Original Research

Sedation and Analgesia in Patients Undergoing Tracheostomy in COVID-19, a Multi-Center Registry

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Abstract

Introduction: Patients with COVID-19 ARDS require significant amounts of sedation and analgesic medications which can lead to longer hospital/ICU length of stay, delirium, and has been associated with increased mortality. Tracheostomy has been shown to decrease the amount of sedative, anxiolytic and analgesic medications given to patients. The goal of this study was to assess whether tracheostomy decreased sedation and analgesic medication usage, improved markers of activity level and cognitive function, and clinical outcomes in patients with COVID-19 ARDS.

Study Design and Methods: A retrospective registry of patients with COVID-19 ARDS who underwent tracheostomy creation at the University of Pennsylvania Health System or the Johns Hopkins Hospital from 3/2020 to 12/2020. Patients were grouped into the early (≤14 days, $n = 31$) or late (15 + days, $n = 97$) tracheostomy groups and outcome data collected.

Results: 128 patients had tracheostomies performed at a mean of 19.4 days, with 66% performed percutaneously at bedside. Mean hourly dose of fentanyl, midazolam, and propofol were all significantly reduced 48-h after tracheostomy: fentanyl (48-h pre-tracheostomy: 94.0 mcg/h, 48-h post-tracheostomy: 64.9 mcg/h, $P = .000$), midazolam (1.9 mg/h pre vs. 1.2 mg/h post, $P = .0012$), and propofol (23.3 mcg/kg/h pre vs. 8.4 mcg/kg/h post, $P = .0121$). There was a significant improvement in mobility score and Glasgow Coma Scale in the 48-h pre- and post-tracheostomy. Comparing the early and late groups, the mean fentanyl dose in the 48-h pre-tracheostomy was significantly higher in the late group than the early group (116.1 mcg/h vs. 35.6 mcg/h, $P = .03$). ICU length of stay was also shorter in the early group (37.0 vs. 46.2 days, $P = .012$).

Interpretation: This data supports a reduction in sedative and analgesic medications administered and improvement in cognitive and physical activity in the 48-h period post-tracheostomy in COVID-19 ARDS. Further, early tracheostomy may lead to significant reductions in intravenous opiate medication administration, and ICU LOS.

Keywords

tracheostomy tube, sedation, physical therapy, covid-19, acute respiratory distress syndrome

Introduction

Critically-ill patients frequently require mechanical ventilation and most ventilated patients require pharmacologic intervention to mitigate the pain and agitation associated with endotracheal intubation.[1] Optimization of analgesia and sedation regimens to minimize sensory-altering medications and encouraging non-pharmacologic interventions (eg, early physical therapy and promoting normal sleep-wake cycle) is now prioritized.[2–5] The rationale behind the paradigm shift is that continuous intravenous sedative medication has been associated with prolongation of mechanical ventilation, longer ICU length of stay, and increased delirium.[3,6–8] Long term cognitive outcomes of COVID-19 have also been reported, and include significant morbidity, particularly in those with severe disease.[9] Despite these data, use of sedation and analgesic medications were exceedingly high during the initial stages of treatment of ARDS in Coronavirus disease 2019 (COVID-19), even when compared to traditional ARDS cohorts.[10,11]

COVID-19 has led to a significant burden of lung disease and acute respiratory distress syndrome (ARDS) requiring

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prolonged mechanical ventilation and in many cases the need for tracheostomy.[12–15]

Tracheostomy tube placement has been associated with decreased administration of sedative and analgesic medications, increased probability of ICU discharge at 28 days, decreased incidence of ventilator associated pneumonia, and decreased resource utilization when performed early.[16–20] These data however, have not been consistently reproduced.[21] During the COVID-19 pandemic, tracheostomy timing was often delayed given concerns for the health and safety of the team performing the procedure.[22,23] Small, single-center studies in COVID-19 have shown decreased sedation medication pre- and post-tracheostomy.[24,25] As we gained a firm understanding of safe procedure performance, the COVID-19 pandemic provided a unique opportunity to assess outcomes in tracheostomy given the increased tracheostomy volume.

