the earlier collected data. This was data on breathing resistance, HME function, swallowing, smell and patient satisfaction. Other data that were collected prior to redesign are still considered valid.

Only participants testing the final version completed the long-term questionnaire at 3 months. Questionnaires addressed speaking, swallowing, coughing, mucus production, breathing, sleeping, olfaction, appearance, satisfaction, practical aspects, and handling of the device. Answers were reported on a 3 or 5 point Likert scale or were quantitative. To determine overall satisfaction a scale from 1 to 10 was used.

The EuroQOL-5D was used to assess influence on general Quality of Life.[17] This is a multilingual validated instrument in which scores on five health care dimensions (mobility, self-care, daily activities, pain/discomfort and anxiety/depression) are recorded.[17] From this data, a balanced health care index is derived in accordance with the EuroQOL guidelines.[18]

Borg scales were used to investigate impact of the device on breathing. The Borg scale is an ordinal scale ranging from 0 to 10 on which participants indicate their currently perceived breathing exertion.[19]

Analysis

Frequencies were explored using the Kolmogorov-Smirnov test. Normal distributed frequencies are shown as the mean ± standard deviation and were analyzed using the paired T-test. Non-parametric values are presented as the median [inter quartile range] and were analyzed using the Wilcoxon-Signed rank test. Questions using a Likert Scale rendered ordinal data. These data were analyzed using the Wilcoxon Signed Rank test. The Borg scale outcomes are categorical and are shown as median [inter quartile range]. Comparative questions were completed after using the DualCare™. Because these are one sample ordinal data, the One Sample Wilcoxon Signed Rank test was used to analyze these data. The median compared to was 2 (neutral).

Results

16 tracheotomized participants were entered into the study, 11 males and 5 females. Before the study, 11 participants used a speaking valve during the day. Six participants used an HME (sometimes changing between an HME and speaking valve). One participant used no device at all. During the night 13 participants used an HME and 3 participants no device (table 1). The age of participants ranged from 34 to 83 with a mean of 58.5 years old. The indications for tracheotomy were tracheal stenosis (3), laryngeal paralysis (8) and laryngeal stenosis by respiratory papillomatosis, edema, trauma or Myasthenia Gravis (5).

Table 1: Device use at baseline

Participant	Age in years	Time between tracheotomy and study	Pre study HME day	Pre study Speaking valve day	Pre study device night	Tested re-design
1	58	2 years	FreeVent Combi*	FreeVent Combi	TrachPhone	Yes
2	64	5 years	FreeVent Combi*	FreeVent Combi	Provox XtraFlow	No
3	66	5 years	Provox Xtraflow	None	None	Yes
4	74	2 years	FreeVent Combi*	FreeVent Combi	Xtramoist	No
5	34	5 years	Provox Xtraflow	FreeVent Combi	Provox Xtraflow	Yes
6	63	7 years	TrachPhone	None	TrachPhone	Yes
7	43	1 year	Provox Xtraflow	None	Provox Xtraflow	Yes
8	50	1.5 years	FreeVent Combi*	FreeVent Combi	Provox Xtraflow	Yes
9	44	11 years	None	None	None	Yes
10	53	11 years	Provox Xtraflow	None	Provox Xtraflow	No
11	66	10 years	FreeVent Combi*	FreeVent Combi	Provox Xtraflow	Yes
12	62	9 years	None	Freevent	None	Yes
13	83	1.5 years	FreeVent Combi*	FreeVent Combi	Provox Xtraflow	No
14	51	1 year	Spiro*	Spiro	Provox Xtraflow	Yes
15	73	5 years	Provox Xtraflow	Freevent Combi	Provox Xtraflow	Yes
16	52	2 years	FreeVent Combi*	FreeVent Combi	Provox Xtraflow	No

*HME in these devices is not functional as no inspired air flows through the device, the HME is therefore not conditioned.

Sixteen participants completed the short term part of the study. Nine participants decided to continue in the long-term follow-up. At this stage, a redesign was implemented after which 11 out of the original 16 participants decided to continue in the study. Only the questions relevant after redesign were completed again and replaced the earlier answers. Therefore, some answers will have an N of 16 while others have an N of 11. Regarding the device itself, results show that 13 of the 16 participants (81%) liked the option to choose between HME and Speaking mode and this functionality was used by all participants. At the end of the study, participants switched between modes with a median of 30 times per day [range 8-40]. The median amount of hours the product was used in speaking mode was 7.5 [range 4.0-12.0] and in HME mode median 6.0 [range 3.0-7.5]. When the DualCare™ was not used, mainly during the night, most participants used their regular HME.

When comparing the DualCare™ to the device they were using before the study, participants reported significantly less stoma pain (p=0.046), significantly better voice and speech sound (p=0.020), significantly less noise during speech (p=0.020), significantly less noise when breathing in HME and speaking mode (p=0.014 and p=0.025, respectively) and a significantly more natural sounding voice (p=0.034).

Table 2: Results Borg Scale

	Subgroup	Borg scale
Baseline (n=11)*	Total	2.0 (0.00-2.50)
	HME users (n=5)	2.0 (0.75-2.75)
	Speaking valve users (n=5)	0.0 (0.00-2.00)
Final version DualCare™ (n=11)	In HME mode	0.5 (0.00-1.00)
	In Speaking mode	1.0 (0.50-3.00)

*1 patient did not use any device at baseline

For breathing, different questions were completed. Breathing exertion was scored using the Borg scale. Results show that breathing in HME mode is significantly easier than breathing through the device used before the study (p=.006). Not surprisingly, breathing through the HME mode is also significantly easier than breathing through speaking mode (p=.017). Results were confirmed when participants were asked to compare breathing resistance in HME mode and speaking mode with breathing resistance of their pre-study device using the Borg scale. (Table 2)

When comparing to the device they were using before the study, participants reported lower breathing resistance with the DualCare™ in HME mode (p=0.034, n=15) and higher breathing resistance in Speaking mode (p=0.020, n=15).

Participants were also asked if they experienced shortness of breath when climbing stairs, when walking on level ground and when resting. Significantly less shortness of breath was reported while climbing stairs with the DualCare™ compared to the pre-study device (p=0.011, n=11).

When participants were asked about breathing, coughing and mucus, two significant results were found: less discomfort breathing dry air (n=16, p=0.031) and less dry coughs during the night when comparing the DualCare™ to the pre-study device (n=16, p=0.039).

The EuroQol-5D was completed at the start of the study using the pre-study device and the DualCare™. Index scores and VAS score for the pre-study device and the DualCare™ are displayed in Table 3. No significant differences were found.

Table 3: EuroQOL 5D Mean index scores and mean VAS scores

	Pre-study device (N=11)	Final DualCare™ 3 month follow-Up (N=11)
Mean Index scores (SD)	0.72 (0.26)	0.76 (0.21)
Mean VAS (SD)	71 (15)	68 (20)

Participants were asked to describe their experiences in free text. The main advantages that were reported for the DualCare™ were: voice quality, ‘more air’ or easier breathing, less noise, and

ability to combine two devices in one. The main disadvantages reported for the DualCare™ were: leakage around the cannula when in speaking mode (compared to pre-study HME); sometimes the device loosening from cannula while coughing; not being able to speak immediately when in HME mode, and the breathing direction being straight forward (an HME has side openings for breathing).
All 11 participants testing the final (=actual) device preferred the DualCare™ to their pre-study device. This is 69% of the original inclusion.

Discussion

After redesign, the ProTrach® DualCare™ proved to be clinically feasible. Overall 69% preferred the final (=actual) design of the DualCare™ to their pre-study device. This is 100% of the participants testing the redesigned device. Most participants liked the possibility to switch between the speaking and HME mode and used this modality consistently. Switching between modes will increase the hours of HME use per day, which can positively influence pulmonary rehabilitation. The fact that patients had less problems breathing in dry air and had less dry coughs per night confirm this positive effect. In this study no changes in quality of life and no differences in mucus production, coughing, shortness of breath or forced expectorations were found. The use of an HME is expected to reduce mucus production, coughing, shortness of breath, forced expectoration and stoma cleaning.[4,5,16,20] This is associated with improvements in quality of life.[4,6,20] The lack of HME effects found in this study may thus be the reason no changes in quality of life were found. The lack of HME effects found may be explained by HME use by most participants before the study started, creating a smaller window of possible improvement.
Compared to the pre-study device the DualCare™ had a comparable or lower breathing resistance. Prigent et al. compared several speaking valves in 10 patients. This study showed mean Borg scale ratings from 1.6±2.2 to 4.6±2.6.[21] The HME mode of the DualCare™ was rated 0.5 'very, very slight', the speaking mode was rated 1.0 'very slight'. Considering this, the DualCare™ is on the lower end of breathing resistance of hands free speaking valves for tracheotomized patients. In HME mode the perceived breathing resistance drops to even lower values. This is also shown in the questions on shortness of breath during exercise, where participants indicated a lower breathing resistance in HME mode.
No differences were found in olfaction and swallowing when using the DualCare™ compared to the pre-study device. Studies have shown improvement of olfaction and reduced aspiration by increased subglottic pressure when tracheotomized patients used a speaking valve.[8,10,12,21] Others could not confirm reduced aspiration.[13,14] Some participants in this study already used a speaking valve prior to the study, which could reduce the found effect. Participants may have also used the DualCare™ in HME mode when eating or drinking, lapsing the benefits of using a bias-closed speaking valve.

With the DualCare™, participants indicated significantly better voice and speech sound, less noise during speech and a more natural voice. Also noise generated when breathing was less. As only participants who preferred the DualCare™ tested the final version of the device, these outcomes may be an important factor in preferring the DualCare™.
Compared to the pre-study device the satisfaction with the DualCare™, measured with a VAS score, was significantly better than the pre-study device. As only participants that chose to continue tested the final version of the DualCare™, this outcome may be biased. As stated above, no changes in quality of life were found in this study.
As this is a feasibility study, it had limitations. A small group of participants was included in the study, which may lead to bias and underestimation of effects. All the questions asked were analyzed using statistical tests and none of the outcomes were corrected. As 9 of the 11 participant that continued to test the redesign in long term follow up preferred the DualCare™ over their original device and the 5 participants preferring their original device over the DualCare™, didn't test the final design of the device, outcome measures based on the redesign of the DualCare™ may be biased. Finally all questions were based on participant experience therefore subjective to bias.
This study indicates that the DualCare™ can decrease breathing resistance, improve voice and speech sound, and improve HME compliance in tracheotomized patients. The switching function of the DualCare™ is used consistently. This will increase the hours of HME use per day, which can positively influence pulmonary rehabilitation. The fact that patients had less problems breathing in dry air and had less dry coughs per night confirm this positive effect. Patients can benefit from an HME while being able to employ hands-free speech with the same device. Overall 69% preferred the final (=actual) design of the DualCare™ to their pre-study device. This is 100% of the participants testing the redesigned device. After redesign, the ProTrach® DualCare™ proved to be clinically feasible.

Conclusion

The DualCare™ is well-tolerated, overall 69% of the participants preferred the DualCare™ over their pre-study speaking valve or HME. All participants testing the final design of the device preferred the DualCare™. No serious adverse events were reported in this study and no device deficiencies were registered after redesign. This study shows the DualCare™ is clinically feasible. To determine a significant difference in the patient preference a prospective study powered for that purpose is needed.

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Chapter 2

A prospective multicenter clinical feasibility study of a new automatic speaking valve for postlaryngectomy voice rehabilitation

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Abstract

Objective: Evaluation of short- and long-term clinical feasibility and exploration of limitations and advantages of a new automatic speaking valve (ASV) for laryngectomized patients with integrated HME, the Provox FreeHands FlexiVoice (FlexiVoice). This ASV not only enables automatic, but also manual closure of the valve.

Patients and methods: Multicenter, prospective clinical study in 40 laryngectomized patients. Participants were asked to use the FlexiVoice for 26 weeks. Primary outcome measure was long-term compliance. Secondary outcome measures were: patient preference, hours of FlexiVoice use, device life of adhesive, voice and speech quality, and quality of life.

Results: After 26 weeks 15 patients (37.5%) were using the FlexiVoice on a daily basis, for a mean of 12.64 hours/day (SD ± 5.03). Ten patients (25%) were using the device on a non-daily basis, for a mean of 3.76 hours/day (SD ± 2.07). The remaining 15 patients (37.5%) discontinued using the FlexiVoice. Sixty percent of the 25 long-term users applied both automatic and manual closure of the valve. Unpredictable fixation of the adhesive was the main reason for discontinuing or not using the FlexiVoice on a daily basis. Overall, 18 patients (45%) preferred the FlexiVoice, 16 patients (40%) their usual HME, 3 patients (7.5%) their usual ASV, 1 patient (2.5%) preferred no device at all, and in 2 patients preference was not recorded. The minor technical issues identified could be corrected.

Conclusion: The Provox FreeHands FlexiVoice appears to be a useful ASV, which allows for longer hands free speech in a larger proportion of laryngectomized patients in the present cohort. The additional manual closure option of the device is experienced as beneficial for longer maintaining the adhesive seal.

Keywords: Total laryngectomy, automatic speaking valve, heat and moisture exchanger, compliance, voice

Introduction

Total laryngectomy (TL) results in significant anatomical changes. The alimentary and respiratory tracts are separated and a permanent stoma is created in the neck[1]. To compensate for the loss of the voice box, currently primary insertion of a tracheoesophageal voice prosthesis is the gold standard for restoring pulmonary driven speech[2]. To compensate for the functional loss of the upper respiratory tract and to prevent and/or treat pulmonary problems, such as excessive coughing and mucus production, continuous use of heat and moisture exchanger (HME) has proven to be effective[3-5]. Speaking with a voice prosthesis requires airtight occlusion of the stoma with a finger in order to divert the pulmonary air into the pharyngoesophageal segment or neoglottis, where mucosal vibrations produce the sound for speech. Airtight stoma occlusion has become easier after the development of specialized HMEs, which improve maximum phonation time and dynamic loudness range and thus compliance rate[6]. However, with these HMEs, it is still necessary to use a finger to occlude the stoma for speech production. To overcome this drawback of tracheoesophageal speech and to obtain hands free speech, automatic speaking valves (ASVs) have been developed. These devices contain a flexible membrane that stays open during normal calm breathing, but closes through the natural increase in air pressure when speaking is initiated[7, 8]. Several ASVs are presently available. The first were the Blom Singer and Bivona tracheostoma valves in the eighties and nineties of the last century[8-10]. Later, several other valves became available, such as the Eska-Herrmann and ADEVA valves[11, 12]. In 2003, the Provox FreeHands HME (further called FreeHands; Atos Medical, Hörby, Sweden) was introduced, which was the first automatic speaking valve with an integrated HME for simultaneous pulmonary rehabilitation[7]. In a long-term (6 months) study, the success rate (defined as patients using this ASV on a daily basis) was 19%[13]. Additionally, 57% of patients in this study used the device on a non-daily basis at special occasions, such as during shopping or social activities[13]. The main reason for not using the FreeHands on a daily basis was the unpredictable fixation of the adhesive to the peristomal skin. This is the main drawback for all ASVs. For a considerable number of patients it can be problematic to obtain a good and long-lasting seal of the adhesive to withstand the pressure necessary for speaking[14-17].

In order to further improve patient friendliness and compliance of automatic speech a new automatic speaking valve was developed, the Provox FreeHands FlexiVoice (further called FlexiVoice; Atos Medical AB, Hörby, Sweden). This new ASV contains a renewed mechanism to lock and unlock the speaking membrane. The air pressure needed to close the membrane is lower than in the earlier FreeHands device, because the available membranes are more flexible. Moreover, there is a novel option to alternatively occlude the device manually: a front opening also allows speech through finger occlusion of the device, even when the membrane is locked, e.g. during physical exertion. Lastly, the coughing mechanism is adapted which also allows easy repositioning of the valve after coughing.

The objective of this prospective clinical study is to evaluate the short- and long-term feasibility of the FlexiVoice, in combination with the currently available attachments, and to explore its limitations and advantages.

Methods

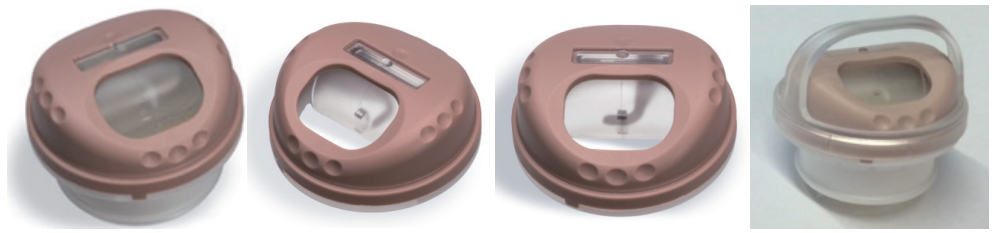
The study was carried out at two tertiary care cancer centers. Inclusion criteria were: TL, 18 years or older, use of a HME and/or ASV, use of a voice prosthesis irrespective of the voice quality, minimum of 3 months after TL and/or postoperative (chemo-) radiotherapy. Exclusion criteria were: inability to remove or operate the FlexiVoice, active recurrent or metastatic disease, inability to understand the patient information, to give informed consent, and/or to complete diaries. The study was performed according to the protocol approved by the institutional review boards and all patients were enrolled in the study between May 2014 and August 2014. Signed informed consent was obtained from all participants.

The FlexiVoice is shown in Figure 1 (left). It combines pulmonary rehabilitation using a HME, with voice rehabilitation using an ASV, which also facilitates manual occlusion. The device is attached in front of the stoma of a laryngectomized patient, who is using a voice prosthesis for speech. There are different attachment options for the subjects to choose from (various stoma adhesives, laryngectomy tubes and buttons). The base of the device is the HME cassette and the speaking valve is anchored on top of that HME cassette. The speaking valve has a front opening and an internal flexible membrane. When the patient starts to speak, the natural increase in exhalation airflow closes the membrane. The exhaled air is thus diverted through the voice prosthesis, which allows hands free tracheoesophageal speech. Alternatively, the patient can choose to occlude the opening in the front with his/ her finger to speak. Rotating the top of the device moves the FlexiVoice into the 'locked mode', or into the 'automatic speaking mode' (Figure 1; middle left). In 'locked mode', the membrane is prevented from closing with a hook grabbing a ring at the backside of the membrane (Figure 1; middle right). Thereby, the patient is ensured of unrestricted and comfortable breathing during physical exertion, still allowing manual occlusion for speech. There are three versions of the speaking valve, each with a different flexibility/strength of the membrane: light, medium and strong. When coughing is needed, the membrane pops out through the front opening and the patient can push the membrane back manually. There is an optional arch that can be attached on top of the device to prevent the front opening of being occluded by clothing (Figure 1; right).

