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New Insight into Laryngo-Tracheal Surgery: High-Flow Oxygen Therapy to Prevent Early Complications after Surgery

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Abstract: Background: Early postoperative airway management after laryngo-tracheal surgery is crucial. Acute respiratory failure due to glottis' oedema may occur, requiring reintubation. This can prolong ventilatory assistance, jeopardizing the anastomosis. To date, only judicious steroid administration and fluid management are available to avoid more invasive procedures. High-Flow-Oxygen-Therapy(HFOT) is a noninvasive O2 support method providing humidification, warmed air, Positive-End-Expiratory-Pressure(AIRVO2). No data exist about HFOT use to prevent early complications after laryngo-tracheal surgery. **Methods**: Between Sept.2020-Sept.2022, 107 consecutive patients underwent laryngo-tracheal surgery received HFOT(Group A). Data and long-term results were compared with those of 80 patients operated between Sept.2018-Aug.2020(Group B), when HFOT was not available. All patients were operated in a single center. No pre- or post-operative settings changed, except for HFOT introduction. We analyzed and compared the risk for "delayed" reintubation (unexpected reintubation within the first 24-48 hours after extubating/laryngeal mask removal) in the two groups. **Results**: No patients reported HFOT-related adverse events. Control group(B) presented "delayed" reintubation in 37% (p= 0.027), Intensive Care Unit admission in 67%(p=0.005) and longer hospital stay(p=0.001) compared to HFOT group(A). Minor complications rate was 3% in both group and overall mortality was 0%. Re-stenosis was described in 4.6% of HFOT group, without a statistically significant difference (p=0.7006). **Conclusions**: Our study is the first to investigate HFOT use in patients undergoing laryngo-tracheal surgery, potentially representing a consistent innovation in the peri-operative management of these patients. With the limit of a retrospective series, we would suggest HFOT use for preventing post-operative reintubation rate, possibly reducing ICU admission and hospital stay.

Keywords: tracheal surgery; peri-operative management; High Flow Oxygen Therapy

1. Introduction

Tracheal surgery for subglottic stenosis is a major therapeutic challenge. To date, single-stage resection with primary end-to-end anastomosis has proved to offer the best option of cure, allowing definitive and stable high success rate. [1–4]

Nevertheless, postoperative complications may occur. Non-anastomotic complications include laryngeal oedema and glottic dysfunction in phonation or swallowing. [5] Acute respiratory failure due to oedema of the glottis could require reintubation or temporary tracheostomy in the immediate postoperative period [6,7]. This may prolong respiratory ventilatory assistance, increasing the rate of

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ICU recovery, and the risk of anastomosis damage, due to the cuff of the endotracheal tube lying on the mucosa or to mechanical ventilation's pressures on the fresh anastomosis.

To date, only judicious steroid administration, diuretics, nebulized epinephrine, and fluid management are available to prevent oedema of the glottis in this set of patients. [8,9]

Nowadays, several preventive strategies such as intraoperative protective mechanical ventilation, postoperative physiotherapy, and non-invasive mechanical ventilation (NIV) are available to reduce the incidence of early- postoperative complications in patients undergoing thoracic surgery. [10] Few and undersized studies have investigated the preventive role of HFOT (high-flow oxygen therapy, using nasal cannulae) after thoracic surgery, and there are no data regarding tracheal surgery. [11,12] The rationale of HFOT application is ensuring adequate oxygenation, increasing the clearance of secretions, and maintaining upper airway function and patency thanks to the moderate levels of generated Positive End Expiratory Pressure (PEEP). [13,14] In fact, acute respiratory failure due to oedema of the glottis could require an unexpected re-intubation, defined in the present study as "delayed" re-intubation: the necessity to intubate patient post-surgery, after being extubated or after laryngeal mask removal. In contrast we define "early re-intubation" the necessity to put an endo-tracheal tube after the cross-field ventilation, during surgery, because the intra-operative evidence of important laryngeal oedema that limits ventilatory assistance.