The overarching goal of this retrospective analysis is to describe patient outcomes with a particular focus on sedative and analgesic medication administration in the 48-h pre- and post-tracheostomy broken into early and late tracheostomy groups.

Methods

This is a multi-center, retrospective cohort of all COVID-19 positive patients who had a consultation for tracheostomy at the University of Pennsylvania Health System (UPHS) and The Johns Hopkins Hospital (JHH) from March of 2020 until November of 2020. This study was approved by the Institutional Review Boards at both centers (IRB00248523 at JHH and exempted with no IRB required at UPHS). UPHS cases are drawn from four of the affiliated hospitals that represent academic, academic trauma, urban community, and suburban community facilities. The JHH cases were all performed at the main campus in East Baltimore. All patients with a consult for tracheostomy were included initially, with exclusion of patients who did not eventually undergo tracheostomy or who required tracheostomy while on extracorporeal membrane oxygenation (ECMO). The consults were placed for failure to timely liberate from the ventilator related to severe ARDS or inability to wean from sedative and analgesic medications. Data was collected on patient demographics, clinical outcomes, method of tracheostomy (ie percutaneous dilational), location of tracheostomy (ie bedside or operating room), dosage of intravenous sedative and analgesic medications, sedation parameters, and physical therapy scoring. The data was collected by a combination of retrospective chart review and data extraction from the electronic medical record. Patients were grouped into an early (day 14 and earlier, $n = 31$) and late (day 15 and later, $n = 97$) based on established practice of performance of tracheostomy on day 14.

For collection of sedative and analgesic medication doses, data was manually extracted from the medication administration record or pulled from EMR query and total dose (both continuous infusion and bolus dosing) was summed for the 48-h pre- and post-tracheostomy. Mean hourly dose is reported as this is standard of practice at both hospitals. For collection of sedation parameters, all values for Richmond Agitation and Sedation Scale (RASS) (Scale from −5 coma to+4 agitated), Glasgow Coma Scale (GCS) (Scale from 3 non-responsive to 15 alert and participating), and Johns Hopkins Highest Level of Mobility (HLM) (Scale from 1 = bedbound to 8 = walked 250 laps in the ICU) were collected in the 48-h pre- and post-tracheostomy. For the GCS, the highest value achieved per patient in those time periods were taken and averaged. For RASS and HLM, all values pre- and post-tracheostomy were averaged and compared in aggregate. Data was analyzed using STATA version 16.

Table 1. Baseline Characteristics, Summary Statistics, and Outcomes.

Age (mean)	66.8
Sex	Female: 55 (43.0%)
Total Patients	128
Race	Black: 64 (50.0%)
	White: 26 (20.3%)
	Hispanic: 21 (16.4%)
	Asian: 6 (4.7%)
	Other: 11 (8.6%)
Time Intubated Pre-Tracheostomy	19.4 ± 8.6 days
Type of Procedure	Percutaneous/Bedside: 86 (67.1%)
	Open/Bedside: 23 (17.9%)
	Open/Operating Room: 19 (14.8%)
Mortality	29 (22.7%)
ICU Length of Stay	41 ± 18.7 days
Number of Patients Decannulated	60 (46.8%)
Hospital Length of Stay	53.9 ± 27.4

Results

A total of 153 patients were evaluated with 135 having tracheostomy performed, 7 were excluded given ECMO status for a total of 128. Tables 1 and 2 show the demographic breakdown, location of procedure, and comparison of early and late tracheostomy groups. Patients had their tracheostomy

Table 2. Baseline Characteristics and Outcomes From the Early Tracheostomy and Late Tracheostomy Groups.