After inclusion patients used the FlexiVoice for the duration of a maximum of 6 months. The primary objective was to assess long-term compliance, based on various aspects of the ASV

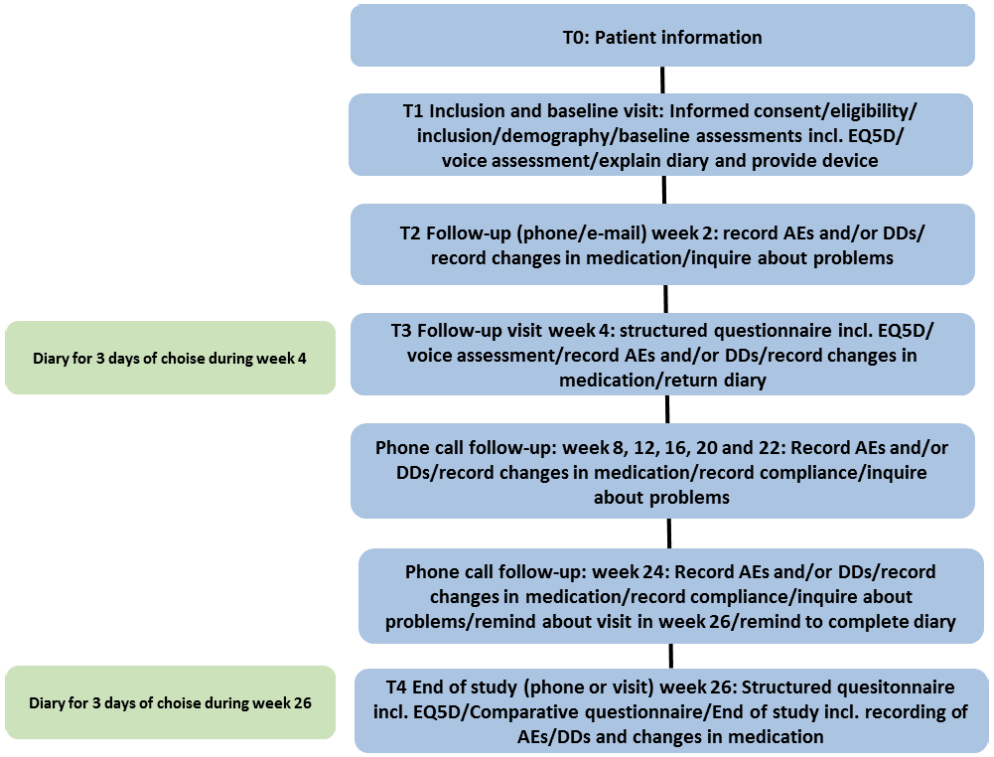
addressed in study specific questionnaires. Secondary outcome measures were: patient preference, hours of FlexiVoice use, device life of adhesive, voice and speech quality and quality of life. The questionnaires were completed at time of inclusion, after 4 weeks and after 26 weeks.

Figure 1: Left: Provox FreeHands FlexiVoice. The heat and moisture exchanger (HME) is attached and the flexible membrane is closed. Middle left: 'automatic speaking mode'. Middle right: 'locked mode': the patient can rotate the top of the device and the membrane is locked by a hook that grabs a ring at the backside of the membrane. Right: the arch is attached. It prevents the front opening being occluded by clothing (left 3 pictures by courtesy of Atos Medical)



The study specific questionnaires addressed use of adhesive, effort needed to speak, noises produced by the FlexiVoice, coughing mechanism, appearance, functioning of the membrane, use of the 'locked mode'/ 'automatic speaking mode', manual occlusion, device life of adhesive, voice quality, speech quality and intelligibility. Additionally, patients rated satisfaction regarding the FlexiVoice, their usual ASV/HME (if applicable), the device life of their adhesive, and their voice quality on a 10-cm Numeric Rating Scale (NRS) (0=worst and 10=best). Quality of life was assessed using the EuroQOL-5 Dimension-5 Level questionnaire (EQ5D5L). This instrument is validated using scores in five health-care dimensions (mobility, self-care, daily activities, pain/discomfort and anguish/ depression) and a 100-mm VAS[18]. Voice and speech quality assessment consisted of reading a text, numbering breathing pauses, maximum phonation time (vowel /a/ and counting) and dynamic loudness range (with calibrated decibel meter). During the study period patients kept a diary twice for 3 days in the week before each follow up visit to record daily hours of FlexiVoice use. At the end of the study patients were asked to complete comparative questionnaires. Patients were asked to compare the FlexiVoice with the usual ASV and/ or HME and to answer questions regarding preference and future use. Patients were contacted by telephone two weeks after inclusion, and at monthly intervals until 26-weeks follow up. If needed, additional practical support from the speech pathologist or the study coordinator was offered. Figure 2 provides an overview of the study design.

Figure 2: study flowchart



Statistics

As this was deemed to be an uncomplicated feasibility study in patients familiar with the use of peristomal adhesives and HME devices and no risks associated with participation in the study were expected, the drop-out rate was estimated to be <5%. Statistical analyses were conducted using IBM® SPSS® 22.0. Frequencies were explored using the Kolmogorov-Smirnov test. Parametrically distributed data is shown as mean ± standard deviation and analyzed using the paired T-test. Non-parametrical data are presented as median (inter quartile range) and were analyzed using the Wilcoxon-Signed rank test. The Likert Scales rendered ordinal data from three related samples. This data was analyzed using the Friedman test. If the groups differed significantly a Wilcoxon-Signed rank test was used to determine which groups were different. A p-value <0.05 is considered significant.

Results

Table 1:. Patient characteristics

Characteristics	Value	%
Gender		
Male	36	90.0
Female	4	10.0
Age at TL	Mean 56.3 years (SD±9.4)	
Age at entry	Median 63.5 years (SD±8.91)	
Post-TL	Median 74.5 months (range 3-317 months)	
TL		
Standard	32	80.0
+ Reconstruction	6	15.0
Gastric pull up	1	2.5
Information missing	1	2.5
Radiotherapy		
No	1	2.5
Preoperative	30	75.0
Postoperative	9	22.5
ASV use		
No	27	67.5
Only ASV	1	2.5
ASV + HME	12	30.0
Experience with ASV		
No	6	15.0
Yes	32	80.0
Information missing	2	5.0

Abbreviations: TL = Total Laryngectomy, ASV = Automatic Speaking Valve, HME = Heat and Moisture Exchanger

In total, 41 laryngectomized patients were entered in the study, 21 in the one and 20 in the other institute. One patient subsequently had to be excluded from the study and further analysis, because the language barrier was larger than anticipated, and he did not understand the patient information. This left 40 patients, 36 males and 4 females, for analysis. Patient demographics and clinical information are provided in Table 1. At baseline, 27 patients were not using an ASV (67.5%), 12 patients were using an ASV in combination with a HME and (30%) 1 patient was using only an ASV (2.5%), also during the night (all ASVs were the FreeHands[7]). Of those 13 ASV users (32.5%), 8 patients were using the ASV on a daily (20%) and 5 patients on a non-daily basis (12.5%). Of the 27 non-users, 19 (70% did have experience with an ASV before entering the

study and 6 (15%) did not (data in 2 patients was missing). Most ASV users were using one of the 'stronger' adhesives, such as the Provox StabiliBase adhesive (Atos Medical AB, Hörby, Sweden). The self-reported median device life of the adhesive was 19 hours (range 1-168) when using an ASV (n=12; data in 1 patient was missing). Patients' satisfaction regarding adhesive device life when using the ASV was rated 7.16 on a scale 1 to 10 (NRS; SD ± 2.35; n=11). This information was missing in 2 patients. For the non-ASV users the median device life of the adhesive was 24 hours (range 6-168 hours; n=26, data missing in 1 patient).

Assessment at 4-weeks

At 4-weeks follow-up, 36 patients were still in the study, and 4 patients had stopped using the FlexiVoice. Nineteen of the original 40 patients (47.5%) used the FlexiVoice on a daily basis, for a mean of 10.87 hours/day (SD ± 4.67; n=18; missing data in 1). Seventeen of the original 40 patients (42.5%) used the FlexiVoice on a non-daily basis, for a mean of 6.82 hours/day (SD ± 6.12; missing data n=1). The reasons for not using the FlexiVoice on a daily basis are shown in Table 2. Most common were unpredictable fixation of the peristomal adhesive (n=3) and familiarity of the usual HME/ASV (n=3). Furthermore, for the 4 patients, who discontinued between inclusion and 4-weeks follow-up reasons given are also summarized in Table 2.

Assessment at 26-weeks

At 26-weeks, 25 patients still used the FlexiVoice, whereas the remaining 11 patients had discontinued its use. Fifteen of these 25 patients (37.5% of the original 40 patients) used the FlexiVoice on a daily basis, for a mean of 12.64 hours/day (SD ± 5.03; n=14; missing data n=1). Ten patients (25% of the original 40 patients) used the device on a non-daily basis, for a mean of 3.76 hours/day (SD ± 2.07; n=6; missing data n=4). Type of surgery (standard TL versus pharyngeal reconstruction) did not influence ASV use. Unpredictable fixation of the adhesive was the main reason (n=4) for not using the FlexiVoice on a daily basis at 26-weeks follow-up. All reasons are shown in Table 2, as well as the reasons for discontinuing between 4 and 26 weeks. Actual FlexiVoice use in the 10 non-daily users was: 5-6 days/week (n=1), 3-4 days/week (n=4), 1-2 days/week (n=2), 1-2 days/month (n=1), and less than once per month (n=2). Occasions when using the FlexiVoice in this non-daily user group are also given in Table 2.

Thus, in total 15 patients decided to end the study earlier than planned, of whom 2 patients did use an ASV at baseline (and went back to that) and 13 patients, who did not use an ASV at baseline. An overview of patient numbers, compliance and rates regarding hands free speech at different moments in de study is given in Figure 3 and 4.

Figure 3: Flowchart patient compliance

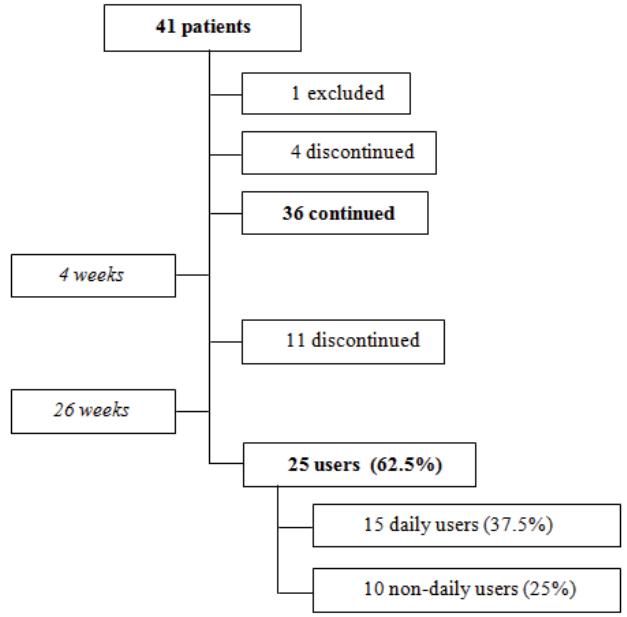
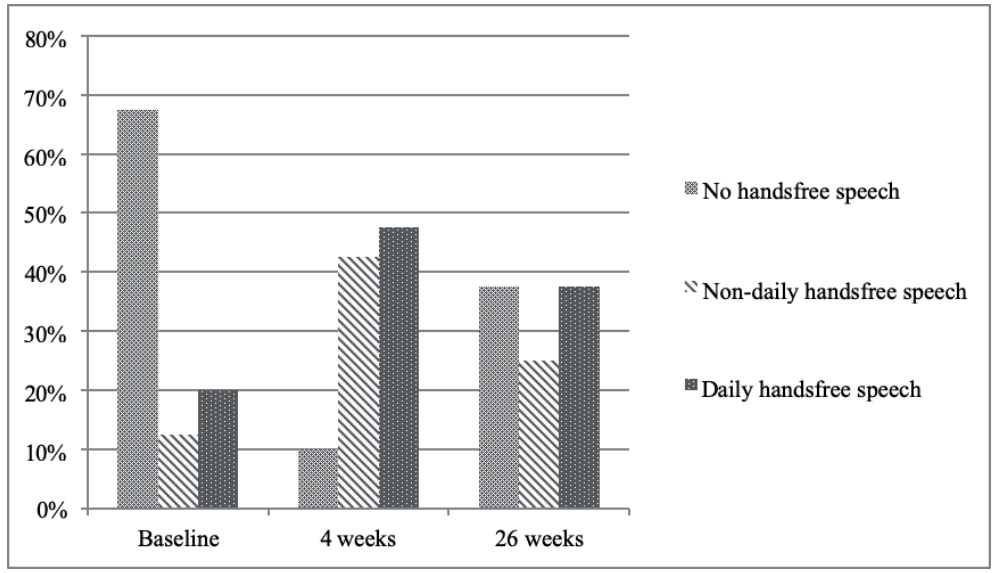


Figure 4: Compliance rates regarding handsfree speech (n=40)



With respect to the attachment of the FlexiVoice to the stoma at 26 weeks, of the 25 FlexiVoice users 13 were using the StabiliBase adhesive to attach the FlexiVoice, 4 FlexiDerm, 3 OptiDerm, 3 StabiliBase OptiDerm, 1 Regular, 1 XtraBase, 3 LaryTube, and 2 LaryButton (more options per patient possible (all

adhesives/devices are from Atos Medical AB, Hörby, Sweden). The self-reported median daily device life of the adhesive was 8 hours (range 0.25-168), when using the FlexiVoice (n=23; 2 patients were not using an adhesive, but a laryngectomy button). Patients' satisfaction regarding adhesive device life with the FlexiVoice was rated on average 6.46 (NRS; SD 2.61; n=23). Four of 11 patients (36%), who used an ASV at baseline, changed their choice of adhesive(s), and 8 of 14 patients (57%), who did not use an ASV at baseline, also changed their choice of adhesive(s).

With regards to practical aspects of the FlexiVoice, patients were e.g. asked to indicate if the membrane was popping out while coughing. Almost all patients answered affirmative and all patients found it easy to push the membrane back. When asked if the membrane sometimes closed unintentionally, 12 patients answered affirmative and 13 patients answered negative. This happened mostly when patients were physically active (n=11). Seventeen of 25 patients (68%) did use the 'locked mode' with a median of 1.5 times per day (range 0-10). All patients used automatic occlusion and 15 of 25 long-term users (60%) used both automatic occlusion and manual occlusion. Main reasons for using manual occlusion were: loosening of the adhesive makes hands free speech impossible, but still allows speech with manual occlusion (n=8), and voice is louder (n=3). Seventeen of 25 patients indicated good intelligibility when using the FlexiVoice in automatic speaking mode, 2 found the intelligibility reasonable, 4 moderate, and 2 poor. No significant differences in quality of life (according to the EQ5D5L) were found between baseline, at 4 weeks and at 26 weeks (data not shown). There were also no significant differences of the objective voice parameters assessed between baseline and 26 weeks follow-up (see Table 3).

Table 2: Reasons for discontinuing the study and not using FlexiVoice on a daily basis, and occasions when using FlexiVoice in the latter non-daily user group

Reasons for discontinuing the study between inclusion and 4 weeks*
Unpredictable adhesion adhesive (n=1); excessive mucus (already at baseline; n=1); voice prosthesis problem (n=1); recurrent disease (n=1)
Reasons for not using FlexiVoice on a daily basis at 4 weeks*
Unpredictable adhesion adhesive (n=3); familiarity with usual HME/ASV (n=3); less easy voicing (n=3); "FlexiVoice cannot be used without HME" (n=2); skin irritation with adhesive (n=1); uncomfortable breathing resistance (n=1); more mucus (n=1); problem with voice prosthesis (n=1); high T-shirt difficult (n=1); mostly using esophageal speech (n=1); air leakage with manual occlusion (n=1); unintentional closing membrane (n=1); when home alone ASV not necessary (n=1)
Reasons for discontinuing the study between 4 and 26 weeks*
Unpredictable adhesion adhesive (n=6); too high breathing resistance (n=6); soft voice (n=2); too easy closing membrane (n=2); usual ASV easier (n=2); not easy with certain clothes (n=1); too much speaking effort (n=1); annoying sounds (n=1); excessive mucus (already at baseline; n=1); poor intelligibility (n=1)
Reasons for not using the FlexiVoice on a daily basis at 26 weeks*
Unpredictable adhesion adhesive (n=4); more mucus (n=2); uncomfortable breathing resistance (n=2); soft voice (n=2); preference for usual HME (n=2); less easy voicing (n=1); when home alone ASV not necessary (n=1); too fast popping out membrane (n=1); too loose arch (n=1)
Occasions when using FlexiVoice in the non-daily user group at 26 weeks*
At home (n=9); during social activities (n=6); in special situations (e.g. when driving a car, on a quiet day, only during patient counseling (e.g. one of the less then once a month patients) (n=3)); when, then during the whole day (n=2); at the work place (n=1)

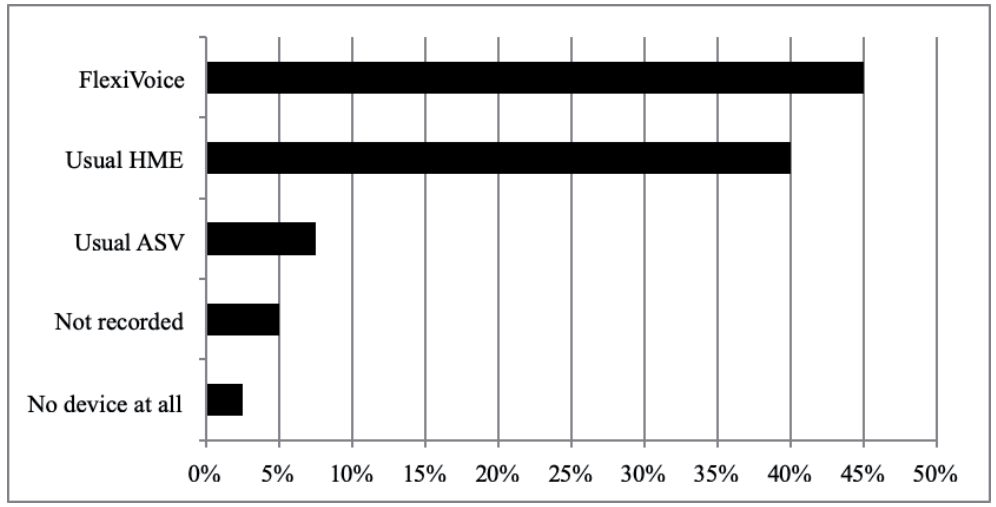
*More options per patient possible. Abbreviations: HME = Heat and Moisture Exchanger, ASV = Automatic Speaking Valve

Comparison with usual ASV

At 26 weeks, 11 patients did compare the FlexiVoice with their usual ASV (in all patients the FreeHands). Regarding the coughing mechanism, 6 patients preferred the coughing mechanism of the FlexiVoice and 5 expressed no preference. Regarding overall voice quality, 5 patients preferred the FlexiVoice, 5 had no preference and 1 preferred the FreeHands. Regarding speaking effort 5 patients preferred the FlexiVoice and 6 expressed no preference. Membrane closing-noise was reportedly less with the FlexiVoice in 4 patients, with the FreeHands also in 4 and similar in 3 patients. Furthermore, 4 of these 11 ASV patients reported that they could speak longer on one intake of breath with the FlexiVoice, whereas 7 patients expressed no difference in this respect. Regarding appearance, 8 patients preferred the FlexiVoice and 3 had no cosmetic preference. Overall, one of these 11 patients preferred to stay with his original ASV.

