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Comparison of three cisatracurium dosing strategies in acute respiratory distress syndrome: A focus on drug utilization and improvement in oxygenation

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ABSTRACT

Purpose: Three continuous dosing strategies of cisatracurium (CIS) for acute respiratory distress syndrome (ARDS) have been described in the literature. After implementation of a ventilator synchrony protocol (VSP), we sought to determine which continuous CIS dosing strategy utilized the least amount of drug without compromising efficacy.

Methods: We retrospectively reviewed patients with ARDS receiving continuous CIS from January 1, 2013 to December 31, 2018. We categorized patients into one of three dosing strategies: fixed dose (FD), titration based solely on train-of-four (TOF), or the VSP. We documented drug consumption and determined efficacy by comparing the change in PaO_2/FiO_2 ratio (P/F) and oxygenation index (OI) from baseline up to 48 h.

Results: A total of 1047 patients were screened, and 189 met inclusion criteria (VSP = 69, TOF = 99, FD = 21). Drug consumption (mg) was significantly lower in the VSP arm: 415 [IQR 318–528] compared to both the TOF: 665 [IQR 472–927] and the FD arms: 1730 [IQR 1695–1800], $p < 0.001$ for each. The change in P/F and OI from baseline were statistically equivalent at all time points.

Conclusion: Without impacting efficacy of gas exchange, a protocol using ventilator synchrony for CIS titration required significantly less drug compared to TOF-based titration and a fixed dosing regimen.

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1. Introduction

Acute Respiratory Distress Syndrome (ARDS) is associated with a high mortality rate with few pharmacotherapeutic options. [1] Research demonstrates that a trial of continuous infusion cisatracurium (CIS) leads to improved PaO_2/FiO_2 (P/F) ratios potentially by decreasing serum inflammatory markers, oxygen consumption, patient-ventilator asynchronies, and ventilator-induced lung injury. [2-7] While data on the impact of neuromuscular blockade on mortality are conflicting, guidelines recommend a trial of neuromuscular blocking agents (NMBA) in life-threatening situations. [8,9] However, optimal continuous infusion dosing strategies remain undefined. [10-12]

Utilization and dosing of CIS in ARDS remains controversial. [13-15] Three continuous dosing strategies have been described in the literature and employed in clinical practice: a fixed dosing approach (37.5 mg/h), weight-based dosing with titration guided exclusively by Train-of-Four (TOF) assessments, and weight-based dosing using ventilator synchrony to guide adjustments. [4,5,10,11,16-20] Despite the two largest randomized controlled trials in ARDS utilizing a fixed-dosing approach, earlier studies report experiences with titrating neuromuscular blockade to target zero twitches on TOF stimulation. [4,5] Several studies support utilizing TOF to reduce NMBA exposure, however, data suggest TOF measurements do not correlate to clinical assessment nor depth of paralysis. [17-19,21-25] A protocolized dosing strategy targeting

Abbreviations: ARDS, acute respiratory distress syndrome; CIS, cisatracurium; DP, driving pressure; FD, fixed dose; FiO_2, fraction of inspired oxygen; ICU, intensive care unit); LOS, length of stay); mPaw, mean airway pressure; NMBA, neuromuscular blocking agent; OI, oxygenation index; P/F, PaO_2/FiO_2 ratio; P_{plat}, plateau pressure; PEEP, positive end expiratory ressure; S/F, SaO_2/FiO_2; SOFA, sequential organ failure assessment; V_T, tidal volume; T0, time zero; TOF, train-of-four; VSP, ventilator synchrony protocol.

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ventilator synchrony allows for titration of NMBA based on a more physiologic and clinically relevant target and therefore potentially limit excessive drug use and potential complications. [17,19] Although clinical practice guidelines recommend the use of TOF in addition to clinical assessment for adjusting neuromuscular blockade, there still remains debate about which dosing strategy is most effective and appropriate. [8,13,14]

Based on the available evidence, we developed and implemented a CIS dosing protocol utilizing a ventilator synchrony endpoint for efficacy, and TOF monitoring for potential toxicity. As the three dosing strategies have not been directly compared, we aimed to compare the effectiveness and drug utilization of the three aforementioned dosing protocols in patients with severe ARDS.