The aim of the present study is to investigate the role of HFOT for the prevention and treatment of intra and post-operative laryngeal oedema, thus avoiding unexpected re-intubation in patients undergoing tracheal resection-anastomosis for laryngo-tracheal stenosis.

2. Materials and Methods

2.1. Ethical Statement

This retrospective cohort study received approbation by the institutional review board (Prot. n. 21 SA/2023, RIF. CE 7063/2023) and it was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients and data were retrospectively analyzed. Consent for photo publication has been obtained from the patient in the central picture.

2.2. Population

Between September 2018 and September 2022, 187 consecutive patients were treated for laryngo-tracheal stenosis in a single centre. From September 2020 HFOT was introduced as a noninvasive O2 support method in the management of patients undergoing laryngo-tracheal resection-anastomosis, providing air humidification, warming, and PEEP (AIRVO2). General population was divided in Group A (HFOT Group), patients treated between Sept. 2020 and Sept. 2022 (n= 107) and Group B (Control Group), patients treated between Sept. 2018 and Aug. 2020 (n=80). Patients in group A received post-operative HFOT and it was applied after extubating/laryngeal mask removal for the first 48 hours after surgery, if not relied-adverse events were referred by the patient. Patients in Group B did not receive HFOT. We included in the study all patients affected by benign laryngo-tracheal stenosis and fit for surgery. Exclusion criteria were: (i) malignant stenosis, (ii) patients unfit for surgery (low-performance status; severely impaired cardiac function; NYHA IV; important neurologic disorders severely limiting or abolishing patients' cooperation), (iii) stenosis limited to medial-cervical and thoracic trachea.

2.3. Pre-Operative Assessment

Preoperative assessment included fiberoptic bronchoscopy (FBO) to verify vocal cords status (motility and integrity), characteristics of the glottis and the stenosis (distance from vocal folds, extent, severity grade according to Cotton-Meyer classification). Also neck and thorax Compute Tomography (CT) scan was used to better evaluate tracheal wall, distance from vocal cords and tissue status (using contrast medium).

Tracheal surgery was performed by a dedicated equip of experienced surgeons and anesthesiologists who have many years of training. Every equip's members applied the same standardized operative methods over the years of the study.

2.4. Intra-Operative Management

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Intraoperative ventilation was achieved by endotracheal intubation with a wire-reinforced small caliber tube (size 4-6.5 mm) passed through the stenosis or by the insertion of a laryngeal mask airway (LMA) device (size 4-5), to avoid dilatation at the time of intubation and the consequent trauma. The choice between endo-tracheal tube (ETT) or laryngeal mask is done according to patients' physical characteristics, type of stenosis (distance from vocal cords, grade of stenosis) and clinic history (Obstructive Syndrome Apnoea Syndrome, previous radiotherapy, or previous laryngeal procedure, pre-operative laryngeal oedema, critical stenosis, obesity counter-indicate LMA use). When LMA was introduced, it was preferentially chosen if not contraindicated.

Laryngo-tracheal resection-anastomosis was performed in accordance with Pearson's technique: through a collar cervical incision the cervical trachea is exposed and circumferentially mobilized from the inferior border of cricoid cartilage to the lower limit of the stenosis; then the distal trachea is transected and intubated through the operative field (cross field-intubation). The upper line of resection continues from the lower limit of the cricoid to the crico-thyroid joints, on both sides, then the anterior arch of the cricoid is transected, leaving the posterior plate. The reconstruction was performed by an end-to-end anastomosis with interrupted suture on the anterior wall and continuous suture on the posterior wall, using an absorbable monofilament (polydioxanone). A personal variation (partial laryngo-fissure) when vocal cords ere involved, is described in detail in a previous work [16], to obtain an enlargement in the antero-posterior diameter of the airway.

During surgery, all patients underwent traditional cross-field ventilation after tracheal transection by an armored 5 mm endo-tracheal tube (ETT). The two groups received the same intra-operative anesthetic management, using fentanyl 2 mcg/kg and propofol 2 mg/kg, i.v. and rocuronium 0.8 mg/kg.