	Early Trach	Late Trach	
Number	31	97	
Age	82.6	61.0	$P = .05$
BMI	30.6	32.5	$P = .13$
Sex (Female)	14 (46.3%)	39 (40.3%)	
Days Intubated Pre-Procedure	Mean: 9.9 Median: 11	Mean: 23.1 Median: 21	
ICU LOS (days)	37.0	46.2	$P = .012$
Hospital LOS (days)	48.8	56.3	$P = .076$
Decannulated (yes)	14 (45.2%)	46 (47.4%)	$P = .12$
Mortality	24.3%	19.2%	$P = .25$

Table 3. Evaluation of Sedation and Analgesic Medication Dosage for Fentanyl, Midazolam, Precedex, and Propofol for *all Patients* (Early and Late Groups Combined).

Drug	Patients Receiving	Mean Hourly Dose	SD	*P*-value to detect difference pre/post
Fentanyl (mcg/h) (pre)	59	94.0	164.0	<.001
Fentanyl, (mcg/h) (post)	57	64.9	131.5	
Midazolam, (mg/h) (pre)	32	1.9	3.8	.0012
Midazolam, (mg/h) (post)	27	1.2	2.8	
Precedex, (mcg/kg/h) (pre)	25	0.58	0.48	.3931
Precedex, (mcg/kg/h) (post)	24	0.57	22.9	
Propofol, (mcg/kg/h) (pre)	12	23.3	18.5	.0121
Propofol, (mcg/kg/h) (post)	5	8.4	12.4	

performed on average 19.4 days post-intubation (early group 9.9 days post-intubation, late group 23.1 days post-intubation), and the vast majority of the procedures were performed at bedside (84.7%). Mortality was 22.5% for all patients undergoing tracheostomy (early 24.3%, late 19.2%, $P = .25$) and none of these were related to the procedure. There was an average ICU length of stay of 41 days (early 37.0, late 46.2; $P = .012$), with a hospital length of stay of 53.9 days (early 48.8, late 56.3, $P = .12$). 60 patients (47.3%) were decannulated at time of censoring (early 13 [41.9%], late 46 [40.9%], $P = .12$).

Data for All Patients

Mean total medication dosage in 48 h (pre- vs. post-, *P*-value to detect significant difference) was determined and is shown in Table 3, with fentanyl in mcg/hr (94.0, 64.9, $P < .000$), midazolam in mg/h (1.9, 1.2, $P = .0012$), precedex in mcg/kg/h (0.58, 0.57, $P = .3931$), and propofol in mcg/kg/h (23.3, 8.4, $P = .0121$).

Table 4. Evaluation of Sedation and Analgesic Medication Dosage for Fentanyl, Midazolam, Precedex, and Propofol for *Early Tracheostomy Patients.*

Drug	Patients Receiving	Mean Hourly Dose	SD	*P*-value to detect difference pre/post
Fentanyl, (mcg/h) (pre)	16	35.6	57.5	.23
Fentanyl, (mcg/h) (post)	15	23.5	47.4	
Midazolam, (mg/h) (pre)	6	1.8	1.9	.04
Midazolam, (mg/h) (post)	4	0.36	0.61	
Precedex, (mcg/kg/h) (pre)	6	1.03	0.31	.28
Precedex, (mcg/kg/h) (post)	6	0.93	0.29	
Propofol, (mcg/kg/h) (pre)	1	28.1	n/a	n/a
Propofol, (mcg/kg/h) (post)	1	0.26	n/a	

Table 5. Evaluation of Sedation and Analgesic Medication Dosage for Fentanyl, Midazolam, Precedex, and Propofol for Late Tracheostomy Patients.

Drug	Patients Receiving	Mean Hourly Dose	SD	*P*-value to detect difference pre/post
Fentanyl, (mcg/h) (pre)	43	116.1	185.2	.16
Fentanyl, (mcg/h) (post)	42	82.8	151.2	
Midazolam, (mg/h) (pre)	26	2.0	4.3	.25
Midazolam, (mg/h) (post)	23	1.3	3.1	
Precedex, (mcg/kg/h) (pre)	19	0.45	0.45	.44
Precedex, (mcg/kg/h) (post)	18	0.47	0.48	
Propofol, (mcg/kg/h) (pre)	11	22.8	19.3	.03
Propofol, (mcg/kg/h) (post)	4	9.1	12.7	

Early and Late Tracheostomy

For *early* tracheostomy, mean total medication dosage in 48 h (pre- vs. post-, *P*-value to detect significant difference) was determined and is shown in Table 4, with fentanyl in mcg/hr (35.6, 23.5, $P = .23$), midazolam in mg/h (1.8, 0.36, $P = .04$), precedex in mcg/kg/h (1.03, 0.93, $P = 0.28$), with only one patient receiving propofol in the early group.