2. Methods

2.1. Patient population

We retrospectively reviewed patients diagnosed with ARDS receiving continuous neuromuscular blockade with CIS from January 1, 2013 to December 31, 2018. The study was approved by the University of Pittsburgh Institutional Review Board (STUDY19050099) and The University of Pittsburgh Medical Center Quality Improvement Committee (QI2339). Data were obtained from Acute Lung Injury Registry and the electronic medical record. Patients with an ICD-9/10 diagnosis code for acute respiratory failure (J80, J9600, J9601, J9602, J9621, 518.5, 518.81) and confirmed ARDS, as determined by the physician progress notes, were identified for inclusion. Patients could have been admitted into one of the eight intensive care units at our institution. We categorized included patients into one of three dosing strategies: fixed dose (FD), Train-of-four (TOF), or the ventilator synchrony protocol (VSP) (Supplement 1) as determined by the ordered titration parameter. All patients in the FD group received a continuous dose of 37.5 mg/h. The three dosing strategies were applied in parallel at our institution over time, with the medical intensive care unit being the primary unit that utilized the VSP. We excluded patients who were less than 18 years of age, received CIS for less than 36 h, had an interruption of CIS for greater than 3 h, had paralysis started at an outside hospital, or required extracorporeal membrane oxygenation.

2.2. Data collection

We considered time zero (T0) as the time of the first dose of NMBA, either bolus or infusion, if the bolus was given within three hours of continuous infusion initiation. Cumulative drug consumption (mg), infusion rate (mcg/kg/min), and number of infusion rate changes were collected through charted values from T0 to 48 h (T48) or the end of the infusion, which ever occurred first. Total infusion duration was defined as the duration of therapy from T0 until the infusion was discontinued, defined as the last charted administration.

Fraction of inspired oxygen (FiO_2), tidal volume (V_T), positive end expiratory pressure (PEEP), plateau pressure (P_{plat}), and mean airway pressure (mPaw), were assessed at T0. Additional values were obtained at subsequent 12-, 24-, 36-, and 48-h time points. FiO_2 and mPaw were documented from the most recent ventilator settings within 3 h of charting prior to the arterial blood gas (ABG), and used to calculate P/F ratio [PaO_2/FiO_2], and oxygenation index (OI) [$(mPaw \times FiO_2)/PaO_2$]. For the ABG to be included in the analysis, it needed to occur within 3 h of the time point. Lack of an ABG documented within each 3-h window did not preclude evaluation at other time points. At any time point, if PaO_2 was not reported, an SaO_2/FiO_2 (S/F) ratio was calculated and transformed to P/F ratio as validated by the ROSE investigators. [10,26] Driving pressure (DP) was calculated as the difference between Pplat and PEEP, and static compliance was calculated as V_T/DP.

All TOF scores were collected from T0 until T48, or discontinuation of the infusion, whichever occurred first. Site of TOF monitoring (ulnar vs orbicular) was not consistently recorded due to this information not being readily available retrospectively. Train-of-four values were not recorded for patients in the FD group. Duration of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), and hospital LOS were assessed in addition to in-hospital mortality.

It was assumed that all patients were managed throughout the study according to the ARDSNet mechanical ventilation protocol as this is a standard across our institution. [27] Sedation was titrated to Riker Sedation-Agitation Scale 1 prior to initiation of the NMBA. Severity of illness was measured by the sequential organ failure assessment (SOFA) scores by including the worst value within 24 h prior to time zero. [28] We collected other baseline demographic data within 24 h of time zero or from ICU admission History and Physical Notes. The use of prone positioning was determined through review of physician progress notes and use of inhaled epoprostenol was recorded during the study period.

2.3. Objectives

We sought to assess total CIS drug consumption and evaluate the efficacy of the three dosing strategies. Cisatracurium dose consumption was normalized to patient actual body weight and calculated as total milligrams divided by weight in kilogram. Cost of CIS was based on average wholesale price. We determined efficacy by comparing the change in P/F ratio and change in OI from T0 to 12 h (T12), 24 h (T24), 36 h (T36), and 48 h (T48). Assessment of change in P/F ratio and OI were mutually exclusive events at each time point, as a missing value at any time point did not preclude any other time point evaluation. Ventilator parameters and airway pressures (if available) were also compared at each time point. Change in compliance from baseline to each time point was also assessed.