With regards to overall stoma occlusion preference at 26 weeks, 18 patients preferred the FlexiVoice (45%), 16 (40%) their usual HME, 3 (7.5%) their usual ASV and 1 (2.5%) preferred no device at all. The preference in the 2 patients (5%), who stopped before the 4-weeks assessment because of recurrent disease/voice prosthesis problem, was not recorded. Figure 5 shows the preferences. Finally, regarding future use, 16 out of 40 patients (40%) would continue to use the FlexiVoice daily, 8 patients reported they would use the FlexiVoice on a non-daily basis (20%), and 16 patients would not continue with the FlexiVoice.

Figure 5: Preference after 26 weeks (n=40)



Abbreviations: ASV = Automatic Speaking Valve, HME = Heat and Moisture Exchanger

During this study 17 clinical and device-related events were registered. One event concerned aspiration of the voice prosthesis, which was not FlexiVoice-related (voice prosthesis was

retrieved from the trachea; no further morbidity). There were 13 device-related events, most of which (n=6) concerned the arch that fitted too loosely on the FlexiVoice. Based on these reports the arch underwent a redesign, which solved this issue. Another issue (n=3) was air leakage from the device when closed manually, which was solved by adapting the attachment of the HME to the FlexiVoice. The other 4 concerned membrane issues, which also led to minor design changes solving this. The remaining 3 registered events concerned 1 patient, who complained twice about excessive moisture collection in the device, and 1 patient, who complained about excessive mucus production (already present at baseline).

Table 3: Objective Voice Assessment: hands free speech parameters at baseline and 26 weeks (median (range)). There are no significant differences between baseline, and 26 weeks

	Baseline (n=13)	26 weeks (n=23*)
Breathing pauses (n)	23 (16-68)	24 (9-66)
Total length text (min)	1:19 (1.05-1.58)	1:14 (0.56-2.37)
Max phonation time (sec)		
Prolonged /a/	7.30 (2.70-30.40)	7.58 (2.57-32.35)
Counting	11.1 (3.90-19.10)	11.76 (2.50-45.00)
Dynamic Loudness Range (dB)		
Softest	58 (42-70)	58 (51-69)
Comfortable	67.3 (62-74)	66 (55-77)
Loudest	77 (73-84)	79 (70-92)

* Two patients did not complete the voice assessment or not all items, because one could not read and the other one could not read Dutch, and his adhesive did not last long enough.

Discussion

This prospective clinical feasibility study on the evaluation of the Provox FreeHands FlexiVoice, a new ASV for laryngectomized patients using prosthetic voice, shows favorable results. The daily use of hands free speech in this cohort increased from 20% (8/40) at baseline to 37.5% (15/40) at 26 weeks follow-up, with 10 of the original 13 FreeHands users switching to the new FlexiVoice. Moreover, besides the original 5 non-daily FreeHands users there were 5 additional non-daily users for a total of 10 patients (12.5% at baseline compared to 25% at 26 weeks), who used/converted to the new FlexiVoice device. Thus, for almost two-thirds of the patients the FlexiVoice is a valuable option, whereas one-third of patients remain fully dependent on finger occlusion. The expectation that the new features/adaptations of this new automatic speaking valve would result in an increased proportion of patients able to use hands free speech, seems to be met.

Several factors could have contributed to this increased hands free-speaking rate. At the end of the study 60% of the FlexiVoice users (15 out of 25 patients) used automatic occlusion in combination with manual occlusion and the main reason for switching to manual occlusion was the unpredictable fixation of the peristomal adhesive. The advantage of this new feature of the FlexiVoice is that, when the adhesive starts loosening, it is still possible to use the device by occluding the opening in the front with a finger, which maintains the seal somewhat longer, obviating the immediate need to switch back to a normal HME and/or change the adhesive. An effective coughing mechanism is another important aspect of hands free speech, both for relieving the tracheal pressure and for maintaining a good seal of the adhesive. In almost all patients the membrane was popping out when coughing and it was easy to push the membrane back, and this might have been an additional reason for patients to keep using the FlexiVoice. It cannot be excluded, though, that an important reason for this increased use might have been that the StabiliBase and StabiliBase OptiDerm adhesives, with a more stable and more anatomically shaped conical base, were popular adhesives in this study population and that these were not yet available during previous studies evaluating hands free speech[19]. Lastly, the increased number of patients using hands free speech, in part, also could have been an effect of the renewed attention to an ASV sometime later during follow-up, something that should be kept in mind during regular aftercare of laryngectomized patients. A failure to acquire hands free speech early on might still be correctable later.

There are several comparable studies on ASVs. The study of Op de Coul et al (2005) evaluating the FreeHands device, describes a higher overall compliance rate of 76% than the 62.5% (daily and non-daily users) in the present study[13]. However, the daily use of hands free speech has doubled from 19% to 37.5% in the present study, as has the number of hours/day from a median of 5 hours/day with FreeHands to more than 12 hours/day with the FlexiVoice. In their study on the FreeHands device in 14 patients, Tervonen et al (2005) found daily use in only 7%, non-daily use in 86%, and non-use in 7%[20]. These figures are again different from the ones found in the present study, but the numbers of patients in the Tervonen study is quite low, and there was a selection bias because only patients with a clear voice when using a HME were included[20]. In the present study no such selection was made and also patients with less clear voices were represented. The heterogeneity of our patient sample (with 32 standard TLs, 6 pharynx reconstructions and 1 gastric pull-up) certainly results in a wide range of voice qualities, but this in fact did not influence long-term ASV use: reconstructed patients did as good as standard TL patients. Schwarz et al (2004) described an acceptance rate of 62% of patients using the device for at least 2 hours per day during 4 weeks[21]. Such early results might not be that relevant, because in our study, compliance rate regarding daily use dropped from 47.5% after 4 weeks to 37.5% after 26 weeks, and overall compliance dropped from 90% at 4 weeks to 62.5% at 26 weeks. To properly assess compliance regarding a complicated device such as an ASV, a longer than 4-weeks follow-up period is thus needed to provide relevant information. The study of Lorenz et al (2006) on the FreeHands

device in 24 patients does have a similar follow-up time as the present study (6 months), and the results are quite comparable with 42% daily users and 29% non-daily users[22]. However, the mean number of hours in the daily users, just like in the Op de Coul study, was also lower (8.4 hours) than with the new FlexiVoice. Furthermore, the firsthand comparison of the FreeHands and FlexiVoice, possible in the present study for 11 patients, showed interesting differences, also supporting the assumption that the new design features of the FlexiVoice are indeed improving its usability. The reported differences in favor of the FlexiVoice were less speaking effort, better overall voice quality, better appearance, easier and less noisy coughing mechanism, and less noisy closing of the speaking membrane.

The key success factor of hands free speech is maintaining the seal of the adhesive[7-9, 19, 21, 23]. It is important to realize that, as reported in the results, the median device life of the adhesive among ASV users at baseline was 19 hours (range 1-168), whereas this was 8 hours (range 0.25-168) reported in diaries after 26 weeks using the FlexiVoice. A possible explanation for this considerable difference in adhesive device life is that the patients, who used an ASV at baseline, were successful because of their excellent adhesive seal. Nevertheless, this study also shows once more that difficulties with adhesion of the adhesive to the skin are still a limiting factor, despite the easier closing of the more flexible/less strong membranes and the wider range of adhesives available for laryngectomized patients. More research and product development thus is needed to further improve peristomal attachment.

No significant differences in objective voice assessment were found between baseline, after 4 weeks and after 26 weeks, which shows that patients using the FlexiVoice are able to produce the same voice and speech quality compared to their baseline measurement with FreeHands as well as with HME. This is in contrast with the Op de Coul study, in which several voice parameters, such as maximum phonation time and dynamic loudness range, were significantly better when speaking with the HME[13]. The lack of such difference in the present cohort seems to further confirm the design improvements of the FlexiVoice.

The present study has some limitations. Although the only inclusion criterion was the ability to tolerate a HME, there still might have been a selection bias towards more motivated patients. Furthermore, some of the variables that (also) might influence hours of use of the FlexiVoice were not collected. In hindsight, it would have been interesting to not only let the patients report daily hours of FlexiVoice use in diaries, but also to ask the patients to give insight in the intensity of speech during the day. Also, information of stoma dimensions and local anatomy might have been of value to correlate duration of adhesive seal and thus hands free speaking time[23].

In conclusion, the Provox FreeHands FlexiVoice is a useful ASV, which seems to allow for longer hands free speech in a larger proportion of laryngectomized patients in the present cohort. The additional manual closure option of the FlexiVoice is experienced as beneficial for longer maintaining the adhesive seal.

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Chapter 3

Comparative study between peristomal patches in patients with definitive tracheostomy

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Abstract

Introduction: To prevent or diminish pulmonary problems in laryngectomized patients, continuous use of a heat and moisture exchanger (HME) is recommended. Therefore, also automatic speaking valves, enabling hands-free speech, often are combined with an HME. To keep these devices in place, most commonly peristomal patches are used.

Objective: This prospective clinical 2x2 crossover study aims at assessing the added value of a new patch for HME application, the Provox StabiliBase OptiDerm (SBO). The device combines the stable and conical base of the Provox StabiliBase with the skin-friendlier hydrocolloid Provox OptiDerm (OD) patch.

Methods: Thirty-two laryngectomized patients were included in this multicenter study. Participants were asked to compare SBO to OD, and to the patch they normally use. Primary outcome measure was patient preference.

Results*:* Overall, 60% of participants had preference for their normally used patch, 23% preferred the SBO and 17% indicated no preference. When comparing the SBO to the OD, 43% preferred the SBO, 40% the OD and 17% had no preference.

Conclusion*:* Most patients preferred their normally used patch and SBO was favored by a subgroup. SBO seems a valuable addition to the existing patches and further increases patients' options for HME application.

Keywords: Laryngectomy, rehabilitation, patch, patient preference

Introduction

Total laryngectomy (TL) is still an indispensable treatment option for advanced larynx and hypopharynx cancer, for recurrent disease, and a dysfunctional larynx after prior (chemo-) radiotherapy ((C)RT). TL results in significant anatomical changes. The alimentary and respiratory tracts are separated and a definitive tracheostomy is created at the base of the neck. The main disadvantage of TL is the loss of upper airway and larynx functions. This leads to pulmonary problems, such as excessive coughing and mucus production, and loss of normal speech[1, 2].

To prevent or diminish pulmonary problems, continuous use of a heat and moisture exchanger (HME) has shown to be highly beneficial[3, 4]. Moreover, most automatic speaking valves (ASVs) presently are combined with an HME, so that also during hands-free tracheoesophageal speech airway protection and rehabilitation is taken care of[5-7]. Laryngectomized patients have several options to keep these devices in place depending on their personal situation. The most commonly used device is a peristomal patch, which creates an airtight seal at the level of the tracheostomy and provides a placeholder for the HME and/or ASV[8].

Currently, there is a wide variety of patches available to suit the patients' personal needs, which is important to optimize compliance[8-10]. Recently, the Provox StabiliBase (SB) was evaluated in a multicenter study. This patch provides a more stable and more anatomically shaped conical base compared to other patches. The study showed that the majority of patients preferred this new patch to their usual comparator patch. Its device life appeared to be significantly longer, and patients with a deep stoma reported the patch to be more comfortable[9].

After its introduction, feedback from clinicians and patients revealed that some patients experienced skin irritation with the standard adhesive material of the SB. It was felt that these patients would benefit from a patch with the same stable and conical base as the SB, but with the more skin-friendly hydrocolloid adhesive as already used in the Provox OptiDerm (OD). Therefore, the Provox StabiliBase OptiDerm (SBO) was developed. To test whether this stable conical hydrocolloid SBO patch is a valuable addition to the variety of peristomal adhesive options needed to suit more laryngectomized patients, this new patch was assessed in a 2x2 crossover prospective multicenter clinical trial.

Methods

This study was performed at two tertiary care cancer centers. Thirty-two, laryngectomized patients were entered in the study, 16 in both centers. Inclusion criteria were: 18 years or older, use of an HME, use of a voice prosthesis, minimum of 3 months after TL and/or postoperative (C)RT. Exclusion criteria were: patient is unable to use the SBO (due to anatomical irregularities that may interfere with the stable base of the patch), medical problems prohibiting the use of HME or patch, active recurrent or metastatic disease, patient is unable to understand the patient information and/or

unable to give informed consent. Skin irritation, which varies between 9% and 40% of patients[4, 10-12], was not a selection criterion. This has the advantage that the study can provide data on the extent of that problem in this patient cohort and prevents selection bias. Moreover, it is likely that, if given more options, patients primarily will decide on the basis of the duration of the seal if there is no skin irritation, which would mean that an unselected patient cohort would provide better insight in the extent of the irritation problem and the place of the new patch in the presently available options. The study was performed according to the protocol approved by the institutional review boards and took place between February and April 2014. Signed informed consent was obtained from all patients. Patient characteristics are shown in Table 1.

Table 1: Patient characteristics

Characteristics	Value	%
Gender		
Male	27	84
Female	5	16
Age at TL	Mean 55.7 years (SD 9.4)	
Age at entry	Median 64.0 years (48-82)	
Post-TL	Mean 100.7 months (SD 77.9)	
TL		
Standard	28	88
+ Reconstruction	3	9
Information missing	1	3
Origin tumor		
Larynx	30	94
Hypopharynx	2	6
Indication of TL		
Primary	9	28
Salvage	23	72
Neck dissection		
No	13	41
Unilateral	6	19
Bilateral	12	37
Information missing	1	3
Post-operative (C)RT		
No	23	72
Yes	9	28
Voice prosthesis		
Provox 2	4	13
Provox Vega	18	56
Provox ActiValve	10	31
Patch		
StabiliBase	11	34
FlexiDerm	10	31
OptiDerm	5	16
XtraBase	4	13
Other	2	6
HME		
Daily	32	100
+ ASV use	9	28

TL Total Laryngectomy, RT Radiotherapy, (C)RT (Chemo)Radiation, HME Heat and Moisture Exchanger, ASV Automatic Speaking Valve

The SBO is manufactured by Atos Medical AB (Hörby, Sweden). The patch is shown in Figure 1. It is a single use patch intended for laryngectomized patients. It is attached to the skin around the tracheostoma in order to provide a connection for HMEs and speaking valves. The SBO consists of a stable base, similar to that of the SB , but with a hydrocolloid adhesive[9]. The patch is suitable for sensitive and/or breached skin and its baseplate is designed to also accommodate deep tracheostomas.

Figure 1: StabiliBase OptiDerm (SBO); left: a technical drawing of the SBO without liner (frontal view) showing the stable and conical base; right: attached to a patient with the heat and moisture exchanger in situ

The SBO was compared to the OD in a feasibility study with a 2x2 crossover design. After inclusion, the patients consecutively used 5 OD and 5 SBO patches in the order assigned by randomization. Primary outcome measure was overall patient preference, based on various aspects of the patch addressed in the study-specific questionnaires (see below). Secondary outcome parameters were: device life, patient satisfaction (skin irritation, comfort, voice/speech), ease of application, and quality of life. Study-specific structured questionnaires were completed at baseline, after the use of the first 5 patches and after the use of the second 5 patches. Questionnaires addressed skin irritation, ease of application, ease of removal, dirtiness, mucus collection, fit, comfort, use of other devices in combination with patch, appearance, voice quality, air leakage, adherence and cleaning tracheostomy/voice prosthesis. Answers were reported on a 4 level Likert-scale. Patients rated satisfaction regarding device life and voice quality using a 10-cm Numeric Rating Scale (NRS) (0=worst and 10=best). Quality of life was assessed using the EuroQOL-5 Dimension-5 Level questionnaire (EQ5D5L) [13]. The EQ5D5L is a validated instrument using scores in five health care dimensions (mobility, self-care, daily activities, pain/discomfort and anxiety/depression) and a 100-mm VAS. During the study period patients kept a diary to record device life of each patch and numbers of hours per day of HME use. At the end of the study patients were asked to complete a comparative questionnaire. Patients had to compare the SBO with the OD and also with their normally used patch if different from the OD.

The primary outcome of this study was patient preference. Goal was that 40% of the participants prefer the SBO to the OD, 5% consider the SBO to be worse, whereas the remainder consider both patches to be equally good (45%) or bad (10%). Based on earlier studies and given the assumption that in the absence of irritation the duration of the seal is the deciding factor, this is a feasible goal and clinically relevant[9, 10, 12]. A sample size of 30 pairs will have 82% power to detect a difference in proportions of 0.350 when the proportion of discordant pairs is expected to be 0.450 using a sign test of equality of paired proportions with a 0.05 two sided significance level. As this was a short study and no risks have been associated with participation in the study, the dropout rate was expected to be <5%. Statistical analysis were conducted using IBM ® SPSS ® 22.0. Frequencies were explored using the Kolmogorov-Smirnov test. Parametrically distributed data is shown as mean ± standard deviation and analyzed using the paired T-test. Non-parametrical data are presented as median (inter quartile range) and were analyzed using the Wilcoxon-Signed rank test. The Likert Scales rendered ordinal data from three related samples. This data was analyzed using the Friedman test. If the groups differed significantly a Wilcoxon-Signed rank test was used to determine which groups were different. A p-value <0.05 is considered significant.

Results

Patient characteristics of the 32 patients enrolled in the study are shown in Table 1. One patient withdrew from the study in the first week because of recurrent disease and was excluded from further analysis. Twenty-seven males and four females remained. Four patients did not use all study patches. Reasons were: skin irritation after using the SBO, poor adherence of the SBO to the skin, poor adherence of the OD to the skin and painful skin after using the OD. An overview of completed questionnaires is shown in Table 2.

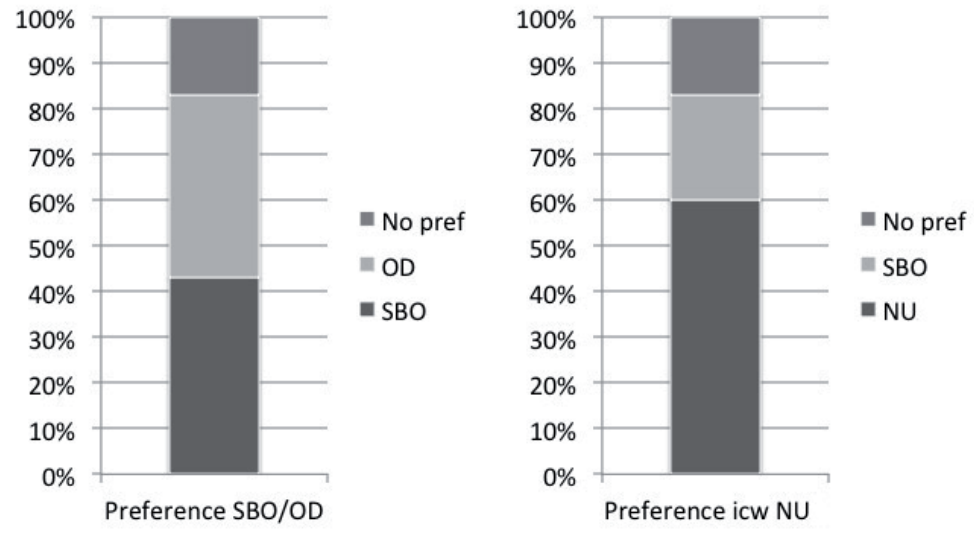
Table 2: Completed questionnaires

Questionnaire	n
Baseline	31*
OD	30**
SBO	30***
Comparative 'Normally used patch' – SBO	25***/****
Comparative OD – SBO	30***

OD OptiDerm, SBO StabiliBase OptiDerm
*One patient dropped out right after baseline data collection. These data were removed for analysis
**One patient did not complete questionnaire OD (poor adherence)
***One patient did not complete questionnaire SBO and comparative questionnaires (poor adherence)
****For five patients who were already using OD at baseline the OD-SBO comparative questionnaire was used as normally used patch-SBO comparative questionnaire.