For *late* tracheostomy, mean total medication dosage in 48 h (pre- vs. post-, *P*-value to detect significant difference) was determined and is shown in Table 5, with fentanyl in mcg/h (116.1, 82.8, $P = .16$), midazolam in mg/h (2.0, 1.3, $P = .25$), precedex in mcg/kg/h (0.45, 0.47, $P = .44$), and propofol in mcg/kg/h (22.8, 9.1, $P = .03$).

Evaluating the 48 h pre-tracheostomy levels in the early and late groups are shown in Table 6 (early, late, *P*-value). Fentanyl in mcg/h (35.6, 116.1, $P = .03$), midazolam in mg/h (1.8, 2.0, $P = .46$), precedex in mcg/kg/h (1.03, 0.45, $P = .003$). Propofol calculations unable to be performed given only one patient in the early-tracheostomy group receiving the medication.

Evaluating the 48 h post-tracheostomy levels in the early and late groups are shown in Table 7 (early, late, *P*-value). Fentanyl

Table 6. (Pre) Evaluation of Sedation and Analgesic Medication Dosing Comparing the pre-Tracheostomy Values for Early and Late Tracheostomy

Drug	Patients Receiving	Mean Hourly Dose	SD	p-value to detect difference early/late
Fentanyl, (mcg/h) (early)	16	35.6	57.5	.03
Fentanyl, (mcg/h) (late)	43	116.1	185.2	
Midazolam, (mg/hr) (early)	6	1.8	1.9	.46
Midazolam, (mg/h) (late)	26	2.0	4.3	
Precedex, (mcg/kg/hr) (early)	6	1.03	0.31	.003
Precedex, (mcg/kg/h) (late)	19	0.45	0.45	

Note: Propofol excluded as only only one patient in early tracheostomy group.

Table 7. (Post) Evaluation of Sedation and Analgesic Medication Dosing Comparing the post-Tracheostomy Values for Early and Late Tracheostomy

Drug	Patients Receiving	Mean Hourly Dose	SD	*P*-value to detect difference early/late
Fentanyl, (mcg/h) (early)	15	23.5	47.4	.049
Fentanyl, (mcg/h) (late)	42	82.8	151.2	
Midazolam, mg (post)	4	0.36	0.61	.22
Midazolam, mg (post)	23	1.3	3.1	
Precedex, (mcg/kg/h) (post)	6	0.93	0.29	.006
Precedex, (mcg/kg/h) (post)	18	0.47	0.48	

Note: Propofol excluded as only one patient in early tracheostomy group received.

in mcg/h 23.5, 82.8, $P = .049$), midazolam in mg/h (0.36, 1.3, $P = .22$), precedex in mcg/kg/h (0.93, 0.47, $P = .006$). Propofol calculations unable to be performed given only one patient in the early-tracheostomy group receiving the medication.

Figures 1–3 depicts all medication dosing for fentanyl, midazolam, and precedex.

Other Metrics

Metrics for assessing sedation and level of mobility are shown in Table 8, including the Richmond Agitation and Sedation Scale (RASS),[26] Hopkins Level of Mobility (HLM),[27] and the maximum value of Glasgow Coma Scale (GCS)[28] in the 48-h pre- and post- tracheostomy. There was a significant improvement in HLM (1.57 pre-, 1.83 post-, *P*-value .001), and maximum GCS (9.46 pre-, 10.41 post-, *P*-value .0041). These values were performed for early versus late tracheostomy and there were no significant differences detected among the subsets.