Intraoperative oedema is defined as reduction of arytenoid and vocal cords motility, augmented width of vocal cords, reduction in glottis space. It is assessed in bronchoscopy, and classified according to Laryngeal Oedema Classification (LOC) [15]: LOC-1 (25% obstruction of the supra-larynx, few symptoms), LOC-2 (50% obstruction of the supra-larynx, moderate symptoms), LOC-3 (75% obstruction of the supra-larynx, severe symptoms), LOC-4 (90% obstruction of the supra-larynx, acute threat of life). Post-extubation and/or laryngeal mask removal oedema was clinically evaluated and defined as "Minor" (presence of stridor, that is to say an audible high-pitched inspiratory wheeze and signs of respiratory distress, that is to say a prolonged inspiratory phase with recruitment of accessory respiratory muscles as seen by subcostal, suprasternal or intercostal retraction) and "Major" (respiratory distress needing tracheal intubation secondary to upper airway obstruction), then confirmed by fiberoptic-bronchoscopy. [17]

2.5. Post-Operative Management

Extubation in operating room was tried for every patient, when possible. Patients with intra-operative evidence of laryngeal oedema, received traditional endotracheal intubation after the cross-field ventilation with a naso-tracheal tube (defined in the present study as an "early re-intubation": re-intubation during surgery, in contrast with the post-surgery delayed re-intubation). From Sept. 2020, patients started HFOT directly in the operating room after being successfully extubated. When extubation failed, a naso-tracheal tube was positioned as described in our previous series, with a 7-7.5 mm caliber ETT with a deflated cuff. This unexpected re-intubation is defined as "delayed re-intubation", occurring within the first 24-48 hours from surgery (in contrast with the early re-intubation). Since we increased the use of LMA, a default intubation post-surgery is avoided and an intra-operative fiberoptic check is routinely performed to check glottis 'status: if intra-operative laryngeal oedema is observed there is the indication to proceed to early re-intubation, leaving a ETT after surgery. Each member of the equip applied the same described evaluation criteria to decide for patient's re-intubation.

No step down or progressive care unit are available in our center. The need for postoperative multiparametric monitoring in ICU was based on the individual evaluation of patient, total operative time, patient stability and cooperation and early re-intubation.

In group A, HFOT is used for the first 48 hours after surgery in addition to classical management: steroids (Metilprednisone i.v. 10 mg, once); fluid management (1.5 lt i.v. and/or orally when the patient re-start feeding); diuretics (Furosemide i.v. 25.0 mg, twice). Patients receiving HFOT did not have air humidification in the room nor nebulizers (epinephrine nebulizer is recommended just in

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case of stridor). Patients who did not receive HFOT, received traditional non-invasive methods (steroid administration, air humidification, diuretics therapy, nebulized epinephrine) to prevent and to threat laryngeal oedema. No other settings in the peri-operative management have changed over the years. When applied, HFOT was routinely set at 40 l/min of oxygen flow, with 40% of FiO2, PEEP 2-3 mmHg, and temperature of humidification 37 °C, to maintain a peripheral oxygen saturation (sP02) ≥ 95%. Arterial blood gases (ABG) and sP02 were controlled after 1h, 6h and 12h. Personal discomfort and HFOT adverse event (throat or nasal pain, abdominal distension) self-reported by patients, were registered. [18]

During the following hospital stay, FBO was done on postoperative day 1 for the re-intubated patients and at discharge for every patient.

2.6. Statistical Analysis

Data were collected and stored in an Excel database (Microsoft Corp, Redmond, Wash) and were analyzed using statistical package SPSS, version 25.0 (SPSS Software, IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation, whereas nominal variables were expressed binarily as presence (1) or absence (0) of the event. Comparison of categorical variables was performed by c^2 test using Fischer exact test. Comparison of continuous variables was performed by student t-test. Significance was defined as a P value of less than 0.05. A univariable logistic regression analyses was performed to derive crude estimates of association between predictors (predictive variables defined as "independent variable", described in Table 2) and outcomes (defined as "dependent variable", such as intra- and post-operative laryngeal oedema), minimizing the potential confounders (the exclusion criteria: release, neoplastic, carinal stenosis). After univariable analyses, variables with P-value less than 0.05 were included in a multivariable logistic regression model to identify potential independent protective or risk factors. The adjusted odd ratios (ORs) and 95% confidence intervals (CI) were calculated to estimate and measure the association using 1000 bootstrapping samples.