2.4. Statistical analysis

Data are reported as median [interquartile range]. The Fisher's exact test was used to compare categorical variables. For continuous variables, Kruskal-Wallis tests were used for comparisons including all three groups. If statistical significance was determined, pairwise comparisons utilizing the Dunn-Bonferroni correction to the Kruskal-Wallis test was completed. Mann Whitney-*U* tests were used for continuous variable when only two groups were compared. After determination of normal distribution, assessment of change in OI and P/F from T0 to each time point were completed using a two-sided *t*-test for equivalence, conducted in a pairwise fashion. [29] Univariate linear regression was performed to assess predictors of total cumulative cisatracurium consumption at 48 h. All covariates with a p-value < 0.1 were added to a multivariate linear regression model. Predictors of improvement in delta P:F were evaluated by creating a multivariate linear regression with backward elimination. A unique model was created for each T12, T24, T36 and T48. All reported p-values are two-sided and a p-value of <0.05 was considered to be significant. Statistics and figures were performed using the R (R Core Team, 2020) software package. [30]

3. Results

3.1. Patient characteristics

A total of 1047 patients were screened, and 189 patients met inclusion criteria (Fig. 1). Baseline characteristics are summarized in Table 1. The median P/F ratios at T0 were <150 in each group, representing a severe ARDS cohort. [1] Baseline SOFA scores were not statistically different between groups. The main etiology of ARDS in each group was pneumonia. Significantly more patients had a concomitant respiratory related comorbidity in the VSP group (52%) compared to the TOF group (31%), $p = 0.01$. The use of prone positioning (VSP = 43%, TOF = 64%) and inhaled epoprostenol (VSP = 28%, TOF = 12%)

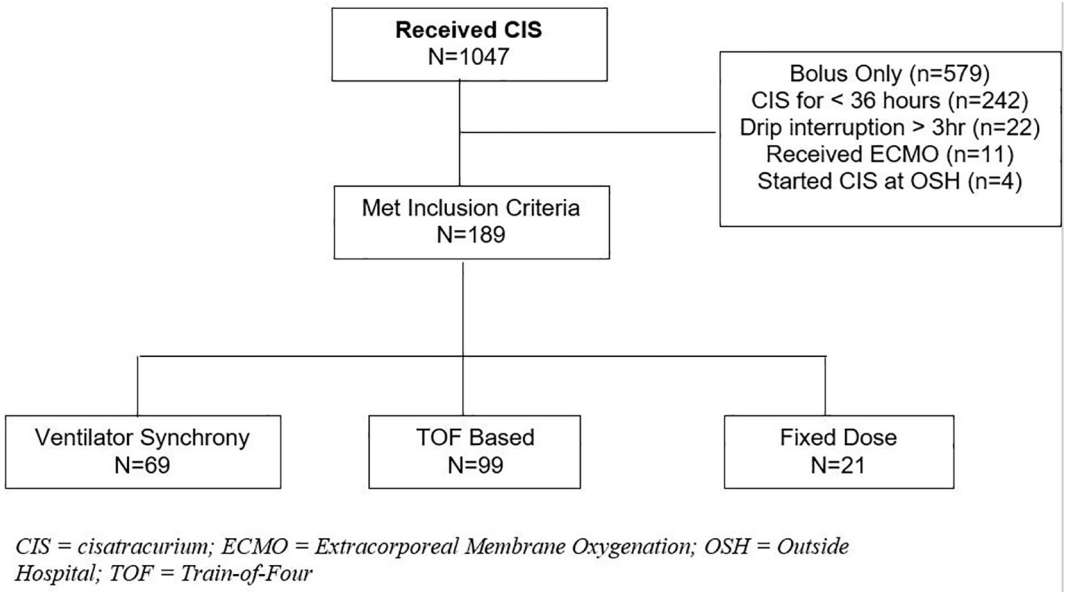

Fig. 1. Patient inclusion and exclusion. Flow diagram of included and excluded patients.

were also statistically different between these groups, p = 0.012 and 0.015, respectively.

3.2. Drug consumption

Table 2 depicts dosing characteristics of CIS infusions. The overall median duration of the CIS infusion (hours) was significantly shorter in the FD group (48 [IQR 45 to 48]) compared to both the TOF group (59 [IQR 46 to 85]) and VSP group (64 [IQR 46 to 94]); however, there was no difference between the TOF and VSP arms. The initial infusion rate (mcg/kg/min) was significantly higher in the FD arm (7.1 [IQR 6.4 to 8.9]), compared to both the TOF arm (2 [IQR 1 to 2]), and the VSP arm (2 [IQR 1 to 2]), p < 0.001 for each. There was no difference between the TOF and VSP groups. The median infusion rate (mcg/kg/min) was lower in the VSP arm 1.80 [IQR 1.5 to 2.0] compared to both the TOF arm 2.5 [IQR 1.8 to 3.6], and the FD arm 7.1 [IQR 6.7 to 8.9], p < 0.001 for each.