Discussion

COVID-19 has had a profound impact on the ability of the medical team to continue evidence-based practice. The ability to perform tracheostomy in a safe and timely manner was unknown at the beginning of the pandemic. Further, national medication shortages disrupted typical practices. The theoretical benefits of early tracheostomy (ie, decreased ICU length of stay, health care utilization, sedation and analgesic medication, reduced risk of endotracheal tube- related tracheal pathology) were initially eschewed, understandably, in favor of protecting health care workers from SARS-CoV2 transmission.[22,23,29] COVID-19 ARDS also provided us with a unique opportunity to evaluate our tracheostomy practices given the increased need for this procedure. This current paper focuses on sedation and analgesia practices associated with tracheostomy, specifically the changes centered in the 96-h periprocedural time.

The average time from intubation to tracheostomy, roughly the 20-day mark, is similar to what other cohorts have described.[30–32] Two-thirds of the tracheostomies were performed percutaneously at bedside and only 15% required the operating room. The delineation between "early" and "late" tracheostomy was based on our current practices of offering tracheostomy at the two week mark of intub ation. While this led to uneven groups (31 patients in the early group vs. 97 in the late), it led to a better representation of our clinical practice. Early tracheostomy in the literature has been defined as less than ten days, and sometimes even less than 96 h.[20] Decannulation (46.8%) and mortality (22.7%) rates are also in line with data reported from other centers.[24,33] We did not see a significant difference in decannulation or mortality in

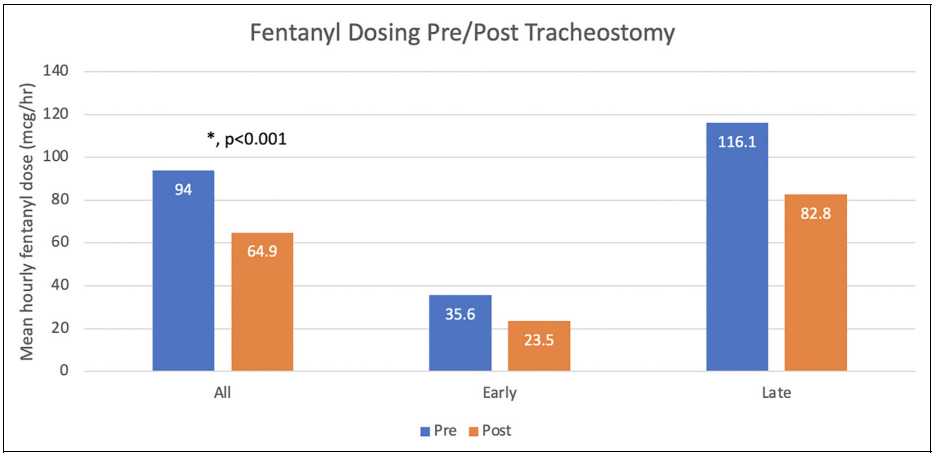

Figure 1. Mean hourly fentanyl dose in the 48-h pre (blue) and post (orange) tracheostomy. Note: there is a significant difference between the pre- and post- groups in the "All" patients category (* denotes). There is also a significant increase in dosing between the early pre and late pre, and early post and late post groups.

