Safety and Putative Benefits of Tracheostomy Tube Placement in Patients on Extracorporeal Membrane Oxygenation: A Single-Center Experience

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Abstract

Purpose: Patients supported with extracorporeal membrane oxygenation (ECMO) have been reported to have increased sedation requirements. Tracheostomies are performed in intensive care to facilitate longer term mechanical ventilation, reduce sedation, improve patient comfort, secretion clearance, and ability to speak and swallow. We aimed to investigate the safety of tracheostomy (TT) placement on ECMO, its impact on fluid intake, and the use of sedative, analgesic, and vasoactive drugs. **Methods:** Prospective data were collated for all ECMO patients over a 5.5-year period. Data included the cumulative dose of sedatives and analgesics, fluid balance, inotrope and vasopressor requirements, and number of packed red cell (PRC) units transfused. Data were analyzed to determine the differences in the aforementioned between 5 days pre-TT and post-TT insertion. **Results:** Thirty-one (22.1%) of 140 patients underwent TT while on ECMO in the study period. Inotrope and vasopressor use was significantly less in the post-TT period compared to pre-TT dose (P value = .01). This was in the setting of Sequential Organ Failure Assessment scores the day before TT placement being significantly greater than those on days 2, 3, and 4. There was a trend toward reduction in analgesic usage in the post-TT period. No major complications of TT were reported. There was no significant difference (P value = .46) in the amount of PRC used post-TT. **Conclusions:** These data indicate that TT may result in a reduction in vasopressor and inotropic requirement. Data do not suggest increased major bleeding with placement of TT in patients on ECMO. The potential risk and benefits of inserting a TT in ECMO patients need further validation in prospective clinical studies.

Keywords

ECMO, sedation, vasopressor, inotrope, tracheostomy

Introduction

Extracorporeal membrane oxygenation (ECMO) is an increasingly used modality in intensive care unit (ICU) for patients who have failed traditional respiratory or cardiac supportive therapy.¹ Use of ECMO has been increasing² despite the lack of robust evidence to support its use.³ Some supportive evidence from CESAR trial and encouraging results from use of ECMO during the influenza epidemic of 2009 in Australia^{2,4-6} have certainly played a role in increased uptake of ECMO. Recently published EOLIA trial⁷ has added further support to the use of venovenous (VV) ECMO in respiratory failure—which seems greater still when assessed in a Bayesian manner.⁸ The optimal mechanical ventilation strategy on ECMO remains debatable, and experienced centers are extubating their patients early and rehabilitating them where feasible.^{9,10} In many others a prolonged period of mechanical ventilation is inevitable, and

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these patients may often have increased sedation requirements.¹¹ Consequently, this may result in increased fluid and vasoactive drug use, immobilization and neuromuscular weakness, and other adverse consequences of sedation in the ICU. To overcome this, some centers perform a tracheostomy (TT) once patients are stabilized on ECMO, although the risks and benefits of such an approach remain unclear.

While there is no strong evidence for performing an early TT (variably defined in literature between <4 and <10 days postintubation)^{12,13} in general critically ill patients, it may still have a role in special patient populations. Tracheostomy is performed within the ICU to facilitate weaning from mechanical ventilation, restore function of the upper airway, continue tracheobronchial toileting, and minimize injury to vocal cords,^{14,15} with percutaneous dilatational tracheostomy (PDT) being more common than surgical TT in ICU.^{16,17} Patients with prolonged ventilator requirements (more than 10 days)¹² often receive a TT.¹⁷ Reported benefits include decreased sedative drug usage,¹⁸ shorter ventilation duration,¹⁹ decreased mortality,¹² improved patient comfort, improved clearance of secretions, ability to recommence oral intake, and facilitation of communication through the use of a speaking valve.^{20,21}

Many of the patients requiring ECMO tend to require prolonged mechanical ventilatory support, especially those on VV ECMO. These patients also have significantly compromised pulmonary compliance, and in some, very little or no tidal ventilation is feasible. However, with optimal control of carbon dioxide via ECMO, it is possible to minimize respiratory drive and awaken a patient. While some patients tolerate this well, others are intolerant of the endotracheal tube and find it difficult to spontaneously breathe, often resulting in being re-sedated. There may be a role for TT in these patients. However, PDT has not been commonly performed in ECMO patients due to a perceived lack of benefit or a perceived increase in the risk of bleeding, which may be caused by anticoagulation, underlying patient pathology, venous engorgement, and acquired von Willebrand deficiency in many of the patients on ECMO.^{22,23}

There is minimal literature available regarding TT in ECMO and none assessing sedation requirements and associated benefits post-TT in patients on ECMO. Interestingly, pharmacokinetics of many drugs, including several sedative drugs, are markedly different with an ECMO circuit in situ.^{24,25} This is associated with conspicuously increased usage of sedative drugs during ECMO.²⁶

Increased usage of fluids, sedation, vasopressors/inotropes, and blood have all been linked to worse outcomes in critically ill patients. These include an increase in mortality, risk of deep vein thrombosis, nursing workload, cost of care in ICU, and risk of arrhythmia, alongside worsening gas exchange and specific risks related to agents used such as propofol infusion syndrome.²⁷⁻³³ We hypothesized that many of these adverse effects may be minimized by timely insertion of TT.