3. Results

Male patients were 20/107 (19%) in HFOT group (group A) and 25/80 (31%) in Control group (group B); the average age of population was 56.11±4.34 in group A and 54.21±3.75 in group B. In group A, 89/107 (83%) patients were operated with laryngeal mask intraoperative assistance, whereas 18/107 (17%) patients were operated with traditional endotracheal tube. In group B, 46/80 (58%) patients were operated with laryngeal mask and 34/107 (42%) were operated with ETT.

In group A, 2/107 (1.9%) patients underwent laryngo-fissure vs 4/80 (5%) in group B, without a statistically significant difference (p=0.4127).

General characteristics are described in Table 1.

Table 1. Patient with High-flow oxygen therapy support (AIRVO2 machine) immediately after laryngo-tracheal resection for subglottic stenosis (original picture, consent for photo publication obtained).

Parameter	HFOT Group A (107/187)	Control Group B (80/187)	p
Gender Male, n (%)	20 (19%)	25 (31%)	0.035
Age (years, mean±SD)	56.11±4.34	54.21±3.75	0.0097
BMI (kg/m², mean±SD)	24.57 ± 2.44	25.21±1.97	0.0158
Operative time (min, mean±SD)	76.50±28.48	77.20±25.51	0.4235
Type of operation, n (%)			
Laryngo-fissure	2 (1.9%)	4 (5%)	0.4127
Pearson's technique	105 (98.1%)	76 (95%)	
Stenosis distance from vocal folds (mm, mean±SD)	1.42±0.78	1.52±1.20	0.2368
Intra-operative assistence n (%)			
LMA	89 (83%)	46 (58%)	0.0001
ETT	18 (17%)	34 (42%)	

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ICU admission, n (%)	50 (47%)	54 (67%)	0.005
Delayed reintubation, n (%)	25 (23%)	30 (37%)	0.027
HFOT duration (h, mean±SD)	48±12.42		
HFOT flow (l/min, mean±SD)	38.5±7.8		
HFOT FiO2 (%, mean±SD)	36.5±10.01		
Discomfort during HFOT, n (%)	20 (%)		
Temporary tracheostomy, n (%)	1 (0.9%)	1 (1.2%)	1.000
ICU stay in days (range, mean±SD)	0-5, 3±2.3	0-7, 4±4.2	0.2610
Hospital stay (days, mean±SD)	5±2.5	7±3.7	0.0010
Re-stenosis, n (%)	5 (4.6%)	2 (2.5%)	0.7006
Mortality, n (%)	0 (0%)	0 (0%)	1.0000

BMI: Body Mass Index; F: female; M: male; HFOT: High flow oxygen therapy; ICU: intensive care unit; LMA: Laryngeal mask assistance; ETT: endo-tracheal tube; delayed re-intubation: re-intubation after post-surgery extubation or laryngeal mask removal.

The mean operative time was not different in HFOT group (76.50±28.48 minutes) compared to control group (77.20±25.51); while ICU admission was higher in group B (n= 54/80, 67%) than in group A (n= 50/107, 47%) with a statistically significant difference, p=0.005. Mean time of ICU stay was not statistically different in Group A (0-5; 3±2.3 days) and in Group B (0-7; 4±4.2 days) but the mean time of hospitalization was longer in Group B (7±3.7 days) than in Group A (5±2.5 days), p= 0.0010.

"Delayed re-intubation" rate was higher in control group (30/80; 37%) vs HFOT group (25/107; 23%), with a statistically significant difference, p=0.027. In HFOT Group, 8/107 (9%) patients operated with laryngeal mask needed delayed reintubation vs 5/80 (10%) in group B.

Mortality was 0% in both groups and minor complications (vocal roughness, initial swallowing difficulty, inaesthetic scar) were 3% in both groups.