The overall drug consumption of CIS (mg) during the study period was significantly lower in the VSP arm 415 [IQR 318 to 528] compared to both the TOF arm 665 [IQR 472 to 927], and the FD arm 1730 [IQR 1696 to 1800], p < 0.001 for each. The results remained similar when normalizing CIS consumption to patient weight. Additionally, while controlling for differences in baseline characteristics, dosing strategy remained a significant predictor of drug consumption (b: 483, 95% confidence interval: 386 to 580), (Supplement 2). The reduction in CIS consumption resulted in a decrease in median cost (USD) of CIS per patient with a total of $954 in the VSP group compared to the TOF group ($1529) and FD group ($3979), p < 0.001.

3.3. Train-of-four monitoring

Train-of-four monitoring was assessed for the ventilator synchrony and TOF-based protocols (Table 3). The TOF arm had a higher percentage of TOF values less than 2 (47%) compared to the VSP arm (27%), p < 0.001. More TOF values per patient were obtained in the TOF group compared to the VSP group (23 [IQR 18 to 30] vs. 13 [IQR 11 to 14], p < 0.001). Patients in the VSP group also had significantly fewer dose titrations compared to the TOF arm (3 [IQR 0 to 5] vs. 8 [IQR 5 to 11], p < 0.001).

3.4. Efficacy endpoints and patient outcomes

The change in P/F ratio from baseline was determined to be equivalent between the TOF and VSP arms at hours 12, 24, 36, and 48 (p < 0.005 for each). Equivalence was also demonstrated when comparing the FD arm to both the VSP and TOF arms, at all time points evaluated, p < 0.005 for each comparison (Fig. 2). The dosing strategy utilized was not a significant predictor of improvement in delta P/F at any of the study time points while controlling for differences in baseline characteristics in a multivariate linear regression analysis. The results remained the same when evaluating OI in place of P/F ratios. There was no difference in change in compliance at 12, 24, 36, and 48 h from baseline between the groups. There were no differences in patient outcomes such as MV time or ICU LOS (Table 4).

4. Discussion

We report a comparison of three unique dosing and titration strategies for continuous infusion CIS in a cohort of severe ARDS patients. Our evaluation demonstrates that a protocol using ventilator synchrony for titration significantly reduced CIS utilization while providing equivalent improvement in oxygenation compared to a FD and a TOF-based protocol. Additionally, we observed a reduction in TOF monitoring and dose titrations in the VSP protocol compared to the TOF protocol. The efficacy of CIS in the overall cohort is consistent with the literature demonstrating an improvement in oxygenation over 48 h of therapy. [4,5,10,11]

There have been numerous studies conducted in ARDS to determine optimal treatment modalities in an effort to decrease mortality in this population. Neuromuscular blocking agents have been the recent focus of pharmacologic options. The ACURASYS trial demonstrated that a 48-h fixed dose CIS infusion reduced 28-day mortality 9.6% compared to placebo in patients with severe ARDS. [11] In 2019, the ROSE trial failed to demonstrate a mortality benefit with CIS utilizing the same fixed-dosing strategy as ACURASYS. [10] The high CIS dosing of 37.5 mg/h, without monitoring or titration, was developed to maintain blinding in ACURASYS and subsequently adopted in the ROSE trial. [13,31] This fixed dosing scheme was not designed for safety or efficacy; however, since these are the two largest prospective randomized trials investigating NMBA in ARDS, it often compels clinicians to consider adopting the fixed dose strategy.

Table 1
Baseline characteristics.