When patients compared the OD with the SBO, 12 of 30 patients (40.0%) preferred the OD. Thirteen patients preferred the SBO (43.3%) and 5 patients (16.7%) expressed no preference. In comparison with their normally used patch, 18 patients (60.0%) indicated a preference for the normally used patch, 7 patients (23.3%) for the SBO and 5 patients (16.7%) indicated no preference. Of 5 patients, who were using the OD at baseline (preference for OD 3, for SBO 1, no preference 1), the answers to the comparative OD-SBO questionnaire were used as 'normally used patch-SBO-data' in these analysis (Figure 2).
Device life assessment was based on the data of patients, who reported on at least 3 out of 5 OD/SBO patches. For the OD the median device life was 18.5 hours (n = 26; range 0.5-109.9) and for the SBO this was 19.6 hours (n= 27; range 0.5-163.0) (p= 0.290). When data were split for patches used to apply an ASV or a HME, no significant differences were found between device life of the SBO and OD. There was an increase in device life in 15 out of 26 patients with the SBO compared to the OD, with a mean factor of 1.44. In 2 patients there was no difference and in 9 patients there was a decrease of the device life with the SBO compared to the OD with a mean factor of 0.76. The overall mean factor was 1.17. The median self-reported device life in the 15 patients, who had an increased device life with the SBO, was 14.47 hours (range 1.9-109.9) with the OD and 19.60 hours (range 2.35-163.01) with the SBO.

Figure 2: To illustrate the added value of more patch choices, on the left the preference at the end of the study for either of the 2 hydrocolloid patches (SBO = StabiliBase OptiDerm, n=13; OD = OptiDerm, n=12; No pref = No preference for either of the two, n=5); on the right the preference in comparison with (icw) the normally used patch (NU = normally used patch, n=18; SBO, n=7; No pref, n=5).



Analysis of fit, comfort, appearance, speech, air leakage and adherence, measured at baseline, after using 5 OD patches and after using 5 SBO patches, showed a statistically significantly better outcome for the normally used patch compared to the SBO and the OD. No significant differences regarding these variables were found between the SBO and OD.

With respect to skin irritation, no significant difference was found between the normally used patch, OD and SBO. When asked to compare these two patches, 17% experienced less skin irritation with the OD, 23% experienced less skin irritation with the SBO and 60% experienced no difference (n=30). Compared to the normally used patch (n=25), 12% experienced less skin irritation with that patch, 32% with the SBO and 56% experienced no difference.

Participants indicated significantly less discomfort with their normally used patch compared to the SBO (p=0.001, n=30). When asked to compare the normally used patch with the SBO 52% found that patch more comfortable to wear, 24% found the SBO more comfortable and 24% found no difference. When asked to compare the OD and SBO, 33% had less discomfort with the SBO, 40% with the OD and 27% indicated no difference.

Overall voice and speech was measured using a NRS. There was no statistically significant difference between the normally used patch and the SBO. Only the OD received a statistically significantly lower score compared to the normally used patch (p=0.004, n=30), and compared to the SBO (p=0.007, n=30). Furthermore, no significant differences in applying the patch and in quality of life (according to EQ5D5L) between the normally used patch, OD and SBO were found.

Finally, regarding future use, 15 out of 28 patients (53.6%) reported that they would keep their normally used patch in the future. Of the 13 remaining patients answering this question, 6 (21.4%) will use the OD, 5 (17.9%) the SBO and 2 (7.1%) a combination of the normally used patch with SBO. Data of 2 patients were missing. Those 7 patients who will use the SBO or a combination of normally used patch and SBO in the future, consists of 2 former regular patch users (29%), 4 SB users (57%) and 1 tracheostomy button user (14%).

During this study six adverse device effects were registered. There were complaints about skin irritation, painful removal of the patch and poor adherence. All reports were expected effects of using a tracheostomy patch.

Discussion

This prospective clinical trial on the evaluation of the SBO, a new patch with stable conical base and hydrocolloid adhesive for peristomal attachment of postlaryngectomy pulmonary and voice rehabilitation, shows that this patch is a valuable addition to the variety of options needed to suit more laryngectomized patients.

With a quarter of the patients choosing the SBO or a combination of the normally used patch with the SBO, it is clear the SBO is suitable for a sub-group of patients. The sub-group might consist of patients who are using a SB as their main patch and would like to alternate with a more skin-friendly patch, keeping in mind that the median device life of the standard SB is roughly 1.8 times longer because of its stickier adhesive material[9]. Those patients may benefit when they prefer a stable base around the tracheostomy, but cannot use the SB (all day) because of their sensitive/breached skin.

The results show that the device life of the SBO is not significantly increased compared to the OD (both hydrocolloid adhesives). However, for those 15 patients who had an increased device life with the SBO compared to the OD, the increase is clinically relevant. The difference (19.60 hours vs. 14.47 hours) made it possible for those patients to often replace the patch only once per 24 hours. Nevertheless, a majority of the patients preferred the normally used patch, because in the absence of skin irritation, the duration of the seal is the decisive factor for their 'patch-choice'. As the mean interval of TL to participation in this study was 6.5 years, most patients have extensive experience with several peristomal attachment possibilities and found their optimal attachment modality. Still, there are patients (23.3%) who prefer the SBO to their normally used patch. These results show there are still possibilities for further innovation, despite the wide range of patches already available to the laryngectomized patient. Given the wide variations in peristomal anatomy, this is not surprising[14]. So far, only a few clinical studies have been conducted to investigate peristomal patches. Because of the wide variety of rehabilitation options for laryngectomized patients, however, a good insight in patients' needs is necessary to find the optimal rehabilitation options. E.g., the study by Hilgers et al. (2012) describes that there is no one-size-fits-all solution and emphasizes the need for a range of device options, which means that this new patch is a welcome development[9].

In the present, relatively small study, although there was no selection based on the presence or absence of skin irritation, there still might have been some selection bias. For example, patients who were unable to use the SBO, such as patients with anatomical irregularities in the area of the patch that interfere with the stable base of the patch, were excluded. Furthermore, some variables that might influence device life were not collected. For example, we did not ask the patients to register hours of ASV use in their diaries and we did not measure tracheostomy dimensions and local anatomy, factors that obviously can influence the outcomes[8].

Costs of these new patches were not a topic of this study. Although according to the manufacturer, the periodical costs for various patches is quite comparable, to analyze costs in a meaningful way, a proper cost-effectiveness study would have been needed. This requires collecting additional data to those of a standard clinical study. Moreover, since costs and reimbursement systems vary widely between countries, even making vague suggestions about cost issues now would be speculative, at best. But this is certainly an interesting topic for studies in other countries.

Conclusion

Most patients preferred their normally used patch and SBO was favored by a subgroup. Therefore, SBO seems a valuable addition to the arsenal of devices already available and widens the options laryngectomized patients have for peristomal attachment of medical devices for pulmonary protection and rehabilitation.

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Chapter 4

Virtual 3D planning of tracheostomy placement and clinical applicability of 3D cannula design: a three-step study

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Abstract

Aim: We aimed to investigate the potential of 3D virtual planning of tracheostomy tube placement and 3D cannula design in order to prevent tracheostomy complications due to inadequate cannula position.

Materials and Methods: 3D models of commercially available cannula were positioned in 3D models of the airway. In study (1) a cohort that underwent tracheostomy between 2013 and 2015 was selected (n=26). The cannula were virtually placed in the airway in the preoperative CT-scan and its position was compared to the cannula position on postoperative CT-scans. In study (2) a cohort with neuromuscular disease (n=14) was analyzed. Virtual cannula placing was performed in CT-scans and tested if problems could be anticipated. Finally (3), for a patient with Duchenne muscular dystrophy and complications of conventional tracheostomy cannula a patient-specific cannula was 3D designed, fabricated and placed.

Results: (1) The 3D planned and postoperative tracheostomy position differed significantly. (2) Three groups of patients were identified: (A) normal anatomy; (B) abnormal anatomy, commercially available cannula fits and (C) abnormal anatomy, custom-made cannula may be necessary. (3) The position of the custom designed cannula was optimal and the trachea healed.

Conclusions: Virtual planning of the tracheostomy did not correlate with actual cannula position. Identifying patients with abnormal airway anatomy in whom commercially available cannula cannot be optimally positioned is advantageous. Patient specific cannula design based on 3D virtualization of the airway was beneficial in a patient with abnormal airway anatomy.

Key Words: 3D planning, Cannula, Neuromuscular disease, Tracheostomy.

Introduction

Tracheostomy is a routine procedure for securing the airway. In most of the cases commercially available, prefabricated tracheostomy cannulas are used to keep the tracheostomy open. These cannulas have fixed variations in size, radius, curvature and diameter. However, in case of aberrant anatomy of the neck or thorax, the choice of the proper tracheostomy site with corresponding cannula type can be challenging.

In patients with abnormal anatomy of the neck and thorax, like e.g. patients with Duchenne muscular dystrophy, the commercially available cannulas often do not fit due to the extreme scoliosis.[1] Beyond discomfort, suboptimal cannula placement may result in inflammation of the trachea, eventually leading to granulation tissue formation, airway obstruction or even in fatal complications.[2] Several case reports and our own experience have shown patients who had a fistula of the trachea and innominate artery, leading to a fatal hemorrhage.[3,4] Therefore, proper and cautious cannula selection is essential to reduce these risks.

Generally, cannula placement is depending on the estimation of the surgeon during the procedure. Especially in case of abnormal anatomy this appraisement is difficult. After surgery an endoscopic control of the position of the tip of the cannula may be performed to optimize the positioning of the cannula and/or to determine what type of cannula is optimal for the patient. The outcome is subjective and highly depending on the experience of the physician.

Pre-operative visualization of the upper airway with determination of the optimal stoma site could theoretically aid in the surgical planning in case of aberrant neck anatomy. Furthermore, optimal choice of standard cannula or a custom-made cannula based on pre-operative visualization of the upper airway can prevent complications. A three-step approach is used for analysis of the added value of 3D visualization and surgical planning of tracheostomy and cannula placement. As a first step, a series of retrospective cases was analyzed to explore the applicability of pre-operative 3D visualization and predictability of surgical placement. As a second step different groups of neuromuscular patients were identified using 3D visualization to predict cannula problems. The third step is the implementation of a custom cannula in a clinical case including design, fabrication, placement and evaluation of the cannula position.

Materials and Methods

1. Virtual cannula placement and comparison with actual post-surgery position

The first series of patients was selected from a cohort of patients who underwent a tracheostomy at the department of Otolaryngology of the University Medical Center Groningen (UMCG) between 2013 and 2015 (N=150). Only patients of whom a pre- and post-tracheostomy CT-scan of the head and neck was available were included for analysis (N=26). Pre- and post-

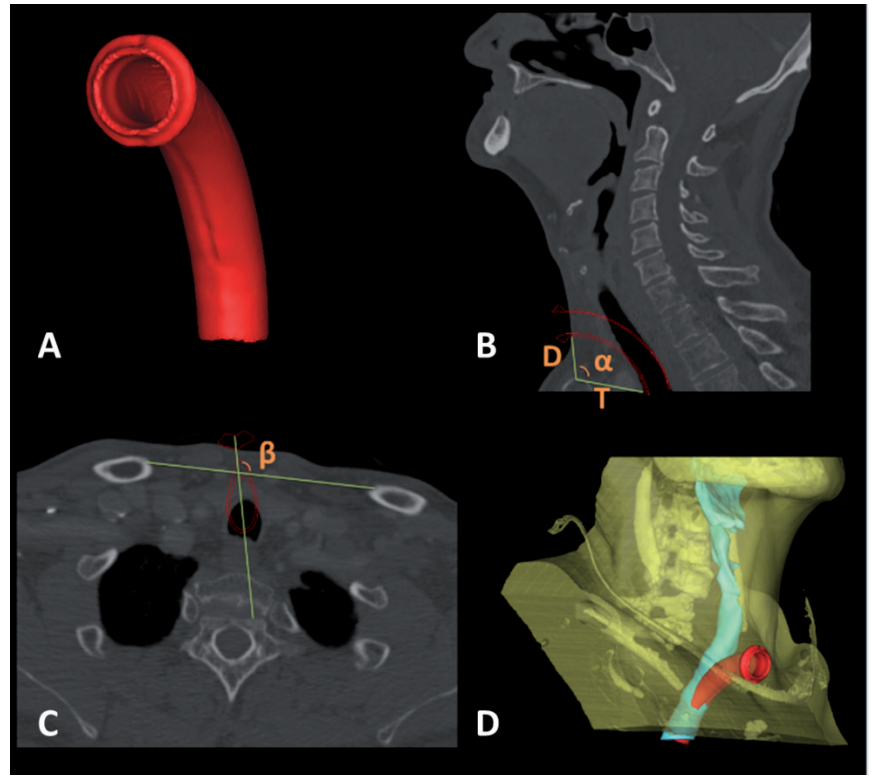
tracheostomy scans of the patient series were assessed by an Otorhinolaryngologist (GBH) and Technical Physician (JK) using the following inclusion criteria: Was the patient positioned in an extended head position? Was the area of tracheostomy entrance (skin) visualized? Was the tip of the sternum visualized? Was the airway visualized? All patient data that did not meet these criteria were excluded from further analysis in this study. Note that no specific scanning protocol was used, as the cases where retrospectively selected. After this quality assessment 10 cases were found to be suitable for inclusion for this study.

The available standard size cannulas, applied in the UMCG, were scanned using a Cone Beam CT-scan, after which a 3D virtual model was made using ProPlan 2.1 (Materialise, Leuven, Belgium) (Figure 1, A). For each patient's CT-scan (pre- and postoperative) a 3D virtual representation was made, using ProPlan 2.1, including airway, thorax and skin visualization. The 3D cannula models were imported in that 3D reconstructed model of the patient, allowing virtual cannula placement.

Using the pre-tracheostomy data, the scanned cannulas were carefully virtually placed in the virtual model by the otorhinolaryngologist and technical physician. Optimal positioning was obtained by evaluating, and adjusting, the cannula tip position in relation to the airway. For the post-tracheostomy data, the actual location of the cannula was identified on the CT-scan.

A systematic 2D virtual landmark comparison provided data regarding the difference between the planned cannula position and the post-operative position. The defined landmarks and measurements are presented in Figure 1, including the apex of the sternum, tip of the cannula, shoulder point of the cannula and line between the clavicles. All of which were selected on the mid-sagittal slice through the center of the tip of the cannula and axial slice presenting the body of the cannula. The distance between the sternum and the cannula flange (D) describes the height of the post-operative placement compared to the planned positioning. The distance between the sternum and the cannula tip (T) describes the position of the cannula tip compared to the planned position. The angle of the cannula in the sagittal plane was related to the sternum (α). In the transverse plane the angle of the cannula was related to a straight line between the clavicles (β) (Figure 1).

Figure 1: Analysis in 2D images of scans using described distances. D = The distance between the sternum and the cannula flange. T = The distance between the sternum and the cannula tip. α = The angle of the cannula in the sagittal plane related to the sternum. (β) = The angle of the cannula related to a straight line between the clavicles in the transverse plane. A: 3D rendered cannula based on CT data. B: Sagittal view with variables D, T and α. C: Transverse view with variable β. D: 3D rendered view bases on CT data with 3D rendered cannula in optimal position



2. Identification of tracheostomy cannula-specific airway anatomy in patients with neuromuscular disease

For the second part of this study, the files of 234 patients treated for neuromuscular disease at the UMCG were reviewed. 14 patients were identified who had CT scan of the head and neck and upper chest, which was applicable for 3D analysis. Most of the patient had no tracheostoma (n=10), some did (n=3) and in one case pre-, and post-tracheostomy scans were available. The same 3D virtual models of scanned cannulas that were used in the first part of the study, were used. Optimal cannula positioning was determined using ProPlan CMF 2.1 (Materialise, Leuven, Belgium). First, of every available CT scan a 3D virtual representation was made. Comparable to the first group, a 3D cannula model was imported in that 3D reconstruction and optimal placement was virtually determined. The cannula was positioned as optimally as possible, the tip of the cannula was tried to be centered in the tracheal lumen and the shield on skin of the lower neck.

3. Evaluation of a 3D designed, fabricated and placed cannula – report of a case

A 42-year-old male patient suffering from Duchenne muscular dystrophy was identified with granulation tissue formation of the trachea due to inadequate cannula position. The patient was not followed up by an otolaryngologist for multiple years and this situation was very likely due to the progression of kyphoscoliosis. Several different brands, types and sizes of cannulas were tried, but none had an optimal position. Attempts to optimize positioning using extra spacers between the cannula and the skin failed, too. A CT scan of the airway (with the cannula in place) was made. For the custom cannula design, a 3D airway model was made based on the CT scan using Proplan CMF 2.1. The conventional cannula that the patients was using was segmented to a 3D model, as well as the bony structures and the skin of the patient for anatomical reference. The optimal entrance point in the trachea and the caudal tip location of the custom cannula was agreed on by the surgeon (GBH) and technical physician (JK). The radius and diameter of the cannula where determined on the 3D models and the cannula was designed using 3-Matic 10.0 (Materialise, Leuven, Belgium). The final design was sent both as an stl-files and a 3D printed physical model to a producer of custom-made silver cannulas. The cannula was produced from silver conform the dimensions of the 3D design and checked afterwards. The cannula was placed and its position was checked by a CT-scan and by fiberoptic endoscopy.

Statistical analysis

For the first part of this study, distances were explored using the Kolmogorov-Smirnov test. They were normally distributed and presented as mean ± standard deviation. A paired T-test was used to determine statistical differences. For the second part and third part of the study, no statistical analysis was possible.

Results

1. Virtual cannula placement and comparison with actual position

The patients characteristics of the first part of the study are described in Table 1. The average age of the patients was 58 years old (range 38-75 years). There were 7 males and 3 females.

Table 1: Patient characteristics of patients in study 1 with normal anatomy

	Age at tracheo-stomy	Sex	Reason for tracheostomy	Duration of cannula use	Complications due to tracheostomy?	Type of cannula
1	61	M	Oncology	7 Months	No	Tracoe 10
2	43	M	Trauma	12 days	No	Shiley 8
3	73	M	Laryngeal paralysis	2 Months	No	Shiley 8
4	38	M	Lymphoma	2.5 Months	No	Tracoe 8
5	75	M	Oncology	2 Months	No	Tracoe 9
6	58	F	Oncology	8 Months	No	Tracoe 6
7	68	M	Post radiation fibrosis	10 Months	No	Tracoe 10
8	61	F	Oncology	1 Months	No	Tracoe 8
9	53	F	Oncology	1 Months	No	Shiley 8
10	50	M	Oncology	4 Months	No	Tracoe 8

The results of the analysis performed are presented in Table 2. Post-operative cannula placement was different from the pre-operative 'optimal' placement. The largest deviation was found between the tip of the sternum and the flange of the cannula (D) on the virtually and operatively placed cannulas, with an average of 14.23 mm. The difference of the tip of the cannula to the tip of the sternum (T) was found to be smaller, with an average of 5.6 mm. Both D and T values between the pre- and post-operative situation were statistically significantly different (p<0.001 and p=0.002, respectively). The measured angles show that the angulation of the cannula in transversal view is mostly not different from pre-operative planning (average difference 1.51°, ns), but the angulation in axial view does significantly differ (average difference 17.36°, p=0.019).