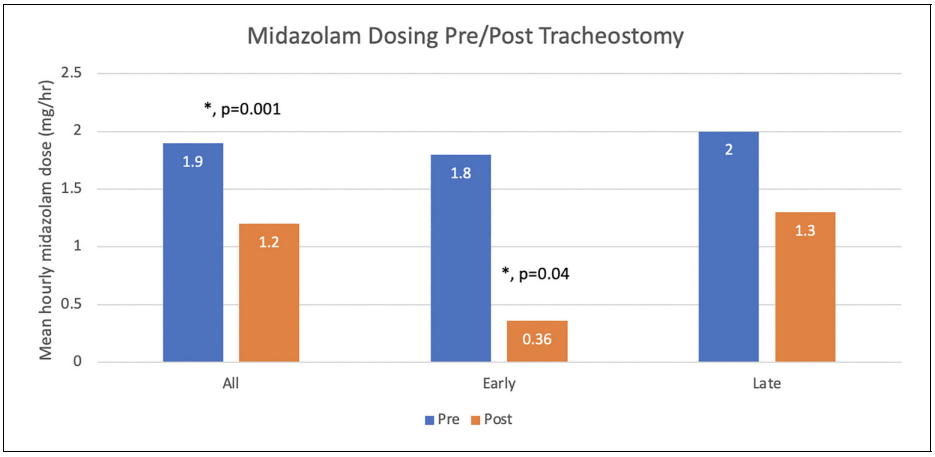

Figure 2. Mean hourly midazolam dose in the 48-h pre (blue) and post (orange) tracheostomy. Note: there is a significant difference between the pre- and post- groups in the "All" and "Early" patients categories (* denotes). There is also a significant increase in dosing between the early pre and late pre, and early post and late post groups.

the early versus late groups. We suspect this is related to the variability of critical illness and our relatively small cohort of patients.

Minimizing operating room utilization was, in most cases, a deliberate decision to reduce risk of aerosol disbursement associated with transport and accidental ventilator disconnects, but it does suggest the safety of this procedure being done at bedside. To further alleviate some of the aerosol generation, a modified percutaneous technique was used in some cases. This featured use of disposable bronchoscopy to confirm correct anatomical site, then disconnection of the endotracheal tube from the ventilator circuit during incision/placement, only reconnecting to the ventilator when the tracheostomy tube was in place and cuff up.[34] This requires expert clinicians to perform in a timely manner to avoid precipitating respiratory failure, but is an option going forward for patients with highly infectious diseases.

The length of stay (LOS) of these patients in the ICU was 41 ± 19 days, with the early group significantly less than the late group (37.0 days vs. 46.2 days). The early group utilized a critical care bed on average 9.2 days less than the late group, allowing for increased throughput and a savings of multiple thousands of dollars per day.[35] One of the determinants of LOS in the ICU is sedative and analgesic medication dosage and duration.[2,4,36] Continuous intravenous sedation typically necessitates an ICU environment and prolonged use of sedative medications can contribute to both short-term cognitive impairment that requires a higher level of care and long-term disability.[37,38] In this multi-center study at large tertiary referral centers, we were able to describe a significant reduction in fentanyl, midazolam, and propofol within 48-h of the tracheostomy procedure. Further, we describe a significantly higher dose of intravenous fentanyl in patients undergoing late-tracheostomy in comparison to the early-tracheostomy cohort. This is likely

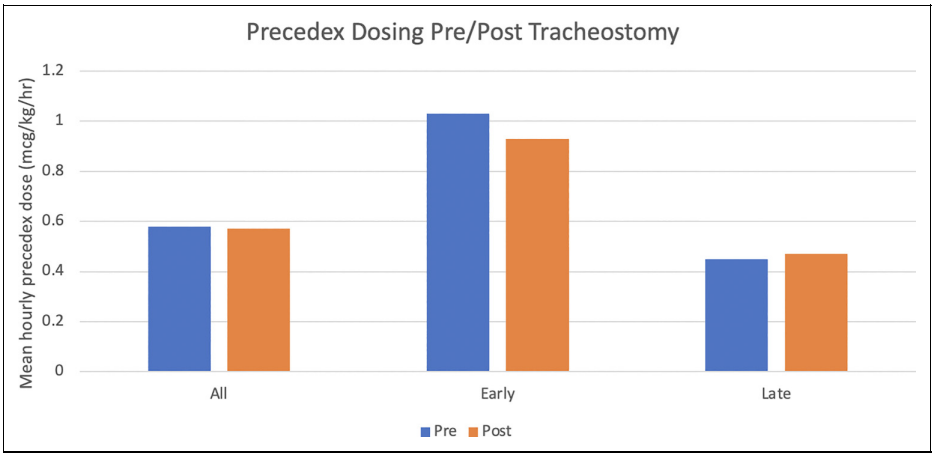

Figure 3. Mean hourly precedex dose in the 48-h pre (blue) and post (orange) tracheostomy. Note: There is a significant increase in dosing between the early pre and late pre, and early post and late post groups.