In this retrospective study we sought to assess whether (1) TT in adult patients on ECMO is associated with benefits of decreased use of analgesia, sedation, fluid usage including

packed red cells (PRC), and vasopressor/inotrope requirements and (2) TT is associated with increased bleeding in adult patients on ECMO.

Methods

Setting

This retrospective observational study was conducted in a primarily cardiorespiratory ICU of a metropolitan teaching hospital in Australia. Ethics exemption was obtained from the hospital's Human Research and Ethics Committee (HREC/16/QPCH/303).

Sample

Medical records of all patients who received a TT while on ECMO from January 2011 to June 2016 were reviewed.

Outcomes Measured

Data included age, sex, primary diagnosis, type of ECMO support, number of days in ICU prior to ECMO, 5-day period pre-TT and 5 days post-TT, the number of days on ECMO altogether, amount of sedative drugs used, daily fluid balance, inotrope and vasopressor usage, any major complication of TT, and PRC transfusions received.

Based on the previously shown benefit of reduced sedation usage in intensive care patients post-TT,¹⁸ we chose sedation usage and other parameters on which sedation is likely to have an impact. All these parameters affect significant patient outcomes. Variables of interest included fluid intake, fluid output and balance, sedative drugs (propofol, midazolam, and dexmedetomidine), analgesic drugs (morphine and fentanyl), inotropes (dopamine, adrenaline, milrinone, and dobutamine), vasopressors (vasopressin, noradrenaline), and PRC usage. We analyzed PRC usage as a surrogate marker of significant bleeding requiring transfusion.

Data Collection

Data were collected for those patients who had a TT placed while on ECMO unless there was discontinuation of ECMO within 48 hours of placement of TT, in which case the patient was not included in the study. The decision for TT was made by the treating intensivist. The procedure was performed percutaneously in 100% of the cases in the ICU by 2 intensivists under direct bronchoscopic visualization. It was ensured that any coagulopathy present was corrected prior to starting procedure, and cross-matched blood and other blood products were readily available. The indication for TT varied among patients and most commonly included the need for prolonged ventilation and airway toileting with a view to also enable increased patient participation when able to tolerate more awake hours.

Anticoagulation was stopped early on the day of the TT, and coagulation profile and/or rotational thromboelastometry was

Figure 1. Data were collected for 5 days pretracheostomy and 5 days posttracheostomy ignoring the values on the day of tracheostomy that was designated day 6 on the patient timeline. Data from day 6 (day of tracheostomy) were not included in the statistical analysis. Patients who were not supported with ECMO for the full 11 days had missing values for the days they were off ECMO. ECMO indicates extracorporeal membrane oxygenation.

checked prior to TT. Coagulation abnormalities were corrected to goals set by treating intensivist.

Data were collected for 11 days in total, with 5 days pre-TT and 5 days post-TT. The date of TT placement was counted as “day 6.” Data for “day 6” were not used (Figure 1). For patients who were provided both venoarterial (VA) ECMO and VV ECMO support, data were analyzed for the 5 days pre-TT and post-TT during their first TT period.

Patients who were not supported by ECMO for the full 11 days had missing values for the days for which ECMO had been withdrawn. Fluid balances were calculated for each 24-hour period starting from midnight. Sedation was calculated using 2 measures. One of the measures used midazolam and propofol (MP) converted to propofol equivalents in milligram.³⁴ Since a large percentage of patients also received dexmedetomidine, a separate measure was used, which converted midazolam, propofol, and dexmedetomidine (MPD) to propofol equivalents $\{\text{Propofol in mg} + \{(0.106 \times \text{midazolam in mg})/1.66\} + \text{Dexmedetomidine}/0.002\}$. Due to total sedative dosages of MPD having a highly skewed distribution, this was log-transformed to enhance graphical presentation. Analgesic medications included morphine and fentanyl, for which doses were converted to morphine equivalents.³⁵ Inotrope score (IS) was calculated using the formula: Dopamine dose ($\mu\text{g/kg/min}$) + Dobutamine dose ($\mu\text{g/kg/min}$) + $100 \times$ Epinephrine dose ($\mu\text{g/kg/min}$).³⁶ Vasopressor inotrope score (VIS) was calculated using the formula: IS + $10 \times$ Milrinone dose ($\mu\text{g/kg/min}$) + $10\,000 \times$ Vasopressin dose (U/kg/min) + $100 \times$ Norepinephrine dose ($\mu\text{g/kg/min}$).³⁶ The PRCs were counted as units, with each unit being 220 to 240 mL. The volume of PRC transfused was measured as part of fluid balance (Figure 2).