Table 2: Variables showing the measured distances and angles of the cannula position in patients with normal anatomy. For details see Materials and Methods (mean ± standard deviation)

	D (mm)	T (mm)	A (° degrees)	B (° degrees)
Pre-operative	23.5 ±5.51	41.06 ±5.04	140.77 ±28.84	86.54 ±7.33
Post-operative	37.75 ±4.02	35.46 ±5.16	123.42 ±28.56	88.04 ±23.50
Mean difference	14.23 ±5.48	5.60 ±4.11	17.36 ±19.22	1.51 ±22.49
T-test	P<0.001	P=0.002	P=0.019	P=0.837

2. Identification of tracheostomy cannula-specific airway anatomy in patients with neuromuscular disease

The patients characteristics of the second part of the study are described in Table 3. The average age of the patients was 24 years old (range 17-42 years). There were 13 males and 1 female.

Table 3: Patient characteristics of patients of study 2 with neuromuscular disease

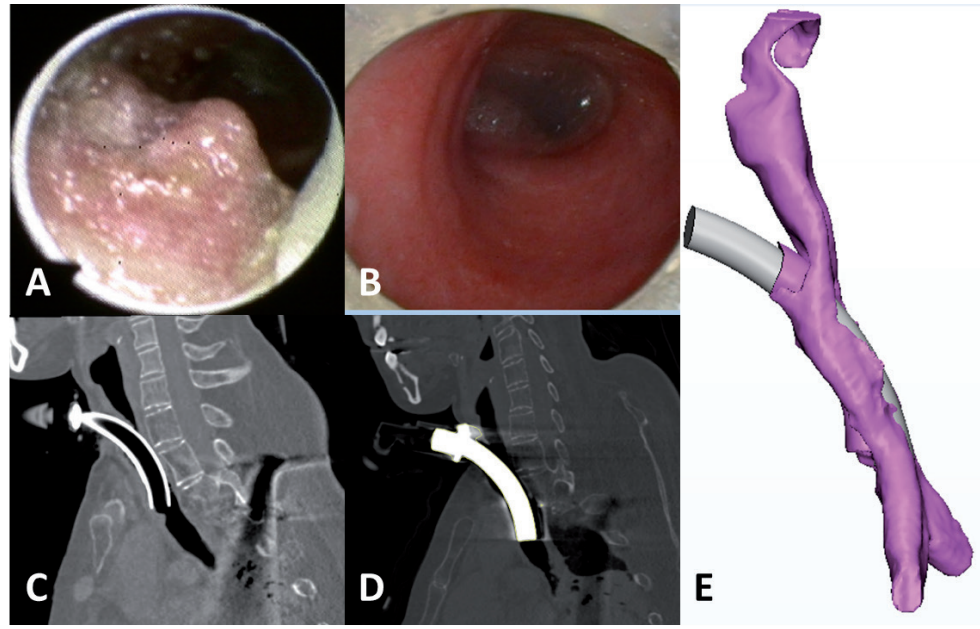
	Neuromuscular disease	Age (at time of scan)	Sex	Tracheostomy?	Complications due to tracheostomy?	Type of cannula
1	Spinal muscular atrophy	33	M	No	N.A.	N.A.
2	Spinal muscular atrophy	25	F	No	N.A.	N.A.
3	M. Duchenne	19	M	No	N.A.	N.A.
4	M. Becker	22	M	Yes	Yes, granulation	Rusch
5	M. Becker	40	M	No	N.A.	N.A.
6	Spinal muscular atrophy	24	M	No	N.A.	N.A.
7	M. Duchenne	16	M	No	N.A.	N.A.
8	M. Duchenne	28	M	Yes	Yes, ulcer	Custom-made Bivona 7
9	M. Duchenne	21	M	Yes	No	Custom-made Bivona
10	M. Duchenne	17	M	No	N.A.	N.A.
11	M. Steinert	19	M	No	N.A.	N.A.
12	M. Duchenne	42	M	Yes	Yes, granulation	Tracoe 8
13	M. Duchenne	19	M	No	N.A.	N.A.
14	M. Duchenne	14	M	No	N.A.	N.A.

Three-dimensional placement of the conventional cannulas and evaluation of their position, identified three groups of patients: 1. Normal or close to normal anatomy and a commercially available cannula would fit (n=7). 2. The anatomy is abnormal but a standard cannula would fit (n=3). 3. The anatomy is abnormal and a standard cannula would not fit (n=4).

3. Evaluation of a 3D designed, fabricated and placed cannula – report of a case

This patient is the first to receive a custom-made cannula based on 3D planning. Comparing the CT scan with the old cannula to the CT scan with the new cannula, the improvement in positioning can be seen (Figure 2). The complaints of the patients were immediately dissolved. Two months after placement of the cannula the granulation tissue healed and the cannula positioning was centered in the airway without any signs of decubitus off the trachea (Figure 2).

Figure 2: Endoscopic (a,b), CT (c,d) and 3D images (e) of the patient with conventional and with 3D designed cannula. Image a,c: with conventional cannula, image b,d: with 3D designed cannula
A: Endoscopic view through the standard cannula with granulation formation in the trachea. **B:** Endoscopic view of the trachea through the 3D designed cannula. **C:** Sagittal CT view of the position of standard cannula. **D:** Sagittal CT view of the position of the 3D designed cannula. **E:** The segmented airway with the conventional cannula in situ and with the 3D designed cannula



Discussion

In this three-step study, using 3D technology (1) we have created a setup for the 3D analysis of tracheostomy cannula and their placement, (2) we have identified cannula-specific airway anatomy in patients with neuromuscular diseases, and (3) successfully designed, produced and placed a 3D planned cannula in a patients after several previous failures of custom-made cannula.
In our study, we show that the virtual planning differs statistically significantly from the actual cannula placement assessed on the postoperative CT-scan. Several factors attributed to this difference. Firstly, because of the retrospective nature of the study the acting surgeon was not informed on a possible ideal position of the stoma and choice of cannula. Secondly, superimposing the pre- and post- op scans was difficult due to different neck extension and subsequent different scanning position. Thirdly, the proper surgical route is not easy to predict due to soft tissues of the neck and therefore flexibility the tissues around the stoma.
In our series of patients with neuromuscular disease we could identify three sorts of anatomical situations regarding virtual cannula placement: 1. The anatomy is not abnormal and a standard cannula would fit. 2. The anatomy is abnormal but a standard cannula would fit. 3. The anatomy

is abnormal and a standard cannula would not fit. The assessment of cannula fit in this group was made by trying to place custom-made cannulas in a 3D model of the airway. This assessment did not suffer from the problem found in the first study in which cannula placement was tried to be predicted from a 3D model. In the second study the cannula was fit in any position possible. These important findings could help preoperatively in identifying patients who might get complications after tracheostomy. These patients could benefit from individualized, 3D designed cannulas.

In this study, we show that it is possible to design a custom-made cannula using 3D virtualization techniques for patients with abnormal anatomy and/or suboptimal cannula positioning.

Especially in patient with neuromuscular diseases like Duchenne muscular dystrophy, suboptimal cannula placement can lead to mild or severe complications.[1-4] As the disease progresses, the progressive changes in anatomy can worsen problems with cannula positioning. The custom design of cannulas can provide a definitive solution for patients in whom optimal care cannot be achieved by the commercially available cannulas.

No studies have been reported on tracheostomy planning and cannula placement using virtual 3D planning. It is apparent that the use of 3D visualization and subsequent development of surgical techniques and 3D printed aids and parts is the next logical step in the treatment of patients with complex tracheal anatomy.

Virtual 3D reconstructions have been used before in otorhinolaryngology, using stereophotogrammetrical analysis or CT-scans.[5-8] Applications vary from laryngectomy stoma assessment to 3D planning of surgical procedures. The overview article of Kaye et al. summarizes the use of 3D printing for educational purposes, auricular prosthesis, 3D printed hearing aids, surgical planning and managing the pediatric airway with 3D models of the airway to optimize stent placement.[9]

When determining the optimal cannula position from pre-operative scans, sometimes a compromise had to be made between the positioning of the cannula tip in the trachea and the position of the flange of the cannula on the skin. The tip was used for alignment, sometimes meaning the cannula flange did not align with the skin. In some cases this led to unrealistic cannula placement with standard sized cannulas. We think that for these cases patient specific 3D designed cannulas could aid in obtaining the optimal cannula position.

The analysis of the series of patients with neuromuscular diseases did not allow statistical analysis. However, the findings are very relevant because they could help identifying patients who might get complications after tracheostomy. Individualized, 3D designed cannulas could help these patients.

This is the first report of using 3D virtualization techniques to design a custom-made silver cannula for a patient with abnormal anatomy and cannula problems. The outcome in this patient show that perfect positioning could be achieved by this technique and complications of suboptimal positioning can be prevented.

To determine if pre-operative planning can influence the surgical outcome a prospective study

is necessary. If superimposing of pre- and postoperative CT-scans is more precise by using a predefined scan protocol, further analysis for 3D planning of the tracheostomy site and cannulas can be done.

Conclusions

In this study, the use of virtual tracheostomy cannula placement using 3D reconstructions of CT-scans was explored. We found that the pre-operative positioning the stoma and subsequent placement of a cannula on a 3D model from the airway did not match with the surgical outcome. However, when stoma placement was not considered, we could identify a group of patients with neuromuscular disease, and abnormal anatomy of the neck that might benefit from 3D design of the cannula, using a post tracheostomy CT scan. This was supported by our case that showed that custom designed cannula using 3D virtualization techniques can reduce complications of suboptimal cannula positioning.

For optimal 3D virtual planning of the tracheostomy site and cannula position a prospective study is required. This study provides the first data towards individual tracheostomy and cannula placement planning in patients with abnormal anatomy of the head and neck.

Compliance with ethical standards

This study was not funded. There are no conflicts of interest. Ethical approval: The study has been reviewed by the Institutional Review Board of the UMCG and a consent waiver was granted for this retrospective chart review. Therefore, no informed consent was needed according to Dutch law. Informed consent was obtained from all individual participants for whom identifying information is included in this article.

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Chapter 5

Short and long term complications of surgical and percutaneous dilatation tracheotomies, a large single center retrospective cohort study

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Abstract

Objectives: The aim of this study was to determine and compare the incidence of long and short term complications of Percutaneous Dilatation Tracheotomies (PDT) and Surgical Tracheotomies (ST).

Design: A single center retrospective study.

Participants: 305 patients undergoing a tracheotomy (PDT or ST) in the University Medical Center Groningen from 2003 to 2013 were included. Data was gathered from patient files.

Main outcome measures: Short term and Long term complications including tracheal stenosis.

Results: The incidence of short and long term complications, including tracheal stenosis, were similar in both groups. Analysis of a small high risk subgroup showed no difference in long term complications.

Conclusions: The rate of short and long term complications, including tracheal stenosis, is equal in PDT and ST. PDT is a safe alternative for ST in selected patients.

Key Words: Tracheotomy, Tracheostomy, Percutaneous Dilatation Tracheotomy, Surgical Tracheotomy, Long term complications, Short term Complications, Intraoperative Complications

Introduction

Tracheotomy* is a surgical procedure that has been used since ancient times. It is performed for several reasons, i.e. upper airway obstruction or in case of an expected need for mechanical ventilation for more than 10-14 days.[1] It provides a safe and well-tolerated airway, providing access for pulmonary lavages, faster weaning from the ventilator and decreasing the risk of ventilator-associated pneumonia.[2] Traditionally a surgical tracheotomy (ST) is used to perform a tracheotomy.[3]

In 1969 the percutaneous dilatation tracheotomy (PDT) using the Seldinger or over-the-wire technique was developed.[4] Intensive care physicians are more familiar and comfortable with this technique and it has become a standard procedure at Intensive Care Units (ICU) all over the world. STs are usually performed in an operation theatre (OT). The consensus is that a PDT can only be performed in stable patients without anatomical abnormalities. The PDT is therefore used in a selected group of patients. Performing a tracheotomy at an ICU instead of an OT implies lower cost, less persons involved and a quicker procedure.[5,6]

In literature there is no consensus if PDT has lower or higher complication rate.[7-10] There is little information on the long term complications of PDT compared to ST.[11-13] A possible and serious long term complication of tracheotomies is tracheal stenosis. When a PDT is performed there is an assumed higher risk of fracturing a tracheal ring, potentially leading to tracheal stenosis.[14,15]

This study is performed to compare the long term complications of PDT and ST. Short term complications are also taken into consideration.

Materials and Methods

Inclusion

This is a retrospective study, in which a total of 305 consecutive patients undergoing tracheotomy between 2003 and 2013 were included. All included patients have had a PDT or ST in the University Medical Centre Groningen (UMCG), a third line referral hospital with 400 new patients with head & neck malignancies annually. Inclusion criteria were: 18 years or older at the time of intervention and registration of technique used (PDT or ST). Variables registered were: indication, anatomical abnormalities, complications, scarring, voice changes and swallowing complaints, use of anticoagulants, history of

*The procedure is called tracheostomy or tracheotomy in literature. We reserve the term 'tracheostomy' for the airway stoma of laryngectomized patients.

neck surgery and radiation. Patients were selected using a coded database for the ST, by doctor's databases and a search for 'Tracheotomy' in electronic patient files. Radiation and/or surgery of the neck may lead to anatomical changes of the neck and are assumed to make patients unsuitable for PDT. As PDT was relatively contra indicated in patients with pre- or postoperative radiation therapy, previous neck surgery or thoracic surgery or a previous tracheotomy, these patients were excluded from the analysis and labelled as 'high risk'. After exclusion, 189 patients were identified for analysis. The other 116 patients are included in a subgroup analysis for long term complications.

Definitions

Short term complications were defined as complications within two weeks of surgery. They include surgical complications (false route, lacerations, bleeding), post-operative bleeding, granulation formation and infection. Long term complications were defined as complications that appear after more than two weeks after surgery and can be related to tracheotomy. The two week time span was chosen as the healing process will be mostly completed after this time. Tracheal cartilage will show effects of trauma after two weeks, possibly presenting in necrosis and collapse.[16] Long term complications include tracheal stenosis, swallowing disorders, voice complaints or scarring. Swallowing disorders were described as difficulty swallowing, pain or aspiration. Voice complains were mainly complaints of hoarseness. Swallowing and voice disorders may not be related to the tracheostomy, but to the intubation or principal problem. Therefore only big differences between the techniques regarding these complications will be noticeable after analysis.

Follow up

Patients in both groups were followed until the end of the study, until death of the patient, when lost to follow up (no records of the patients for 6 month or more) or until a new tracheotomy or a laryngectomy was performed. During regular follow up patients were asked for symptoms indicating long term complications. Diagnostic procedures for the detection of complications were only performed when indicated.

Techniques

In the UMCG the Ciaglia Blue Rhino® (Cook medical, Limerick, Ireland) is used for performing a PDT. This is a one-step tracheal dilatator that is introduced over a guided wire and is always placed with endoscopic guidance. STs were performed using a Björk flap to prevent false routes when changing the tracheotomy tube.

Ethical considerations

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen (M13.142044). No patient consent was needed in this retrospective study.

Analysis

Data was gathered using Microsoft Access 2010 and statistical analysis was performed using IBM SPSS Statistics 22. Several methods were used to analyse the differences between the two techniques. The Chi-Squared test was used for ordinal data and Independent samples T-test was used for normally distributed continuous data. The Kolmogorov Smirnov test of normality was used to determine non-parametric distribution. A Mann-Whitney U test was used to compare means between the two groups for non-parametric data.

Results

Baseline Characteristics

As shown in table 1, 52.9% of included patients underwent ST. Almost all patients in the IC unit have prophylactic anticoagulants administered to prevent thrombosis. In table 1 'anticoagulant use' therefore is limited to therapeutic anticoagulant use (Acenocoumarole or Heparin).

Table 1: Registered baseline characteristics of 189 study subjects who underwent either PDT or ST. PDT: percutaneous dilatation tracheotomy. ST: surgical tracheotomy. † A Man Whitney U test was used to compare the age during surgery (non-parametric data).The Chi squared test was used for ordinal data.

PDT	**47.1% (n=89)**			
ST	**52.9% (n=100)**			
	PDT	**ST**	**P-value†**	**Total group**
Male	n=56(62.9%)	n=64(64.0%)	0.878	63.5%
Age during surgery (means in years)	59.8	56.0	0.070	57.8
Anticoagulant use	n=1(1.1%)	n=3(3.0%)	0.371	2.1%
Obesity	n=8(8.9%)	n=9(9.0%)	0.998	8.9%

Indication

As shown in table 2, the indication for performing the tracheostomies is different for both techniques. The ST was more often used in patients with ENT tumours. PDT is used in selected patients of the ICU when the expected need for mechanical ventilation is longer than 14 days.

Table 2: Indication for tracheotomy in a cohort of 189 subsequent patients. PDT: percutaneous dilatation tracheotomy. ST: surgical tracheotomy. † The Chi squared test was used for ordinal data.

Indication	PDT (n=89)	ST (n=100)	P-value†
Oncology	n=1 (1.1%)	n=27 (27.0%)	<0.001
Post-Operative	n=9 (10.1%)	n=1 (1.0%)	0.005
Neurology	n=5 (5.6%)	n=26 (26.0%)	<0.001
Benign obstruction	n=0 (0%)	n=12 (12.0%)	0.001
Vascular	n=5 (5.6%)	n=6 (6.0%)	0.911
Pulmonary	n=37 (41.6%)	n=12 (12.0%)	<0.001
Swallowing	n=1 (1.1%)	n=0 (0%)	0.288
Others	n=27 (30.3%)	n=16 (16.0%)	0.019
Not Registered	n=4 (4.5%)	n=0 (0.0%)	0.032

Short term complications

No statistically significantly differences in short term complications were registered in either group (Table 3). Perioperative complications consisted of tracheal laceration or airway obstruction during surgery. In one patient in the 'high risk' group it was necessary to convert the PDT to an ST. The conversion was performed because of tracheal laceration with positioning of the tracheotomy tube in the oesophagus. One other patient in the 'high risk' group needed surgical intervention days after the PDT because of narrow tracheal opening rendering switching of the tracheotomy tube difficult. Neither reintervention had long term sequelae.

Table 3: Short term complications in a cohort of 189 subsequent patients. PDT: percutaneous dilatation tracheotomy. ST: surgical tracheotomy. Major bleeding is defined as bleeding during the procedure that requires ligation of vessels or surgical intervention. Normal haemostasis during surgery is not taken into account. † The Chi squared test was used for ordinal data.