Only 2/80 (2.5%) patients in the control group experienced re-stenosis (1 of them after re-intubation) at the follow-up compared to 5/107 (4.6%) patients in HFOT group (no one of these experienced re-intubated), without a statistically significant difference (p=0.7006).

Univariable logistic regression was applied to identify the independent variables (among age, sex, idiopathic stenosis, Mayer Cotton stage, presence of intra-operative oedema, vocal cords distance, and HFOT application) related to post-operative laryngeal oedema: idiopathic stenosis (p=0.001) and HFOT (p=0.004) resulted significatively related to post-operative laryngeal oedema and the multivariable analysis confirmed idiopathic stenosis (p=0.001) as a risk factor and HFOT (p=0.010) as a protective factor for post-operative laryngeal oedema. (Table 2)

Table 2. Multivariable logistic regression for post-operative laryngeal oedema.

Variables	OR	P value	95% CI
IDIOPATHIC STENOSIS	3.859	0.001	1.946 – 7.650
HFOT APPLICATION	0.409	0.010	0.206 – 0.810

HFOT: High-Flow-Oxygen-therapy.

4. Discussion

Laryngeal oedema is one of the most challenging intra and post-operative non-anastomotic complications following laryngo-tracheal surgery, eventually requiring patient's re-intubation.

Despite the possible complications, many authors concluded that primary resection-anastomosis is the gold standard for the treatment of tracheal and/or laryngo-tracheal stenosis: Grillo et al. [19] reported a 91% rate of good to excellent outcome over a series of 35 single-staged laryngotracheal resections for idiopathic stenosis; Ashiku et al. [20] observed the same rate (91%) of good to excellent long-term results; Morcillo et al. [21] in a Spanish multi-institutional study reported a 97% final success rate and finally, Maurizi et al. reported a series with a definitive success rate of 98.7%. [17] The Society of Thoracic Surgeons General Thoracic Surgery Database (STS GTSD) as well, analyzed 1,617 patients undergoing tracheal resection between 2002 and 2016 and reported an overall 30-day mortality of 1%. [22]

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Post-operative care for patients after tracheal surgery included judicious use of steroids, ambient humidification, and diuretics to prevent the risk for oedema of the glottis, eventually causing respiratory failure and the need for patient's re-intubation. Recently, high-flow oxygen therapy using nasal cannulae (HFOT), a system capable of delivering a high flow (30-60 l/min) of heated and humidified gas at a controlled oxygen concentration, is becoming increasingly used in the prevention and treatment of post-extubation respiratory failure in surgical patients. [23] Several studies have shown that HFOT reduces postoperative hospital stay, ICU readmission, risk of intubation in acute hypoxic respiratory failure, and moreover it increases respiratory support compared with traditional oxygen administration. HFOT humidification and warming of inspired gas, guarantees secretions' dilution, enhancing mucociliary clearance and expectoration. [24]

In addition, HFOT results in a positive end-expiratory pressure (PEEP), reaching values of 5-6 cmH2O, ensuring airway patency.

For the best of our knowledge, HFOT in tracheal surgery has not yet been reported and the present study is the first investigating the potential role of HFOT in the prevention and treatment of laryngeal oedema in patients undergoing laryngo-tracheal surgery. (Figure 1)