Table 8. Pre and Post Tracheostomy Scores for the Richmond Agitation and Sedation Scale (RASS), the Johns Hopkins Highest Level of Mobility (HLM) and Glasgow Coma Scale (GCS).

Variable	Number of Observations Pre	Mean Score Pre	Number of Observations Post	Mean Score Post	*P*-value
RASS	97	−1.703	100	−1.44	.144
HLM	58	1.57	58	1.83	.001
GCS Max	53	9.46	53	10.41	.0041

attributed to the tachyphylaxis seen with opiate medications. Our findings suggest that identifying patients early, who will likely be unable to liberate from the ventilator may help reduce length of stay, reduce sedative and analgesic medication accumulation, and improve neurocognitive functioning, though this has proven difficult to do aside from patients with neurologic deficits.[21,39–41]

It was interesting to note that the dose of precedex was significantly higher in the early tracheostomy group in comparison with the late group. We suspect this is related to attempting to use precedex as a single agent in the early group for sedation as opposed to an adjunct in the late group.

The GCS is a three-pronged tool used to assess cognition by providing points for eye-opening, oral response, and motor response.[28] While not a direct assessment of delirium, it can provide valuable information on brain function and a means to track cognitive trajectory. Consistent with our finding of reduced sedative use, our data demonstrate that maximum GCS was significantly higher in the 48-h post tracheostomy. Our data did not show a significant change in RASS scores in the pre- and post-tracheostomy period, likely owing to the fluctuating and transient nature of cognitive state in critical illness.

Physical therapy has been described to decrease delirium in patients in the intensive care unit.[42] The Johns Hopkins Highest Level of Mobility Scale – (JH-HLM) is a tool used to describe patients' ability to function in the hospital and provides a means to measure physical functioning.[42] In this study we describe a significant increase in HLM in the 48-h post-tracheostomy. Despite a low average HLM scale (1.83), our data show that even after only 48 h following tracheostomy, physical functioning improved. This improvement is likely attributable to the reduction in sedation, anxiolytic and analgesic medications after tracheostomy.

We recognize the limitations and generalizability of this retrospective cohort including the lack of a control group who remained intubated without a tracheostomy. Additionally, this cohort spanned changing practices throughout the pandemic as providers became more comfortable managing the disease process. The first few months of the pandemic, a period where patients likely received larger doses of sedative/analgesic medications given the initial uncertainty, may not be generalizable even to the last months studied.[10] Additionally, early in the pandemic, aerosolization and spread of the virus was not well elucidated, so tracheostomy performance was often times deferred while protocols and consensus guidelines could be developed.

We also did not explicitly control for delirium as defined by the confusion assessment method in the intensive care unit (CAM-ICU). Rather, the focus of this investigation was to evaluate the peri-tracheostomy period in an effort to specifically characterize the impact of the tracheostomy procedure on sedation administration. We recognize that taking a 96-h snapshot in a multiple week ICU stay may not be representative, but the data are consistent in both the early and late groups to suggest that tracheostomy creation and removal of the ETT does aide the weaning process from intravenous sedative and analgesic medication. Additionally, use of oral anti-psychotic, opiate, and benzodiazepine medication was not tracked, which could play a role in weaning from intravenous medications. We also recognize that all currently used sedation assessment tools are not ideal measures of cognitive state and are static measures at one point in time while cognition in ICU patients can vary substantially across time periods, particularly in the setting of delirium. We also did not control for disease severity, which could impact medication usage and provider decisions on treatment.

We have described a reduction in sedative, anxiolytic and analgesic medication, and an improvement in GCS and highest level of mobility in the 48-h post-tracheostomy. We have also shown a significant increase in opiate medication dosage as length of mechanical ventilation increases. This supports early tracheostomy performance in patients that will ultimately not liberate from the ventilator. Further study should be guided at determining which patients will benefit from early tracheostomy.

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Declaration of Conflicting Interests

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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