Complication	PDT (n=89)	ST (n=100)	P-value†
Perioperative complications	n=3 (3.4%)	n=6 (6.0%)	0.397
Operative Major Bleeding	n=0 (0.0 %)	n=1 (1.0%)	0.344
Postoperative Granulation	n=3 (3.4%)	n=9 (9.0%)	0.113
Postoperative Infection	n=0 (0.0 %)	n=2 (2.0%)	0.180

Long term complications

Only patients with a follow up of more than two weeks were included for analysis of long term complications, leaving 87 PDT and 84 ST patients. Patient that had complaints of swallowing or voice before removal of the airway cannula were excluded as the cannula influences swallowing and voice quality. All long term complications registered were comparable between the two tracheotomy techniques (Table 4).

Tracheal stenosis was registered in 3 patients (3.4%) in the PDT group and 4 (4.8%) in the ST group (p=0.665, Chi Squared test). Routine examination of the trachea did not take place. In the ST group 1 patient had a subclinical (i.e. had no complaints) tracheal stenosis. This stenosis was discovered by laryngeal endoscopy for other reasons. The proportion of patients that certainly was not having a tracheal stenosis, confirmed by endoscopic laryngeal examination, was 4.5% for PDT and 3.0% for ST. In the majority of the patients, tracheal stenosis was not objectified by direct observation, or the findings were not reported. The number of subclinical stenosis can therefore not be assessed.

Table 4: Long term complications in a subgroup of the study population (n=171 of total population) that have a follow up of 2 weeks or more, and a 'high risk' subgroup (n=107) also with a follow up of 2 weeks or more. PDT: percutaneous dilatation tracheotomy. ST: surgical tracheotomy, † The Chi squared test was used for ordinal data.

Long term complications

Complication	PDT (n=87)	ST (n=84)	P-value†
Tracheal stenosis	n=3 (3.4%)	n=4 (4.8%)	0.665
Swallowing disorders	n=2 (2.3%)	n=1 (1.2%)	0.581
Voice complaints	n=1 (1.1%)	n=0 (0.0%)	0.324
Scarring	n=1 (1.1%)	n=9 (10.7%)	0.014

Long term complications in 'high risk' subgroup

Complication	PDT (n=14)	ST (n=93)	P-value†
Tracheal stenosis	n=0 (0%)	n=4 (4.3%)	0.429
Swallowing	n=0 (0%)	n=4 (4.3%)	0.429
Voice complaints	n=0 (0%)	n=3 (3.2%)	0.495
Scarring	n=2 (14.3%)	n=6 (6.5%)	0.299

High risk patients

The above analyzed group consisted of all patients who underwent a PDT or ST without pre- or postoperative radiation therapy, previous neck surgery or thoracic surgery or a previous tracheotomy. Patients who underwent pre- or postoperative radiation therapy, previous neck surgery or thoracic surgery or a previous tracheotomy can be determined as high risk. Using these criteria 107 high risk patients were identified. Sub analysis are shown for high risk patients (table 4). The patients that had a PDT is small (n=14) in this group as the risk factors are a relative contra indication to perform a PDT. No statistically significantly differences were found.

Follow up

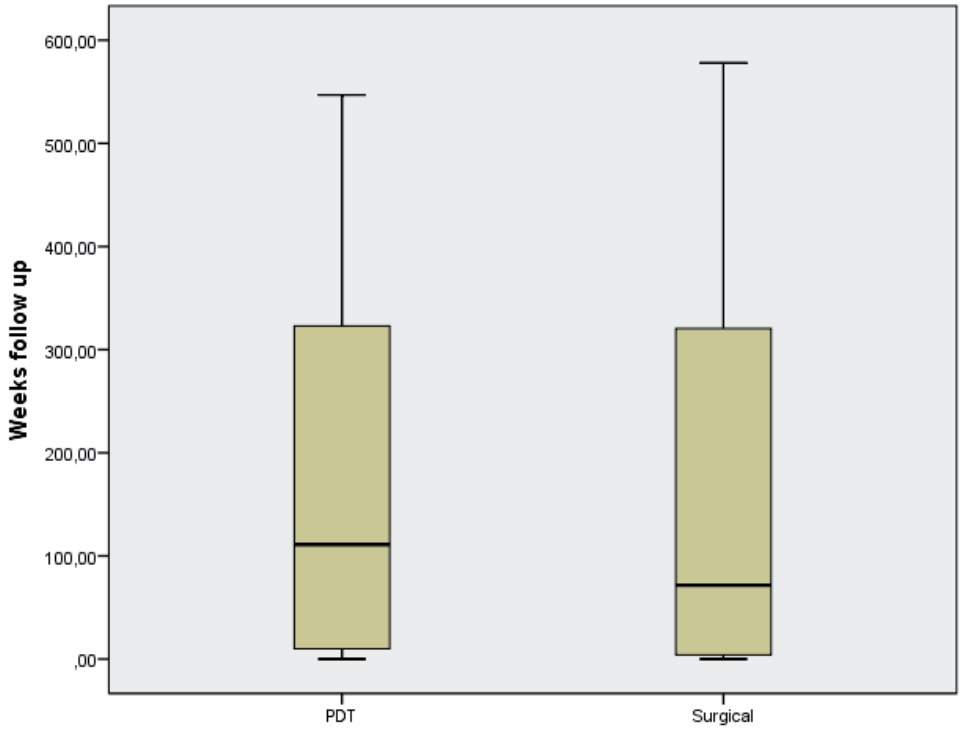
Follow up rates were comparable (figure 1). There are many reasons for ending follow up. The main reason is death of the patient. The reasons for ending follow up differ without statistical significance (table 5). The amount of patients that died within follow up of this study is comparable in both groups (P = 0.188, Chi Squared test). Median time to death after tracheotomy was 6

month for PDT patients and 5 month for ST patients, with a similar distribution (Man Whitney U test, P=0.278).

Table 5: Reasons for ending follow up in a cohort of 189 subsequent patients. PDT: percutaneous dilatation tracheotomy. ST: surgical tracheotomy. † The Chi squared test was used for ordinal data.

Reason ending follow up	PDT (n=89)	ST (n=100)	P-value†
Deceased	n=45 (50.6%)	n=41 (41.0%)	0.188
Lost to Follow Up	n=20 (22.5%)	n=28 (28.0%)	0.383
New Tracheotomy	n=3 (3.4%)	n=5 (5.0%)	0.579
Laryngectomy	n=0 (0%)	n=6 (6.0%)	0.019
End of Study	n=21 (23.6%)	n=207 (20.0%)	0.549

Figure 1: Box plot for follow up in weeks. PDT (percutaneous dilatation tracheotomy): Median 111,0, Range [0-574]. ST (surgical tracheotomy): Median 71,5, Range [0-578]. Distribution is the same across the groups (P = 0.316, Man Whitney U test for non-parametric distributed continuous data).



Discussion

As this was a retrospective study no randomisation between the two techniques was performed. The indication for performing the tracheotomy is different in both groups (Table 2). This is mainly because a PDT is performed on stable patients in the ICU when the expected need for mechanical ventilation is longer than 14 days. A ST is performed in ENT patients and in patients that are not on the ICU or have a high risk profile. To limit the bias caused by the difference in indication to perform the tracheotomy, high risk patients were excluded from analysis. Still the indication differs between the groups. A ST is statistically significantly more often performed in case of oncology, neurologic problems and benign airway obstruction. A PDT is statistically significantly more often performed for pulmonary reasons or post-operative. As tumours may change anatomy and can cause a change in routine, a bias is introduced, leading to a more favourable outcome for PDT patients. This bias can only be prevented by performing a randomized study.

This retrospective study allowed for analysis of baseline, operative, short term and long term characteristics. There was no significant difference in perioperative complications. Conversion to a surgical procedure during PDT or surgical intervention after PDT is rare, with 2% in our total series. This is comparable with Voelker et al.[17] A limitation of this retrospective study is that the information about perioperative complications of the ST were primarily found in surgical reports and no structured reports were made for PDT. There is probably a substantial discrepancy in registration, especially of minor complications.

There is a lack of consensus in literature regarding short term complications in PDT compared to ST. Several studies show more short term complications in ST patients.[9,18,19] Oliver et al. found more early complications in PDT compared to ST.[20] Other studies do not show any differences.[6,7,21-23] The meta-analysis by Higgins et al. illustrated no clear difference, but a trend toward fewer short term complications in PDT.[21] In our study short term complications do not differ statistically significantly. The lack of consensus in literature could be explained by the more accurate registration during and after ST compared to PDT. Also a ST is more often performed in high risk patients with specific comorbidities and tumours in the neck region. In our study these patients were excluded from the analysis.

An important outcome measure in our analysis concerned the presence of tracheal stenosis after tracheotomy. Tracheal stenosis can lead to shortness of breath. Depending on the severity patients either have no discomfort, or have shortness of breath during exercise or even when resting. Many patients will not notice a small degree of stenosis, depending on their physical exercise capacity. It is to be expected that patients report symptoms of clinical stenosis during follow up visits. Subclinical stenosis may be missed if patients are not examined for tracheal stenosis. As this was a retrospective study no screening tests were performed to detect tracheal stenosis. Most subclinical stenosis were therefore not detected. It is to be expected that a proportion of patients have subclinical tracheal stenosis.

Only two studies have compared the long term complications between PDT and ST.[20,24] Both studies used pooled data and showed that PDT and ST have a comparable number of long term complications. Our article is the only original article using single centre data to compare long term complications. In our study we found 3.4% tracheal stenosis in patients after PDT and 4.8% after ST (not statistically significant), most of them with clinical symptoms. Low rates of clinical tracheal stenosis after PDT have been described in literature.[12-14] Young et al., performing magnetic resonance imaging of 50 patients that underwent a PDT ≥ 3 months before, found a stenosis rate of 10%, none of them showing clinical symptoms.[25] A subgroup analysis of high risk patients was performed for long term complications. No statistically significant differences were found, but the PDT group is small (n=14). PDT is less often performed in this high risk group as pre- or postoperative radiation and previous surgery causes scarring, fibrosis, atrophy and changes the anatomy of the neck. This can make a PDT more difficult to perform and facilitates long-term complications such as tracheal stenosis. PDT is therefore mainly used in patients with a low risk profile. The use of PDT has been extended to higher risk patients in recent years, there are reports showing the safety of using PDT in patients after thoracic organ transplant procedures.[26] We believe the use of PDT will be extended to higher risk patients in coming years.

Strengths and limitations

This study was performed in a large cohort. All patients above 18 years old in a large medical centre were included and sub analysis were performed for high risk patients. It is a retrospective study so registration bias is expected. Also, as all ST patients were traceable from operation logs, none will have been overlooked. PDT patients were gathered using a patient file search as no records were held. Some PDT patients may therefore have been overlooked. Not all patients were examined post operatively for subclinical tracheal stenosis. Therefore subclinical stenosis could be underrepresented in this study.

Conclusion

This study shows PDT as a safe alternative to ST in selected patients. The rate of short term and long term complications including tracheal stenosis is equal in PDT and ST. We believe the use of PDT will be extended to higher risk patients in coming years.

Compliance with Ethical Standards

None of the authors have conflicts of interest to declare. No funding was received for this study. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen (M13.142044). No patient consent was needed in this retrospective study, in accordance with the Helsinki declaration.

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Chapter 6

Pitfalls of a conducting multicenter study - lessons learned

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Introduction

As described in chapter I, the ProTrach® DualCare™ is deemed to be clinically feasible. To determine if there is a significant difference in the patient preference for the ProTrach® DualCare™, a powered prospective study is needed. The ProTrach® DualCare™ has several advantages compared to other speaking valves as it combines a speaking valve and functional HME in one product.

Tracheotomised patients lack the function of the upper airway: moisturizing, warming and filtering the air. Heat and Moisture Exchangers (HME) are developed to regain some of these functions. An HME works by retaining the heat and moisture of exhaled air passing through it. When inhaling, the air is conditioned using the retained heat and moisture. Also the air is filtered by the HME. This is associated with better lung function and less secretions.

Furthermore, tracheotomised patients are unable to speak as the air is not passed through the vocal cords. The loss of speech is resolved by patients closing their tracheostomy tube with a finger or by a speaking valve redirecting the air through the upper airway. A speaking valve contains a membrane that is closed when patients exhale. Advantages of a speaking valve are hands free use, reduction of aspiration by maintaining subglottic pressure, better olfaction and less damage of trachea and skin.

Until now, one had to choose between a speaking valve and an HME. With the ProTrach® DualCare™ (Atos Medical, Hörby, Sweden) a speaking valve and functional HME are combined in one device, using a 'speaking' and an 'HME' mode. This is expected to improve lung function and quality of life (QOL) of tracheotomised patients depending on their original device. The patient preference is therefore expected to favour the ProTrach® DualCare™.

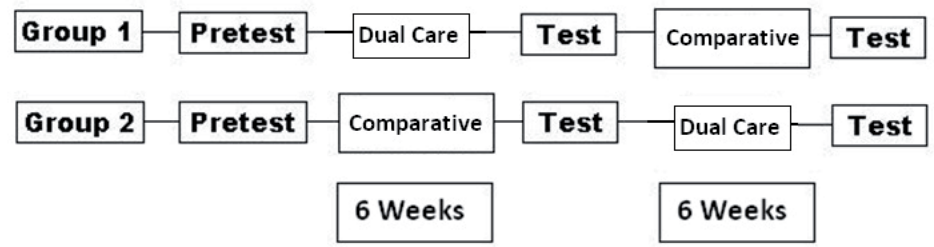
In this chapter, the process of preparing, starting and eventually stopping a multicentre randomized 2x2 cross-over study will be described. The goal was to test the DualCare™ for patient satisfaction in a multicentre, clinical crossover study. The aim of this chapter is to demonstrate the difficulties setting up a multicenter study.

Materials and Methods

Methods

The study design was a multicentre, randomized, 2x2 cross-over study (Figure 1). Allocation of the patients to the two groups was randomized within the centres, but the study was not blinded as the patient and the investigator knew which product was used.

Figure 1: Study design



The main parameter tested was patient preference. Secondary parameters were quality of life (QOL), lung function, breathing resistance, swallowing, olfaction, quality of speech and compliance. The parameters were tested at three moments: baseline, after the first treatment period (six weeks) and after the second treatment period (twelve weeks). The QOL was scored using the EQ5D and the VR-QOL. The secondary parameters were scored using questionnaires.

As this was an investigator initiated study, the documents and protocol needed for the study were prepared by the main researcher. Ethical committee approval was obtained in the UMCG and several other participating hospitals, including the University Medical Centre Groningen (UMCG), Netherlands Cancer Institute (NKI), Radboud University Nijmegen (RU) and Maastricht University Medical Centre (MUMC).

Participants

Tracheotomised patients using a cannula who were expected to need the cannula for at least six more months, were asked to participate. Inclusion criteria were: 18 years or older and tracheotomised, the patients had to have the mental and physical capacity to operate the ProTrach® DualCare™ and had to be able to use a speaking valve. Patients that were mechanically ventilated, who could not use a speaking valve due to airway obstruction or thick and copious secretions, were excluded. Forty-five participants were needed to complete the study, based on a power calculation using results from the feasibility study.

We used PASS11 package to perform Power Analysis to calculate the proposed sample size for testing one proportion. A minimal patient preference of 50% is tested against a preference of 73%. This percentage was determined at the feasibility study. Using an alpha of 0.05 and a target power of 0.80, 37 patients are needed using a two tailed test. To allow for some dropout and problems not related to the device (e.g. stoma problems) and loss of degrees of freedom for multicenter issues, we propose to add 20% and include 45 patients in total in the study. The current caseload in the participating centers was deemed large enough to obtain the patients needed for this study.

Ethical considerations

The study was approved by the Medical Ethical Committee of the University Medical Centre Groningen. Before inclusion, a signed informed consent was obtained from all participants. The study was monitored for patient safety and data validation. The ethical commission in all participating centres reviewed and approved.

Investigational product

The ProTrach® DualCare™ (ATOS Medical, Hörby, Sweden) was the same as used in Chapter I. Sufficient devices for the participants and for educational purposes were provided by ATOS Medical.

Results

After the first round of inclusion, less than 20 participants were included in the study. A new round was set up, even contacting patients in the region known to Atos Medical, that were not under treatment in the participating hospitals (after approval of the Ethical Committee). After this round, in total 23 participants were included.

Unfortunately, the inclusion ended after inclusion of these 23 participants. As the population of patients with long term cannula use does not grow quickly, several new centres in the Netherlands and even two German hospitals were contacted for participation in the study. Initially, a fifth Dutch tertiary centre would also participate in the study but cancelled after seeing the research protocol. This centre was also contacted again but declined. Most non tertiary hospitals do not have a large enough population of tracheotomised patients enabling them to participate in the study. Some suitable hospitals declined because of the foreseen time investment.

As the intended study population could not be reached, the study was closed before inclusion was completed because it was not possible to gather enough patients to fulfil the pre-determined power of the study. As only 16 new participants were included compared to the feasibility study (also having 16 participants), the data was not analyzed as it would not contribute new information to the already gathered information. Resources, time invested by doctors, patients and several ethical commissions was lost.

Discussion

Conducting a multicentre trial has advantages over a single centre trial. Bias due to local protocols or population differences are lowered, inclusion can be completed faster and studies can be completed in less time when more centres participate.[1] However, there are several challenges

in conducting multicentre clinical trials. Treatment differences, inclusion problems, funding, ethical review, patient safety and protocol adherence are some important problems.[2-4] When conducting a multicentre study, several essential points are necessary to bring it to a successful end.[3,5] Site selection, hiring staff, review board approval and communication are some examples. Inclusion is one of the most important reasons for medical studies to take longer than planned or not succeed at all.[2] A realistic estimate of available patients that are willing to participate in research is hard to make and is often lower than expected. Careful and realistic planning is important, but often hard to do.

It is advisable to launch a multicentre study from a pilot study. This strengthens the power calculation and assumptions can be made on patient availability, consent rate and how many participants complete the study. Also the used case report forms (CRF) (the questionnaires) can be evaluated before using them in the multicentre study. The study discussed in this chapter was launched from a feasibility study, CRF's were adjusted before starting the study and an assessment of population size per hospital was made. After the inclusion started, it became clear that several centres had overestimated the number of participants they would be able to include in the study. This was not foreseen. The feasibility study was conducted in a similar tertiary medical centre. This shows that information about the population gathered from a feasibility or pilot study is not always applicable to a multicenter study.

A motivated team of local coinvestigators and study coordinators will increase chances of success. Investigators need to be familiar with the topic of the study and experienced in the field of research. Collaboration between all involved scientific staff is necessary to keep the study on track and to keep everybody motivated. In this DualCare™ study, local investigators were all researchers of the ENT department. Some were PhD candidates, some staff members. Especially the staff members had limited time to conduct patient visits and complete questionnaires. As this was an investigator initiated study, funding was limited and the time investments were to be done without compensation. This may limit the motivation in several centres to include and follow-up patients. To fore come this problem, the principal investigator did travel to all participating centres to conduct the initial inclusion of participants, but not all follow-up visits could be conducted by the principal investigator, leaving the necessity for time investment by local investigators. No additional funding was available to hire research staff to unburden the local investigators. This may have played a role for some centres to decide not to participate. As described by Weinberger et al, a way of keeping participating researchers motivated is to make guidelines for authorship.[1] This study did not have such guidelines, but all researchers were promised an authorship when including participants and taking part in the writing process. Good communication between the different centres may prevent mistakes and therefore drop outs and keeps all centres motivated to continue inclusion. Several independent parties can play a role in communication by monitoring patient safety, data quality and adherence to protocol. A data safety monitoring board (DSMB), data coordination centre (DCC) are examples. Also a

steering committee (consisting of the principal investigator and coinvestigators) and operations committee (consisting of the principal investigator, DCC members, and study coordinators). As this was a small multicentre study, no DCC or DSMB were set up and there was no financing to do so. Therefore, most of the tasks were performed by the principal investigator. There were no disputes leading to drop out or refusal of medical centres.