Data were also collected for Sequential Organ Failure Assessment (SOFA) scores for all the patients for the first 4 days of their admission to the ICU and for the 24 hours prior to TT. This was used as a surrogate marker for severity of illness to check for a possible change in requirement of sedation, analgesia, vasopressor, and inotropes resulting from significant improvement or worsening in patient condition.

Figure 2. Patient selection during the study.

Table 1. Demographics, ECMO, and Tracheostomy.^a

Male	20
Female	11
Median time from admission to tracheostomy, days	7 (IQR 5-11)
Median time from ECMO initiation to tracheostomy, days	6 (IQR 4-9)
Total patients on VA ECMO with tracheostomy	16 ^b
Range, days	1.9-85.9 ^c
Total patients on VV ECMO with tracheostomy	20 ^b
Total duration in hours, days	9205 (383.54)
Mean duration in hours, days	460.27 (19.17)
Range, days	109-1990 hours (4.5-82.9)
Total ECMO days for patients with tracheostomy	561.8
Average days	18.1
Underlying diagnosis for VA ECMO	Cardiogenic shock (5) Cardiomyopathy (3) Cardiac arrest (2) Other (1) ARDS (7) Pneumonia (4) Pulmonary hemorrhage (1)
Underlying diagnosis for VV ECMO	Other (3)

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation, IQR, interquartile range; VA, venoarterial; VV, venovenous.

^aFor all patients, the first tracheostomy period while on VV or VA ECMO was analyzed.

^bFive patients were on both VA ECMO and VV ECMO.

^cFour of the patients on VA ECMO were transferred to left ventricular assist device (LVAD) during their ICU stay.

Statistical Analysis

The distribution of variables was examined, and boxplots were obtained by day for each variable. Patient-level summary measures were derived for the pre-TT and post-TT periods. For

Figure 3. Boxplots of inotrope and PRC dose by day for patients with data. The center line in each box represents the median and the shaded area comprises the interquartile range (with the middle 50% of the observations). The whiskers (at the end of the middle line) denoted the range that contains 95% of the observations. Outliers are represented as dots. PRC indicates packed red cell.

Figure 4. Boxplots of VIS by day for patients with data. The center line in each box represents the median and the shaded area comprises the interquartile range (with the middle 50% of the observations). The whiskers (at the end of the middle line) denoted the range that contains 95% of the observations. Outliers are represented as dots. VIS indicates vasopressor inotrope score.

Figure 5. Boxplots of fluid intake, output, and balance by day for patients with data. Volume of packed red cells transfused was included in the fluid calculations. The center line in each box represents the median and the shaded area comprises the interquartile range (with the middle 50% of the observations). The whiskers (at the end of the middle line) denoted the range that contains 95% of the observations. Outliers are represented as dots.

variables that were normally distributed (ie, fluid intake, output, and balance) mean values were calculated for each patient for each period (pre-TT and post-TT). For variables with a skewed distribution median values (pre-TT and post-TT) were used as the measure of interest. The mean values of the pre-TT and post-TT fluid variables (ie, patient-level means) were compared using paired *t* tests. The distribution of values for pre-TT and post-TT variables with skewed distributions was compared using Wilcoxon matched-pairs signed-rank test. Analyses were performed using the Stat Statistical Software Package (version 15).

Results

A total of 140 adult patients were supported by ECMO from January 1, 2011, to June 30, 2016. Of these patients, 31 (22%) received a TT while on ECMO. Of these, 15 received VV ECMO, 11 were placed on VA ECMO, and 5 patients were on both VA and VV ECMO during their ICU stay. Total number of days on ECMO for these 31 patients was 561.8 with a mean of 18.1 days. Total VA ECMO days were 151 with a mean duration of 13.1 days. For VV ECMO, 340 days were

spent on ECMO with average of 22.7 days per patient. Median duration of time from admission to TT placement was 7 days, and median duration from initiation of ECMO and TT placement was 6 days.