	Ventilator synchrony (N = 69)	Train-of-four (N = 99)	Fixed dose (N = 21)	p-value
Age, years	53 [39 to 62]	57 [38 to 65]	56 [46 to 64]	0.648
Male	37 (54)	66 (67)	9 (43)	0.064
Caucasian	57 (89)	74 (79)	15 (75)	0.15
Weight, kg	89 [70 to 107]	92 [77 to 107]	88 [70 to 94]	0.368
DM	18 (26)	33 (33)	7 (33)	0.58
CAD	15 (22)	27 (27)	2 (10)	0.21
CKD	17 (25)	19 (19)	4 (19)	0.69
Respiratory Dx	36 (52)[a]	30 (31)	11 (52)	0.01
Hepatic Dx	8 (12)	15 (15)[b]	10 (48)[c]	0.002
Immunosuppressed	28 (41)[a]	25 (25)[b]	11 (52)	0.197
Prone positioning	30 (43)[a]	63 (64)[b]	8 (38)	0.012
SOFA, points	9 [8 to 11]	8 [5 to 10]	8 [6 to 11]	0.08
Cause of ARDS, PNA	36 (52)[a]	35 (35)[b]	15 (71)	0.03*
Cause of ARDS, Trauma	4 (6)[a]	23 (23)[b]	0 (0)	
Cause of ARDS, Non-pulmonary Sepsis	9 (13)	8 (8)	2 (10)	
Cause of ARDS, Aspiration PNA	6 (9)	18 (18)	2 (10)	
Cause of ARDS, Other	14 (20)	15 (15)	2 (10)	
Corticosteroids	35 (51)	26 (27)	7 (33)	0.06
Inhaled Epoprostenol	19 (28)[a]	12 (12)	2 (10)	0.026
PaO_2/FiO_2^	88 [69 to 117]	95 [71 to 118]	136 [91 to 144][c]	0.023
Oxygenation index	17 [12 to 24]	15 [12 to 22]	11 [9 to 33]	0.418
Tidal volume, mL/kg of IBW	6.2 [5.7 to 6.9]	6.3 [5.9 to 6.9]	6.2 [6.0 to 6.6]	0.695
PEEP, cm H_2O	12.5 [10 to 15]	12 [10 to 14]	12 [10 to 15]	0.133
mPaw, cm H_2O	17 [14 to 21]	16 [13 to 19]	14 [13 to 18]	0.296
P_{plat}, cm H_2O	28 [26 to 34]	28 [27 to 30]	30 [22 to 31]	0.662
Driving Pressure, cm H_2O	15 [23 to 19]	15 [13 to 18]	14 [11 to 15]	0.323
Compliance, mL/cm H_2O	26 [19 to 32]	27 [24 to 32]	28 [23 to 33]	0.768

Data reported as median [IQR] or N (%).
^ *S/F substitutions were used for the calculation of P/F ratio in 29% of patients.
ARDS = Acute Respiratory Distress Syndrome; CAD = Coronary Artery Disease; CKD = Chronic Kidney Disease; DM = Diabetes Mellitus; Dx = Disease; IBW = Ideal Body Weight; mPaw = Mean Airway Pressure; OI=Oxygenation Index; PEEP=Positive End-Expiratory Pressure; PNA = Pneumonia; P_{plat} = Plateau Pressure; SOFA = Sequential Organ Failure Assessment Score.
[a] Significant difference between VSP and TOF group, $P < 0.05$.
[b] Significant difference between TOF and FD groups, $P < 0.05$.
[c] Significant difference between VSP and FD groups, $P < 0.05$.
* Cause of ARDS was completed as a 3 × 5 comparison. Based on statistically significant finding, pairwise comparisons were completed for each cause of ARDS and each dosing strategies. Statistical significance of these comparisons is denoted by the appropriate superscript (a, b, c).

In contrast to the fixed-dose approach, two previously completed randomized trials utilized a dosing strategy targeting TOF goals. [4,5] Hraiech and colleagues compared these two approaches by evaluating a nursing driven CIS titration protocol targeting TOF 0 of 4 against a theoretical amount of CIS that the same group of patients would have received in the fixed-dosing protocol utilized in the ACURASYS study. The average duration of CIS infusion in was 54 h, with a mean final dose of 14 mg/h (approximately 2.9 μg/kg/min for an 80 kg patient), which resulted in a median reduction of nearly 1500 mg compared to if the same patient were to be prescribed a fixed dose of 37.5 mg/h. [21] We found similar results in our study, which observed a 76% reduction in CIS consumption when comparing the TOF arm to the FD arm. Our findings further support that the use of a fixed dose of 37.5 mg/h results in a dramatic increase in CIS exposure compared to TOF-based protocols. The use of TOF monitoring for NMBAs remains common, as a survey of intensivists revealed that 68% reported using TOF as the primary method for NMBA monitoring and titration. [32] A recently published evaluation of a large cohort of ARDS patients questioned the validity of TOF monitoring in the ICU patient by finding discrepancies between the clinical appreciation of muscle paralysis and TOF monitoring. [22] Additional literature and practice guidelines state that TOF alone may not provide the optimal assessment of depth of neuromuscular blockade. [8,13,17,23,24] Based on the literature, our multi-disciplinary Medical ICU leadership team developed a protocol that incorporated assessment of respiratory parameters and TOF to design the VSP utilized in this study (Supplement 1).