This study has taught us several lessons. To prevent inclusion problems, a realistic plan, time investment and agreements in effort needed from the local researchers and principal investigator are needed. Even before presenting the study protocol and documents to the Ethical Committee, it would be preferable to have an agreement, in writing or spoken with the participating centres. Most importantly a buffer, or backup plan is important to succeed in a prospective study. If possible, do not start a study before the number of participants is clear and meets the pre-defined power of the study. If this is not possible, try to involve more hospitals than expected to be needed, so there is a source of extra participants if needed. Finally, a well-planned and well prepared study has the best chance of succeeding. Preferably, a multicentre study is preceded by a feasibility study. But even then, a realistic estimate of available patients often remains difficult.

Conclusion

This study was discontinued before reaching the pre-defined inclusion goal. Clinical research (on medical devices) will always be dependent on patients willing to participate. Careful planning and clear agreements with the participating centres increase the chance of success. However, it does not guarantee a successful completion of a study. The only way to improve medical care with medical devices, is to keep developing, researching and improving these devices.

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General Discussion

Future of medical devices

Introduction

This thesis evaluates multiple airway related medical devices used in Ear, Nose and Throat (ENT) patients. In chapter 1, 2 and 3 feasibility studies are presented, showing that these devices for patients with tracheostoma are ready for clinical use. These studies may also form the base for further research on these products. New techniques using 3D modeling for tracheostoma management are explored, and a large retrospective study comparing percutaneous dilatation tracheotomies to surgical tracheotomies is presented. In the following paragraphs, the findings of these studies and future aspects of patient care with medical devices and new techniques are discussed.

General discussion

Chapter one shows a clinical feasibility study of the ProTrach® DualCare™. The ProTrach® DualCare™ combines a speaking valve and a Heat and Moisture Exchanger (HME) for tracheotomized patients. Before the DualCare™ was developed, patients had to choose between an HME for optimal lung care and a speaking valve for the benefits of hands free speech. As a bi-directional airflow is needed for a fully functional HME, previously available speaking valves combining an HME with a speaking valve did not provide optimal care.[1] Sixty-nine percent of patients testing the DualCare™ preferred it over their conventional device.

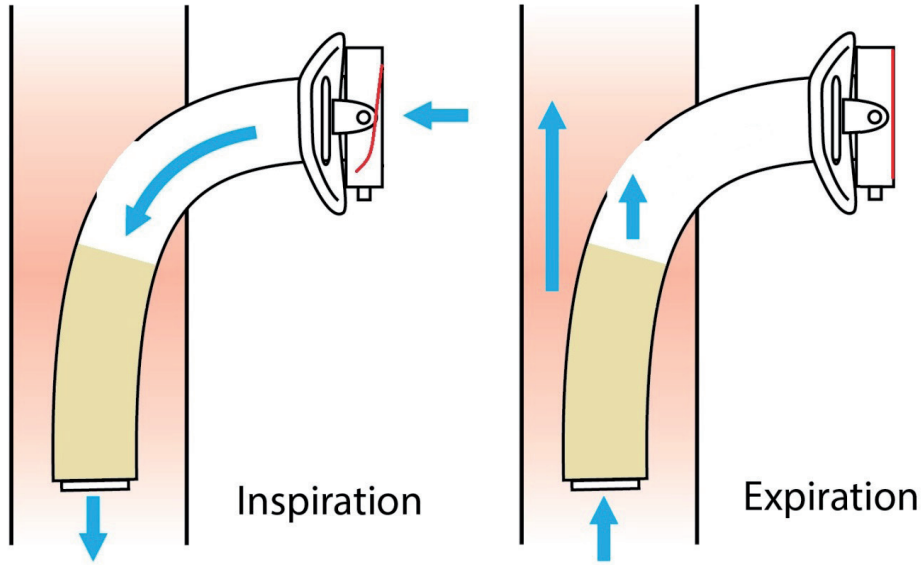
The DualCare™ uses a light membrane that closes easily. This leads to reduced speaking noise, better speech quality and lower breathing resistance. Some patients complained about stickiness of this membrane to the outer casing of the DualCare™. This complaint led to a re-design of the product, solving the problem and leading to higher patient satisfaction. The re-design further underlines the importance of clinical testing with cooperation of objective test subjects to optimize the product before releasing it on the market.

The study indicates that the DualCare™ can decrease breathing resistance, improve voice and speech sound, and improve HME compliance for tracheotomized patients. In the study, the DualCare™ was compared to other speaking valves and HME's. There are several producers of speaking valves for tracheotomized patients, including Passy Muir, Montgomery, Olympic, Ashon, Shiley and Medtronic.[2] All of these speaking valves have different clinical properties.[3] None of the participants in the study used a speaking valve by one of these producers as they are not widely available in the Netherlands. Users of medical devices are dependent on the products they get provided by insurance companies and doctors. With the upcoming of the global economy, patients have access to different products via the internet. As different products have different properties, it is important to keep on discussing the available options with patients and advice patients in the possibilities. As for now, none of the speaking valves, except the ProTrach® DualCare™, contain a functional HME. This may be a reason to advice the ProTrach® DualCare™. HME's improve the moisture percentage and temperature in the trachea.[4-6] An HME reduces coughing, shortness of breath, mucus production and respiratory infections.[7-10] On the other hand, the currently used HME's only have a limited capacity of containing moisture and heat, not reaching physiological levels of moisture and temperature of inhaled air. The capacity of an HME is depending on the density of the HME, the coating used on the HME and the size of the HME. At this point, it is not possible to improve the capacity of the current HME because this would lead to an increase in volume of the HME's, being uncomfortable for patients esthetically, and generating increased breathing resistance. New materials, designs and coatings can lead to improvement of these parameters.

In future product designs, it may be possible to create a disposable inner cannula with fenestrations for tracheotomized patients that contains an HME and a speaking valve (figure 1). Benefits of such a design would be a bigger space that could be used for an HME, improving its capacity. Furthermore, the profile of the product can be very small as everything can be built in. This may lead to better quality of life and patient satisfaction.

Other improvements that could enhance HME function are the use of other coatings and materials. HME coating can improve filtering capacity of HME's, preventing microorganisms form passing through.[11] The clinical effect of these new coatings have to be investigated to determine their clinical utility. Other materials could lead to a denser filter without increasing breathing resistance.

Figure 1: potential new design for cannula with integrated HME and speaking valve.



Chapter two shows a multicenter prospective study to evaluate the clinical feasibility of the FreeHands FlexiVoice™. Like the the ProTrach® DualCare™, the FlexiVoice™ combines an HME and a speaking valve in one device for laryngectomized patients. The Provox® FreeHands HME™ has already combined an HME with a speaking valve, but had a low compliance rate due to unreliable fixation of the adhesive to the peristomal skin.[12] To improve compliance with the speaking valve and HME, the FlexiVoice™ was designed, using two modes to increase the durability of the adhesive and to allow more effortless speech. The FlexiVoice™ allows for hands-free speech in a large proportion of laryngectomized patients.

There are two other producers of speaking valves for laryngectomized patients: The Blom-Singer® Hands free and FAHL Laryvox Hands free valve. The Blom-Singer® hands free is comparable to the FreeHands FlexiVoice™, although it does not have the possibility of closing it using a finger when needed. The FAHL® Laryvox does not have an integrated HME. The Blom-Singer and FAHL® Laryvox are not widely available in the Netherlands; therefore, most patients use a FreeHands FlexiVoice™ for hands free speech after a laryngectomy. Interpatient variability and availability of different speaking valves determine the preference for individual patients.

The most serious problem of using a hands free speaking valve after laryngectomy is the fixation of the valve. Compared to tracheotomized patients, a lot of pressure is needed to generate speech through the voice prosthesis and esophagus. The adhesives, used to fixate medical devices in front of the stoma, are not ideal for this amount of pressure. Plenty of different peristomal adhesives are available from different producers. Some with good results, but hands free speech with a speaking valve keeps reducing device life.[13-15] Van Kalkeren and van der Houwen et al. showed the diversity of peristomal geometry and adhesive fit in a large group of patients.[16,17] Future studies should be conducted to circumvent these problems, using differences in periostomal geometry and adhesive qualities of skin glue to a more personalized design of the adhesives.

Chapter three of this thesis shows the 2 × 2 crossover prospective multicenter clinical trial of the Provox® StabiliBase OptiDerm™, one of the adhesives developed to give a longer and more stable device life whilst providing a skin friendly adhesive. The StabiliBase OptiDerm™ was favored by some patients, but most patients preferred their previously used peristomal adhesive. The StabiliBase OptiDerm™ is an addition to broaden the choice in peristomal adhesives for laryngectomized patients and can be used when the peristomal skin is irritated or when extra stability is required.

As mentioned before, the device life of peristomal adhesives is reduced when using hands free speech. Recently, a moldable external neck brace has been developed, aiding the fixation of the hands free speaking valve.[18] The thermoplastic properties of the used material make the product customizable for individual patients, aiming for individualized care. This brace is fixated around the neck and improves device life of the peristomal adhesive when using free hands

speech. Furthermore, the Provox®FreeHands Support™ recently came available on the market. This medical device fixates the hands free speaking valve with a metal ring that is fixated on the sternum.[19] In the future, these products may be further improved and in combination with further developments in peristomal adhesives, it may enhance daily functioning of patients and consequently increase patient satisfaction and quality of life.

Individualizing care leads to better patient satisfaction and quality of life. Medical devices can be modified to suit personal needs, or can be adjusted to the needs of an individual patient. Recent days, the use of 3D techniques has made an enormous progress leading to custom designed devices, osteosynthesis material and surgical planning.[20-22]

In **chapter four** the introduction of 3D technique in airway management for patients requiring a tracheotomy cannula is investigated. This three-step study analyzed the added value of pre- and post-operative 3D visualization of the airway for the planning of the tracheotomy and the first 3D custom designed cannula is also presented. This achievement is especially relevant in patients with aberrant anatomy (e.g. patients with Duchenne muscular dystrophy), where standard positioning of the tracheotomy and/or the use of commercially available cannulas may lead to serious complications (airway stenosis through granulation formation or even fatal bleeding).[23-26] In the first step of this study, the airway of patients with normal anatomy was analyzed and virtual planning of the airway cannula was performed and compared with actual cannula placement. As the second step, the airway of patients with neuromuscular diseases and aberrant anatomy was also analyzed. Finally, a 3D planned and customized cannula was successfully designed, produced and placed in a patient. This is the first report of using 3D techniques to design a custom-made airway cannula for a patient with aberrant anatomy due to neuromuscular disease. Perfect placement was achieved by forging a silver cannula after the 3D printed design made virtually with a 3D image of a CT scan. By using this promising technique, complications of suboptimal placement can be prevented.

Further research is needed to optimize the process of 3D airway management and design of medical devices. It can be expected that by pre-operative 3D planning of the tracheotomy, less minor or major complications after cannula placement will occur. A prospective study with predefined scan protocol is needed to further analyze the added value of virtually planned tracheotomy site. It is almost impossible to compare soft tissue in two different CT scans of one patient as by different positioning of the head and neck, the soft tissues are displaced over the underlying structures. The positioning of the patient would therefore be very important in a study aimed to compare the accuracy of the stoma when using a 3D modeled and pre-defined tracheotomy site.

The use of 3D techniques is not limited to imaging, but can also lead to design of personalized medical devices like peristomal adhesives. Recent studies also show 3D bio printing can be used to reconstruct bone, cartilage or even soft tissue.[27]

In the **fifth chapter** a single centre, retrospective comparative study of Percutaneous Dilatation Tracheotomy (PDT) versus surgical tracheotomies (ST), comparing short term and long term complications is presented. As PDT uses pressure to dilate the trachea to create an opening for an airway cannula, it is expected to cause more damage to tracheal rings and surrounding tissue, leading to a higher rate of long term complications, like tracheal stenosis.[28,29] Until now, there is little known about the long term complications of PDT compared to surgical tracheotomies.[30-32]

Our study showed no differences in perioperative complications. PDT is a safe procedure with a 2% conversion rate to a surgical intervention. This finding is comparable to other studies.[33] Short term complications were also comparable. In the literature there is no consensus regarding short term complications after PDT compared to surgical tracheotomies.[34-42]

No statistically significant differences were found in long term complications. Two other studies have compared the long-term complications between PDT and ST.[39,43] The results of both of these studies used pooled data and are in line with our results, found comparable rate of long term complications.

It is to be expected that most subclinical stenoses were not detected and registered as patients did not have complaints that lead to additional clinical tests. Rates of clinical tracheal stenosis after PDT have been reported in literature to be low.[28,31,32] The amount of subclinical stenosis is expected to be higher, even up to 10%.[44] However, as stated before, due to the retrospective nature of our study these stenosis were not diagnosed in our study. In this retrospective study, PDT is shown to be a safe alternative to surgical tracheotomies with comparable long term complication rates.

In recent years, medical devices are used increasingly for surgery. The da Vinci Xi®, 3D navigated surgery and 3D scopes are being used on a daily basis. These devices will make more challenging surgical interventions possible and may reduce complication rate and patient morbidity.

Most studies presented in this thesis are feasibility studies. In these studies, the product is tested in a small group of patients to determine optimal functioning and to measure patient satisfaction. To get a better insight in the patient satisfaction of the products, a prospective comparative study between two or more products, using a cross over, would be preferable. Leading up to this thesis, an attempt was done to perform a multicenter randomized 2x2 cross-over study for patients satisfaction and function of the ProTrach® DualCare™. Four tertiary medical centers (University Medical Center Groningen (UMCG), Netherlands Cancer Institute (NKI), Radboud University Nijmegen (RUN) and Maastricht University Medical Center (MUMC)) participated to reach the needed group size of 45 participants. This was thought to be possible after analysis of the current patient population of these hospitals and following the 16 participants in the feasibility study, performed in the UMCG.

As shown in **Chapter six,** the inclusion did not succeed and the study was dropped. A calculation of power analysis on the required participants and an estimate on the available patients always needs to be made before a study can pass the medical ethical committee and start. Careful planning and assessment of patients are important factors; however, it still does not guarantee the success of this kind of research.

Future Prospects

The optimization of medical devices used by patients on a daily basis to improve quality of life and patient satisfaction is an important part of medical care. It will always be important to keep developing and improving medical devices by using new designs, materials and customization techniques. The use of new medical devices can also lead to new surgical techniques.

Design

As shown above, there are a lot of different solutions to solve the problems patients face after necessary medical interventions. **Chapter one to three** show products designed to aid with these difficulties, optimizing patient care. New designs improve the usability of the devices. All devices tested in this thesis are ‘analog’ devices, meaning no electronics are used to control or adjust the devices. It is expected with the recent, fast development of electronic devices and wearables that electronic technology will also be used in medical devices for airway management. This development is already ongoing in hearing rehabilitation, for instance using a smartphone app to adjust volume or selecting programs of the hearing aids or other hearing devices.[45] For speaking valves, this could mean adjustment of stiffness of the speaking membrane and switching between modes using a smart phone or watch. The devices themselves could also be improved with the introduction of electronics. Think of the use of an integrated electric voice simulator in the voice prosthesis improving the quality of the voice after laryngectomy.[46]

Materials

The development of new materials leads to more user-friendly products. As stated before, the ProTrach® DualCare™ (discussed in **chapter one**), the FreeHands FlexiVoice™, (discussed in **chapter two**) and the StabiliBase OptiDerm™, (discussed in **chapter three**) use new and/or combined materials to improve patients satisfaction.

The ProTrach® DualCare™ uses a very light membrane to occlude the speaking valve. Different strengths of membranes used in speaking valves influence the usability. Furthermore, patients’ preference is very subjective and individual. This is also seen in the design of the FreeHands FlexiVoice™, providing the patients with three different strengths of membranes for occluding

the speaking valve. Also, in the use of peristomal adhesives, there is a lot of inter-patient variation regarding skin quality, stoma shape and usage of an adhesive. There are a lot of different peristomal adhesives available, all using different materials to improve stability, skin friendliness and ease of use. Therefore, the development of new materials that can be used in medical devices leads to an improvement in quality of life and patient satisfaction.

Customization techniques

As shown in **chapter five,** customization of medical devices can lead to better care. 3D techniques are currently used by different medical specialists, mainly by specialists operating on bones like orthopedics, trauma surgeons and maxillofacial surgeons.[22,47] Also in otorhinolaryngology, virtual 3D reconstructions have been used using CT-scans or stereophotogrammetrical analysis.[48-52] These techniques have been used for 3D printed hearing aids, auricular prosthesis, educational purposes and surgical planning and managing the pediatric airway by printing external tracheal splints.[53] Future techniques, using 3D printers, can lead to customized medical devices. We have shown that it is possible to customize tracheotomy cannula in case of aberrant airway anatomy. This technique can be easily accessible in the future in every hospital where a 3D laboratory is available. Recent studies utilizing bio printing have shown promising results for reconstruction of the trachea, maybe even resolving the need for medical devices for some patients in the future.[54]
Furthermore, 3D technology could also be used for better analysis of the geometry of the tracheostoma of laryngectomized patients. The use of a hands-free speaking valve for laryngectomized patients is difficult because the peristomal adhesives are not always optimal and the geometry of the stoma is very individual. Therefore, there is no 'one size fits all' stoma patch.[55] Peristomal adhesives that are made using stereophotogrammetrical analysis and can be done in minutes, could be used to optimize patient satisfaction. In the future, patients could even print their adhesives at home using a 3D printer.

Surgical Techniques

New surgical techniques lead to minimal invasive procedures. The use of PDT has been shown to be a safe alternative to surgical tracheotomies in selected cases, as described in **chapter five**. It has been used in high risk patients in recent years.[56] Future techniques regarding tracheotomy may be even less invasive and with lower risks. Think of a catheter that can be introduces through a needle that expends to dilate the trachea without outward pressure. This would make the procedure less invasive and would probably reduce the risk of tracheal stenosis even further. The use of 3D techniques in the operating room and use of robot surgery may eventually lead to lower morbidity for patients, and may make inoperable patients operable.

Conclusion

The research presented in this thesis has evaluated and contributed to the development of medical devices for ENT patients with affected airways. Medical devices make up for a large part of the quality of life for patients depending on them. The optimization of medical devices, used by patients on a daily basis, is an important part of medical care. Developing new medical devices by cooperation between companies, researchers, doctors and patients will lead to better products and improve patient satisfaction. I believe that the development of medical apps for smartphones and wearables and integration of electronics in medical devices, 3D techniques and the development of new materials will lead to further improvement of the quality of life of our patients in the years to come.