Seven patients had data missing for 1 or more of the 5 days prior to placement of TT and 8 patients had data missing in 1 or more of the 5 days after placement of TT. Missing data occurred due to either patients having less than 5 days between initiation of ECMO and placement of TT (pre-TT period) or being weaned off ECMO sooner than 5 days post-TT insertion (post-TT period). The underlying causes for placement of both VA ECMO and VA ECMO are included in the attached Table 1.

The distribution of IS (*P* value .01) and VIS (*P* value .01) differed between pre-TT and post-TT periods and showed a substantial reduction in post-TT period. Although 13 of the 31 patients did not receive inotropes, and 6 patients had no inotropic or vasopressor usage during the period assessed (ie, value = 0), the interquartile range is larger in pre-TT compared to post-TT, as shown in Figures 3 and 4.

The overall mean daily fluid intake was 4157 mL, output was 4003 mL, and fluid balance had a mean of 154 mL

Figure 6. Boxplots of total sedative (MPD) dose on the logarithmic scale by day for patients with data. The center line in each box represents the median and the shaded area comprises the interquartile range (with the middle 50% of the observations). The whiskers (at the end of the middle line) denoted the range that contains 95% of the observations. Outliers are represented as dots. MPD indicates midazolam, propofol, and dexmedetomidine.

positive. These did not differ significantly between periods defining pre-TT and post-TT (P value .69, .65, and .55 for input, output, and fluid balance, respectively; Figure 5).

The overall median sedative dose was 18 units, while the interquartile range (10-783) reflects the large amount of variability and the highly skewed distribution for this variable. This is particularly evident for the post-TT interquartile range (6-2 000 000). Sedative dose (P value .54 and .31 for the 2 measures of sedation, MP and MPD) and PRC (P value .46) did not differ significantly between periods defining pre-TT and post-TT. There was a trend toward reduction in analgesia usage, which did not reach statistical significance (P value .1) as shown in Figures 6 and 7 and Table 2.

Differences between mean SOFA scores on days 1 to 4 from day of admission were compared to values during the 24-hour period prior to placement of TT (1 day pre-TT) using a paired t test. Mean values on each day and averaged over 4 days (days 1-4) are shown in Table 3 along with the results of significance tests. Overall SOFA scores ranged from 3 to 20. Mean scores were significantly lower on days 2, 3, and 4 compared to scores during the day pre-TT. The difference between mean values on day 1 (mean: 9.4; standard deviation [SD] 3.5) and day pre-TT (mean: 10.6; SD 3.1) did not reach statistical significance.

A3 (APACHE III) scores ranged from 46 to 156. The median A3 score was 71 (interquartile range: 57-97).

Discussion

This is the first study reporting the safety of TT placement and its putative benefits in patients on ECMO. There is increasing awareness of the possibility and potential benefits of early mobilization and rehabilitation of ECMO patients where possible.^{37,38} Therefore, the risk and benefits of strategies such as early extubation versus TT placement to enable the same need scrutiny.

This study confirmed that TT can be safely performed in ECMO patients. There was no increase in PRC use in tracheostomized patients. Use of PRC in our patients undergoing TT did not differ significantly in the pre-TT and post-TT period, suggesting there were no major bleeding events. We used this as a surrogate for safety of TT. On review of all charts, no other major adverse events such as loss of airway, major airway bleeding, arrhythmias, worsening of ventilation, and so on were noted. A previous study examining complications of TT in patients on ECMO also reached a similar conclusion.³⁹ However, hemostasis can become a challenge if a major complication is encountered and the risk and benefits of TT need to be carefully examined on a case-by-case basis. Especially, patients on VV ECMO who are likely to have a prolonged ECMO run and cannot be extubated may be considered for TT once they are stabilized on ECMO. Considering the risks, it is important that attempts be made to wean sedation and to assess suitability for extubation prior to performing a TT, as in general critically ill patients.

Figure 7. Boxplots of sedation dose (MP) and analgesic dose by day for patients with data. The center line in each box represents the median and the shaded area comprises the interquartile range (with the middle 50% of the observations). The whiskers (at the end of the middle line) denoted the range that contains 95% of the observations. Outliers are represented as dots. MP indicates midazolam and propofol.