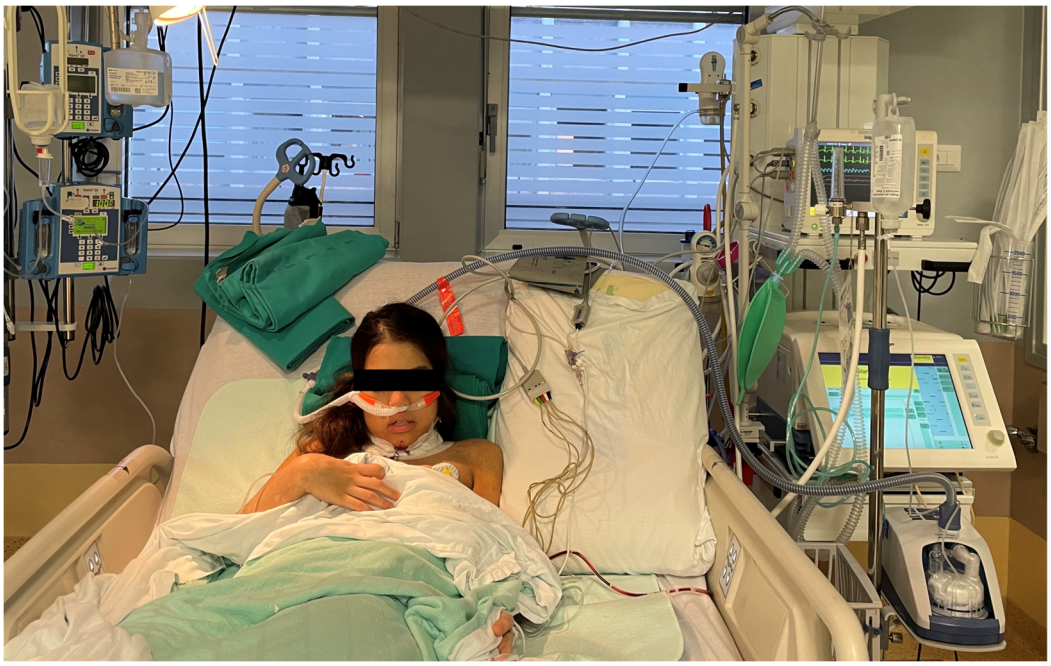

Figure 1. Patient with High-flow oxygen therapy support (AIRVO2 machine) immediately after-tracheal resection for subglottic stenosis (original picture, consent for photo publication obtained).

HFOT in tracheal surgery takes advantage of airways' warming and humidification, to guarantee mucosal integrity and physiology and, mainly, it takes advantage of the PEEP generated that may contribute to keep the upper airways open, thus contrasting laryngeal edema [25–27]

The oxygen inflow was set at the minimum because its application was nor for hypoxic problem nor for hyper-carbic respiratory failure. In fact, the rational was no longer oxygen administration (as well useful to mucosal integrity) but the dilution of secretions due to the direct flow of humidification, and the patency of upper airway, guaranteed by the minimal PEEP. [28,29] In fact, the main observed effect is the reduction of secretions 'density, allowing their easier expectoration, thus reducing the risk of mucous plugs that can cause temporary desaturation and a sense of breathiness and discomfort. [30] Moreover, HFOT allows an enhanced recovery after surgery because patients can move from the bed, just wearing the nasal-canula and they are not bedside constricted because of the necessity of continuous traditional air humidification.

The present study reports a significative reduction in ICU admission (p=0.005) in patients underwent HFOT, compared to the control group. Similarly, the incidence of delayed re-intubation was lower in group A: in the uni- and multivariable analysis, HFOT was identified as a protective factor for post-operative laryngeal oedema, thus probably preventing an unexpected re-intubation due to post-operative oedema of the glottis.

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No difference was noticed in ICU stay, but patients who did not receive HFOT (group B) had a higher rate of access to ICU and a longer hospitalization, in accordance with the higher rate of delayed re-intubation described in this group. In fact, ICU is not necessary for every patient, and it is avoided, if possible, to enhance early recovery after surgery. Probably the higher rate of ICU admission in Group B is also related to the most frequent use of ETT in this group (42% of patients operated on with ETT in group B vs 17% in group A; p=0.0001), left in site after surgery. In fact, patients operated with LMA, generally do not require nasal-tracheal tube positioning if intra-operative oedema does not occur, reducing ICU admissions. ICU length of stay has a standard length of stay of 12-24 hours in both groups, but it must be considered that unexpected re-intubation, occurs in the first 12-24 hours after extubation/laryngeal mask removal so at the end, many days of hospitalization added up in goup B, independently from the single ICU length of stay. Moreover, patients underwent delayed re-intubation require a precautionary wait-and-see management and more conservative approaches using standard methods (nebulizers, diuretics, rest, FBO controls) before discharge, increasing the total length of hospital stay.