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Summary

Medical devices used in ENT patients are diverse. Hearing aids, bone conductive devices, cochlear implants, ear drum grommets, nasal splints, speaking valves, voice prosthesis and peristomal adhesives are some examples. The field of medical devices is always progressing to provide optimal care and quality of life for patients. New techniques like 3D modeling and progression in operative techniques are constantly tested and implemented in daily care. Several medical devices used in patients with a tracheotomy or tracheostomy have been developed and are distributed by Atos Medical (Hörby, Sweden). In this thesis, the ProTrach® DualCare™, FreeHands FlexiVoice™ and Provox® StabiliBase OptiDerm™ by Atos Medical are tested in chapter 1 to 3. Chapter 4 describes the use of 3D techniques in airway management and in the fifth chapter two operative techniques to perform a tracheotomy are compared. Chapter six describes the process of a multicenter study that did not succeed due to incomplete inclusion. In the near future, medical apps, wearables, 3D techniques and the development of new materials will almost certainly lead to further improvements of available medical devices aiming to improve quality of life for patients depending on these products.

Product evaluation

The clinical feasibility of the ProTrach® DualCare™ was tested in chapter one. The DualCare™ is a device combining a hands free speaking valve and a Heat and Moisture Exchanger (HME) for tracheotomized patients. The DualCare™ was tested in a prospective single center study. In total 16 tracheotomized patients participated. The DualCare™ was tested for two weeks, after this period a long-term follow-up period of three month was offered to participants that preferred the DualCare™ over their normally used devices. Using the EuroQOL-5D, Borg scale and questionnaires, patients preferences and experiences were registered. Due to some complaints, a minor redesign was implemented. The device was well-tolerated and overall 11 participants preferred the DualCare™ to their standard device. Therefore, the DualCare™ was deemed clinically feasible.

The FreeHands FlexiVoice™ was tested in chapter two. The FreeHands FlexiVoice™ is a speaking valve with integrated HME for laryngectomized patients. This study was conducted as a prospective, multicenter study to evaluate the short- and long-term feasibility of the FreeHands FlexiVoice™. Key properties of this speaking valve are the integrated HME, the option to use manual and automatic occlusion and the choice of three types of membranes. In two medical centers, 40 laryngectomized patients were included and used the FlexiVoice™ for 26 weeks. As the fixation of hands free speaking valves for laryngectomized patients in front of the stoma is problematic, long-term compliance was the primary outcome measure. Patients preference, voice and speech quality and quality of life were also taken into account amongst others. After the study period, 15 patients (37.5%) used the FlexiVoice™ on a daily basis. Ten patients (25%) used

the FlexiVoice™ on a non-daily basis and the 15 remaining patients did not use the FlexiVoice™ at all. Problems with fixation of the peristomal adhesives when using the FlexiVoice™ were the main reason for participants to not use it on a daily basis or discontinue using it altogether. Overall, 18 patients (45%) preferred the FlexiVoice™ over their original product. It allowed for longer hands free speech compared to other speaking valves (mainly the Provox® FreeHands HME®). Therefore, the FlexiVoice™ was deemed clinically feasible.

To use medical devices in front of the stoma, laryngectomized patients often use a peristomal adhesive. In chapter three a new peristomal adhesive, the Provox® StabiliBase OptiDerm™, is evaluated in a prospective clinical 2x2 crossover study. The StabiliBase OptiDerm™ combines the stable and conical base of the Provox® StabiliBase™ with the skin-friendlier hydrocolloid adhesive used in the Provox® OptiDerm™. It is therefore designed for a subgroup of patients that need the conical base of the Provox® StabiliBase™ but have vulnerable peristomal skin that irritates when using this adhesive. In total 32 laryngectomized patients were included in the study and asked to compare the StabiliBase OptiDerm™, to the Provox® OptiDerm™ and their normally used adhesive. Patient preference was used as primary outcome measure. In total 23% of participants preferred the StabiliBase OptiDerm™ over their normally used adhesive. When compared to the Provox® OptiDerm™ 43% preferred the StabiliBase OptiDerm™. It therefore seems that the StabiliBase OptiDerm™ is a valuable addition for a subgroup of patients and it further increases patients' options.

Development of techniques used in device design and surgery

New techniques used in design of medical devices will eventually lead to more individualized products. Combining this with the development of new products and materials leads up to personal care for patients that need it. In chapter four the introduction of 3D techniques in airway management for patients requiring a tracheotomy is investigated. This is done in a three-step study that leads up to the design of a personalized silver cannula for a patient with aberrant anatomy using 3D techniques. The aim of the study was to investigate the use of 3D virtual planning of tracheostomy tube placement and personalized 3D cannula design in order to prevent complications due to inadequate cannula positioning. 3D models of several commercially available cannula were created and positioned in 3D reconstructions of CT scans. The scans were of patients who underwent a tracheotomy between 2013 and 2015 in the UMCG and that had a pre- and postoperative scan (n=26). The virtual optimal positioning was compared to the actual position post operatively. The optimal virtual placements differ significantly from the actual post-operative placement. After this, the second step was performed, virtually placing cannula in 3D reconstructions of CT scans of patients with neuromuscular disease (n=14) to determine if problems could be anticipated. Using this information, three groups were identified: 1. Normal

anatomy; 2. Abnormal anatomy and commercially available cannula fits; 3. Abnormal anatomy and custom-made cannula may be necessary. Finally, a patient-specific cannula was designed for a patient with Duchenne muscular dystrophy using virtual 3D techniques. With the use of a 3D printer a model was created that could be copied in silver. The positioning of this personalized cannula was optimal. This shows that 3D techniques lead to more individualized care for patients that cannot be optimally treated with commercially available medical devices.

Medical devices are used in the full extent of patient care. Diagnostics are performed using blood pressure monitors, CT or MRI scans, blood is drawn using needles. Physical examination is performed using endoscopes, a stethoscope and microscopes. Surgery is also performed using medical devices like stents, prosthesis, scopes, robots and 3D printed molds. The fifth chapter evaluates the use of percutaneous dilatation tracheotomy (PDT) compared to surgical tracheotomies (ST) in a single centre, retrospective comparative study. The PTDs are performed using a Seldinger or 'over the wire' technique like the Blue Rhino® utilizes. This is a medical device to dilate a tracheal puncture so a cannula can be placed. The aim of the study was to determine and compare the incidence of short and long term complications of PDT and ST. Therefore, 305 patients undergoing a tracheotomy in the UMCG between 2003 and 2013 were analyzed. A comparable cohort was selected for analysis. The incidence of short and long term complications were similar in both groups. Therefore, PDT is deemed to be a safe alternative for ST.

In chapter six a multicentre study of the ProTrach® DualCare™ that was not completed due to inclusion problems is presented. In this chapter the pitfalls of conducting a multicentre study are discussed and the lessons learned are described. Clinical research will always be dependent on the participation of patients. Careful planning and clear agreements with the participating centres increase the chance of success. Communication, motivation, time management and a good backup plan are important. However, this does not guarantee a successful completion of a study.

Finally, a general discussion is presented including future prospects of development of new medical devices and implementation of new techniques.

Samenvatting

Er zijn veel medische hulpmiddelen beschikbaar voor KNO-patiënten. Hoortoestellen, Bone Conductive Devices, cochleaire implantaten, trommelvliesbuisjes, septum splints, spreekkleppen, stemprothese en peristomale pleisters zijn enkele voorbeelden. Medische hulpmiddelen worden voortdurend door ontwikkeld om patiënten optimale zorg en kwaliteit van leven te bieden. Nieuwe technieken zoals 3D-modellering en nieuwe operatietechnieken worden voortdurend getest en geïmplementeerd in de dagelijkse zorg. Verschillende medische hulpmiddelen die worden gebruikt bij patiënten met een tracheotomie of larynxextirpatie zijn ontwikkeld door Atos Medical (Hörby, Zweden). In dit proefschrift worden de ProTrach® DualCare ™, FreeHands FlexiVoice ™ en Provox® StabiliBase OptiDerm ™ van Atos Medical getest in **hoofdstuk 1 tot en met 3**. **Hoofdstuk 4** beschrijft het gebruik van 3D-technieken voor luchtweg management en in het **vijfde hoofdstuk** wordt een percutane dilatatie techniek voor het maken van een tracheotomie vergeleken met de chirurgische procedure. **Hoofdstuk 6** beschrijft het proces van een multicenter onderzoek dat niet slaagde vanwege onvolledige inclusie. In de toekomst zullen medische apps, wearables, 3D-technieken en de ontwikkeling van nieuwe materialen vrijwel zeker leiden tot verdere verbetering van beschikbare medische hulpmiddelen om de kwaliteit van leven van patiënten die hiervan afhankelijk zijn te verbeteren.

Evaluatie van medische hulpmiddelen

In **hoofdstuk 1** wordt een klinische haalbaarheidsstudie van de ProTrach® DualCare ™ gepresenteerd. De DualCare™ is een hulpmiddel dat een handsfree spreekklep en een warmte- en vochtwisselaar (HME) combineert voor patiënten met een tracheotomie. De DualCare™ werd getest in een prospectieve single center studie. In totaal hebben 16 canule patiënten deelgenomen. De DualCare ™ werd gedurende twee weken getest, na deze periode werd een lange termijn follow-upperiode van drie maanden aangeboden aan deelnemers die de DualCare™ verkozen boven hun normaal gebruikte hulpmiddelen. Met behulp van de EuroQOL-5D, Borg-schaal en vragenlijsten, werden voorkeuren en ervaringen van patiënten vastgelegd. Vanwege enkele klachten over de DualCare ™ tijdens deze test periode heeft er een aanpassing aan het ontwerp van de DualCare™ plaatsgevonden. De DualCare™ werd goed getolereerd en in totaal 11 deelnemers gaven de voorkeur aan de DualCare™ ten opzichte van hun normaal gebruikte hulpmiddel. Daarom werd de DualCare™ klinisch haalbaar geacht. In **hoofdstuk 2** is de FreeHands FlexiVoice™ getest. De FreeHands FlexiVoice™ is een spreekklep met geïntegreerde HME voor gelaryngectomeerde patiënten. De studie was een prospectieve, multicenter studie bedoeld om de klinische haalbaarheid van de FreeHands FlexiVoice™ op korte en lange termijn te evalueren. De belangrijkste eigenschappen van de FreeHands FlexiVoice™ zijn de geïntegreerde HME, de keuze uit drie soorten membranen

en de mogelijkheid om de spreekklep handmatig en automatisch af te sluiten. In twee medische centra werden 40 gelaryngectomeerde patiënten geïncludeerd en de FlexiVoice™ werd gedurende 26 weken getest. Omdat de fixatie van handsfree spreekkleppen voor gelaryngectomeerde patiënten problematisch is, was gebruik van de spreekklep op de lange termijn de primaire uitkomstmaat. Als secundaire uitkomstmaten werden de voorkeur van de patiënten, de stem- en spraakkwaliteit en de kwaliteit van leven geëvalueerd. Na de onderzoeksperiode gebruikten 15 patiënten (37.5%) de FlexiVoice™ dagelijks. Tien patiënten (25%) gebruikten de FlexiVoice™ op niet-dagelijkse basis en de 15 resterende patiënten gebruikten de FlexiVoice™ helemaal niet. Problemen met de fixatie van de peristomale pleisters bij het gebruik van de FlexiVoice™ was de belangrijkste reden voor deelnemers om de spreekklep niet dagelijks te gebruiken of het gebruik helemaal te staken. In totaal gaven 18 patiënten (45%) de voorkeur aan de FlexiVoice™ boven hun oorspronkelijke product. De FlexiVoice™ gaf de mogelijkheid voor langere handsfree spraak in vergelijking met andere spreekkleppen (voornamelijk de Provox® FreeHands HME®). Daarom werd de FlexiVoice™ als klinisch haalbaar beschouwd.

Om medische hulpmiddel voor het stoma te gebruiken, gebruiken gelaryngectomeerde patiënten vaak een peristomale pleister. In **hoofdstuk 3** wordt een nieuwe peristomale pleister, de Provox® StabiliBase OptiDerm™, geëvalueerd in een prospectieve klinische 2x2 cross-over studie. De StabiliBase OptiDerm™ combineert de stabiele en conische basis van de Provox® StabiliBase™ met de huidvriendelijkere hydrocolloïd pleister die wordt gebruikt in de Provox® OptiDerm™. Het is daarom bedoeld voor een subgroep van patiënten die de conische basis van de Provox® StabiliBase™ nodig hebben, maar een kwetsbare peristomale huid hebben die makkelijk irriteert. In totaal werden 32 gelaryngectomeerde patiënten geïncludeerd in de studie. Hen werd gevraagd om de StabiliBase OptiDerm™ te vergelijken met de Provox® OptiDerm™ pleister en hun normaal gebruikte pleister. De voorkeur van de patiënt werd gebruikt als primaire uitkomstmaat. In totaal gaf 23% van de deelnemers de voorkeur aan de StabiliBase OptiDerm™ boven hun normaal gebruikte pleister. In vergelijking met de Provox® OptiDerm™ gaf 43% de voorkeur aan de StabiliBase OptiDerm™. Het lijkt er daarom op dat de StabiliBase OptiDerm™ een waardevolle toevoeging is voor een subgroep van patiënten.

Ontwikkeling van technieken gebruikt voor ontwerp van medische hulpmiddelen en chirurgie

Nieuwe technieken die worden gebruikt in het ontwerp van medische hulpmiddelen zullen uiteindelijk zorgen voor meer gepersonaliseerde producten. Samen met de ontwikkeling van nieuwe producten en materialen leidt dit tot persoonlijke zorg voor patiënten die het nodig

hebben. In **hoofdstuk 4** wordt het gebruik van 3D-technieken in luchtwegmanagement voor patiënten die een tracheotomie vereisen onderzocht. Dit wordt gedaan in een studie die in drie stappen is uitgevoerd. De studie leidt tot het ontwerp van een gepersonaliseerde zilveren canule voor een patiënt met een afwijkende anatomie. Hierbij werden 3D-technieken gebruikt. Het doel van de studie was te bepalen of gebruik van virtuele planning van de plaats van de tracheotomie en een aangepast 3D-canuleontwerp complicaties als gevolg van slechte positionering van de canule kan voorkomen. 3D-modellen van verschillende regulier verkrijgbare canules werden gemaakt en gepositioneerd in 3D-reconstructies van CT-scans. De scans waren van patiënten die tussen 2013 en 2015 een tracheotomie ondergingen in het UMCG en die een pre- en postoperatieve scan hadden (n=26). De virtuele positionering werd vergeleken met de daadwerkelijke positie van de canule post-operatief. De optimale virtuele positionering verschilde statistisch significant van de postoperatieve positie. Hierna werd de tweede stap uitgevoerd, waarbij de canule virtueel in 3D reconstructies van CT-scans van patiënten met neuromusculaire aandoeningen (n=14) werd geplaatst om te bepalen of problemen met positionering konden worden verwacht. Aan de hand van deze informatie werden drie groepen geïdentificeerd: 1. Normale anatomie; 2. Abnormale anatomie en reguliere canules passen; 3. Abnormale anatomie en op maat gemaakte canule kan noodzakelijk zijn. Ten slotte werd een patiënt-specifieke canule ontworpen voor een patiënt met Duchenne spierdystrofie. Met behulp van virtuele 3D-technieken en een 3D-printer werd een model gemaakt dat in zilver kon worden gekopieerd. De plaatsing van deze gepersonaliseerde canule was optimaal. Dit toont aan dat 3D-technieken leiden tot meer geïndividualiseerde zorg voor patiënten die niet optimaal kunnen worden behandeld met regulier verkrijgbare medische hulpmiddelen.

Medische hulpmiddelen worden in het hele zorgproces gebruikt. Diagnostiek wordt uitgevoerd met behulp van bloeddrukmeters, CT- of MRI-scans, bloed wordt afgenomen met behulp van naalden. Lichamelijk onderzoek wordt uitgevoerd met behulp van endoscopen, een stethoscoop en microscopen. Chirurgie wordt ook uitgevoerd met medische hulpmiddelen zoals stents, prothesen, robots en 3D-geprinte mallen. Het **vijfde hoofdstuk** evalueert het gebruik van percutane dilatatie tracheotomie (PDT) in vergelijking met chirurgische tracheotomie (CT) in een single center, retrospectieve studie. De PTD's worden uitgevoerd met een Seldinger of 'over de draadtechniek' zoals de Blue Rhino® gebruikt. Dit is een medisch hulpmiddel dat wordt gebruikt om de luchtpijp op te rekken zodat een canule kan worden geplaatst. Het doel van de studie was om de incidentie van korte en lange termijn complicaties van PDT en CT te bepalen en te vergelijken. Daarom werden 305 patiënten die een tracheotomie ondergingen tussen 2003 en 2013 in het UMCG geanalyseerd. De incidentie van complicaties op korte en lange termijn waren vergelijkbaar in beide groepen. Daarom wordt PDT als een veilig alternatief voor CT beschouwd.

In **hoofdstuk zes** wordt een multicenter studie van de ProTrach® DualCare ™ gepresenteerd die niet werd voltooid vanwege inclusieproblemen. In dit hoofdstuk worden de valkuilen van het uitvoeren van een multicenter onderzoek besproken en worden de geleerde lessen beschreven.

Klinische studies zullen altijd afhankelijk zijn van deelname van de patiënten. Zorgvuldige planning en duidelijk afspraken met de deelnemende centra verhogen de kans om de studie succesvol af te ronden. Communicatie, motivatie, tijds management en een goed reserve plan zijn belangrijk. Echter, dit garandeert niet dat de studie succesvol wordt afgerond.

Ten slotte wordt een algemene discussie gepresenteerd met tevens toekomstperspectieven van de ontwikkeling van nieuwe medische hulpmiddelen en de implementatie van nieuwe technieken.

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Bertram Josef de Kleijn was born on the 9th of April 1987 in Nijmegen, the Netherlands. He grew up in Wijchen with his parents and older brother. He graduated from the Maaswaal college in Wijchen in 2005, receiving his Gymnasium diploma. Subsequently, he studied Medicine at the Radboud University Nijmegen. He fulfilled internships in Nijmegen, Arnhem, Den Bosch, Venray, Geldermalsen, Moshi and Mkuu (Tanzania). During the study, he worked at several wards as an assistant nurse and at the sterilization department, preparing surgical instruments for use on the operation room. During his studies he published a case report named 'Behandeling van neusseptumperforatie met prothese op maat' in the Dutch Magazine for otorhinolaryngology. Bertram wrote his master thesis, named 'Tweede tumoren hoofd hals en p53 mutatie analyse' at the department of Otorhinolaryngology and Head & Neck surgery, Radboud University (Nijmegen, the Netherlands), supervised by Dr. Takes. In the year between his Bachelor and Master he traveled South East Asia and New Zealand. In his spare time he was member of two rock bands called 'Navarone' and ' Harvest Moon'.

Bertram received his Master's degree in 2012. In February 2013 he started his PhD research, described in this thesis, at the department of Otorhinolaryngology and Head & Neck surgery, University Medical Center Groningen (UMCG) under supervision of Prof. Dr. B.F.A.M. van der Laan and Dr. G.B. Halmos. Since May 2015 Bertram is resident at the department of Otorhinolaryngology and Head & Neck Surgery (UMCG) under prof. dr. B.F.A.M. van der Laan, and since 2016 he has been a member of the medical team for implantation of the new electronic patient file.