Table 2. Summary Statistics for Patient-Level Summary Measures Pre- and Posttracheostomy Placement.^a

Variable	Overall (Pre and Post)	Pre, n = 31	Post, n = 30	P Value ^a
Mean fluid intake, mL	4157 (894)	4194 (920)	4118 (881)	.69
Mean fluid output, mL	4003 (1254)	3920 (1383)	4089 (1122)	.65
Mean fluid balance, mL	154 (1358)	274 (1295)	30 (1432)	.55
Median sedative	18 (10-783)	18 (11-32)	34 (6-2 000 000)	.54
Median propofol + midazolam	13 (6-25)	15 (10-25)	8 (2-31)	.31
Median analgesic	361 (100-491)	416.6 (225.5-500.7)	246.9 (5.0-452.2)	.10
Median inotrope	0.0 (0-3)	0.0 (0.0-4.5)	0.0 (0.0-0.1)	.01
Median vasopressor inotrope score	0.1 (0-5)	3.3 (0.0-6.8)	0.0 (0.0-3.3)	.01
Median packed red cell usage	0.5 (0-1)	0.0 (0.0 -1.0)	1.0 (0.0-2.0)	.46

^aStatistics are mean (standard deviation) with P values from paired t test or median (interquartile range) with P values from Wilcoxon signed-rank test.

Interestingly, although the use of vasopressors and inotropes showed a significant reduction in post-TT period, this was not associated with a difference in use of sedation. Clearly, a decrement in vasoactive drug use is desirable as an increased requirement is usually associated with increased fluid administration and inability to minimize extravascular lung water whether by use of diuretics or ultrafiltration. Fluid balance, along with usage and output, was not found to be different before and after TT insertion.

Though not clearly explained without an associated reduction in sedation, this is an important outcome and needs to be explored further with a larger sample size. Possible reasons for this may be related to a reduction in sedation post-TT, which failed to reach the prespecified significance level, especially with wide variation in sedation usage. A larger study to assess the differences specifically for a longer period of pre-TT and post-TT follow-up may clarify this hypothesis generating finding.

Table 3. Comparison of SOFA Scores from Days 1 to 4 of Admission Compared to Day Prior to Tracheostomy.^a

SOFA Scores	Comparison Day		Day Pre-TT		P Value
	Mean	SD	Mean	SD	
Day 1	9.4	3.5	10.6	3.1	.0612
Day 2	9.1	3.6	10.6	3.1	.0152
Day 3	8.6	3.9	10.6	3.1	.0065
Day 4	8.2	3.6	10.6	3.1	.0003
Mean (days 1-4)	8.8	3.4	10.6	3.1	.004

Abbreviations: SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TT, tracheostomy.

^aDays 1 to 4 on this table refer to days on admission to intensive care. This is compared to the SOFA scores calculated for the day prior to tracheostomy.

There was no significant difference (P value .06) in the severity of illness of patients between the day of admission and 24-hour period prior to TT placement as assessed by SOFA scores. However, the patients had significantly greater SOFA scores on day before TT when compared to days 2, 3, and 4, indicating that the reduction in vasopressor and inotrope doses was not related to resolution of illness itself and may at least in part be attributed to placement of a TT.

Although there was no statistically significant difference in the use of sedation or analgesia, there was a trend toward reduction in analgesia usage, and it would be interesting to see if the trend became stronger with a larger sample size. Lack of a significant sedation difference could be because of inability to reduce sedation due to various ongoing clinical indications unrelated to TT. Fear of ECMO cannula movement is one such common reason, as dislodgement could be catastrophic.

Placement of a TT (instead of an endotracheal tube) may have other additional benefits for the patient and clinician who were not investigated as part of this study, including improved patient communication, rehabilitation participation, mobilization, easier access to tracheobronchial tree for toileting and suctioning, and reduced sedation. Larger studies with longer follow-up may help in identifying a difference in these parameters for patients on ECMO.

This single-center study does suffer from its size, but it highlights some important findings that are of relevance to the evolving practice of ECMO. Blinding of clinicians to sedative and analgesic usage was not possible in this retrospective study. It is reassuring that complications of TT can be minimized when risk and benefits are acceptable. In addition, the potential for reduction in requirements of vasopressors and inotropes is physiologically significant. A larger sample size may clarify this further along with identifying many other patient-centered benefits of performing a TT in ECMO patients.

Conclusions

Tracheostomy can be safely performed in selected ECMO patients in who benefits outweigh the risks without an associated increase in use of PRC. Performing a TT for patients while

they are still requiring ECMO support may result in reduction in inotropic or vasopressor usage although this needs to be further assessed in a larger study. Similarly, there may be a benefit in terms of reduction in analgesic usage, which may be seen in a study with larger sample size.

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Authors' Note

Jatinder Grewal, Anna-Liisa Sutt, Kiran Shekar, and John Fraser contributed to conception and design, data analysis, and interpretation. George Cornmell gave administrative support. All authors provided study materials or patients, collected and assemble data, wrote manuscript, and gave final approval of manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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