The present work confirms the most frequent incidence of laryngeal oedema in very high subglottic stenosis ($p< 0.001$) and idiopathic stenosis (which are very high-subglottic stenosis) represent an independent negative prognostic factor for post-operative laryngeal oedema, eventually requiring re-intubation. In fact, the closer to vocal cords is the stenosis, the greater is the risk for inflammation involving vocal cords, and a consequent oedema with respiratory failure and the necessity for re-intubation may occur in these cases. [31] Moreover, we found a significant difference in patients' sex: over the last years more female underwent laryngo-tracheal resection in our unit and this data is probably even related to the well-known most frequent incidence of idiopathic stenosis in female sex.

Since we have started using LMA, the gold standard was the extubation in the operating room so the need for the use of preventive ETT for the first 24 hours (how we did in the past) has been avoided, when possible. [9]

The use of laryngeal mask is less associated to post-operative laryngeal oedema, compared to ETT (p=0.0001): only the 9-10% of patients operated on with a laryngeal mask needed a "delayed" re-intubation (after laryngeal mask removal). These results are in accord with a previous published study by Menna et al. [32], also supporting the hypothesis that LMA assistance reduces the risk of stenosis manipulation; moreover, LMA allows the intra-operative assessment of vocal cords status. So, LMA has certainly improved peri-operative management and the consequent outcomes, but its use does not totally avoid laryngeal oedema, as previously described in literature [28], so we do not think that the improvements described in the last years are linked to a single factor but probably the association of both LMA and HFOT are advantageous to achieve increased post-surgical outcomes compared to the past.

The increased rate of delayed re-intubation presented in this series respect to our past published series [16] is probably related to a higher incidence of idiopathic stenosis in the last years and to the increased age of patients; in fact, we observed a significant difference ($p < 0.001$) in age between the 2 groups, with a higher age of patients treated in group A.

HFOT represents a simple and safe method, with low costs, easy applicability in the routinary post-operative clinical practice, causing little or null discomfort as it was self-reported by patients that experience no adverse effects relied to its use (such throat or nasal pain, abdominal distension).

Moreover, we found that the impact of reintubation on long-term airway patency was not statistically different in the groups: only 2 patients operated on between Sept 2018-Aug 2020 experienced re-stenosis (1 of them after re-intubation); while 5 patients operated between Sept 2020 – Sept 2022 experienced re-stenosis (no one of them received re-intubation), without a statistically significant difference (p=0.7006). So, re-intubation seems not to affect the re-stenosis rate in the present series.

Our study has some limitations. Despite the high volume of patients, it is a single-centre retrospective study, it deals only with early post-operative complications (not long-time of follow-up), and during last years the complexity of the pathology has increased (augmented age of surgery, idiopathic subglottic stenosis) as well as the use of laryngeal mask, identifying some possible selection bias. Nevertheless, the population appear homogeneous and our preliminary results on HFOT after laryngo-tracheal resection-anastomosis are promising.

5. Conclusions

In conclusion, the results of the study suggest that the use of HFOT could be recommended as post-operative support in patients undergoing laryngo-tracheal resection-anastomosis, reducing the risk for delayed re-intubation due to post-operative laryngeal oedema, and possibly reducing ICU admission and hospital stay.

Further prospective multicentric studies would be useful to confirm the promising demonstrated results of the present retrospective cohort study.

Author Contributions: Conceptualization, B.T.M., A.S., G.M.; methodology, B.T.M., A.S. G.M.; sofware, S.F.; validation, E.A.R. and M.I.; formal analysis, B.T.M., C.M. and S.F.; investigation, M.T., A.DA, AM.C.; resources, B.T.M. and M.T.; data curation, B.T.M., C.M., M.T., S.F.; writing review and editing, B.T.M. and G.M.; visualization and supervision, E.A.R., M.I., D.M., F.V. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Sant'Andrea Hospital, La Sapienza University (Prot. n. 21 SA/2023, RIF. CE 7063/2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this Figure 1.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author

Conflicts of Interest: The authors declare no conflicts of interest.

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