Table 2
Dosing characteristics of cisatracurium.

	Ventilator synchrony (N = 69)	Train-of-four (N = 99)	Fixed dose (N = 21)	p-value
Duration of infusion, hours	64 [46 to 94]	59 [46 to 85][b]	48 [45 to 48][c]	0.009
Initial Infusion Rate, mcg/kg/min	2.0 [1.0 to 2.0)]	2.0 [1.0 to 2.0][b]	7.1 [6.4 to 8.9][c]	<0.001
Mean Infusion Rate, mcg/kg/min	1.8 [1.5 to 2.0][a]	2.5 [1.8 to 3.6][b]	7.1 [6.4 to 8.9][c]	<0.001
Max Infusion Rate, mcg/kg/min	2.0 [2.0 to 3.0] [a]	3.5 [2.5 to 5.0][b]	7.1 [6.4 to 8.9][c]	<0.001
Total Cumulative Dose, mg/kg	5.1 [4.3 to 6.1][a]	6.8 [5.2 to 9.6][b]	20.4 [17.9 to 23.6][c]	<0.001
Total Cumulative Dose, mg	415 [318 to 528)][a]	665 [472 to 927][b]	1730 [1696 to 1800)][c]	<0.001

Data reported as median [IQR].
[a] Significant difference between VSP and TOF group, $P < 0.05$.
[b] Significant difference between TOF and FD groups, $P < 0.05$.
[c] Significant difference between VSP and FD groups, $P < 0.05$.

Table 3
Train-of-four monitoring and assessment.*

	Ventilator synchrony (N = 69)	Train-of-four (N = 99)	p-value
Number of Charted TOF Values, per Patient	13 [11 to 14]	23 [18 to 30]	<0.001
Number of Rate Changes, per Patient	3 [0 to 5]	8 [5 to 11]	<0.001
Total Number of TOF 0/4	205 (23)	755 (31)	<0.001
Total Number of TOF 1/4	36 (4)	377 (16)	<0.001
Total Number of TOF 2/4	93 (11)	655 (27)	<0.001
Total Number of TOF 3/4	48 (5)	158 (7)	0.7
Total Number of TOF 4/4	500 (57)	471 (19)	<0.001

Data reported as median [IQR] or N (%).
TOF = Train-of-Four.
* The FD group is not depicted in this table as TOF monitoring was not completed on these patients.

Previous comparisons between ventilator synchrony and TOF-based protocols have been limited by small sample sizes and lack of evaluation of efficacy endpoints. [17,19] A recent trial in cardiac surgery patients randomized 77 patients to receive continuous infusion atracurium dosed using clinical assessment with TOF compared to a protocol using clinical assessment alone. [33] The target for clinical assessment was the absence of movements, coughing, and ventilator asynchronies. In the clinical assessment plus TOF arm, atracurium was adjusted to maintain a TOF of 1 or 2 of 4. Similar to our study observations, the authors demonstrated a reduction in atracurium consumption in the clinical assessment alone protocol compared to the clinical assessment plus TOF arm and found significantly more absence of twitches (0/4) in the TOF arm. These results are consistent with our evaluation, which demonstrated a nearly 40% reduction in overall CIS consumption with the VSP compared to the TOF arm.

The results of our evaluation have important implications for drug conservation, cost containment, nursing time, and fluid balance. In addition to using less drug overall, the VSP resulted in less dose titrations and less TOF assessments compared to the standard TOF protocol corresponding to less nursing time spent adjusting NMBA medication and allowing for increased attention to other bedside duties. Additionally, the decrease in drug consumption by default led to a decrease in the volume of diluent administered. This is important since it has been previously shown that conservative fluid management is associated with more ventilator free days and reduced ICU length of stay in this patient population. [34] Our investigation is the largest direct comparison of three different dosing strategies of continuous infusion CIS in a severe ARDS cohort. Not only did we compare differences in dosing requirements between cohorts, but also evaluated equivalence in terms of

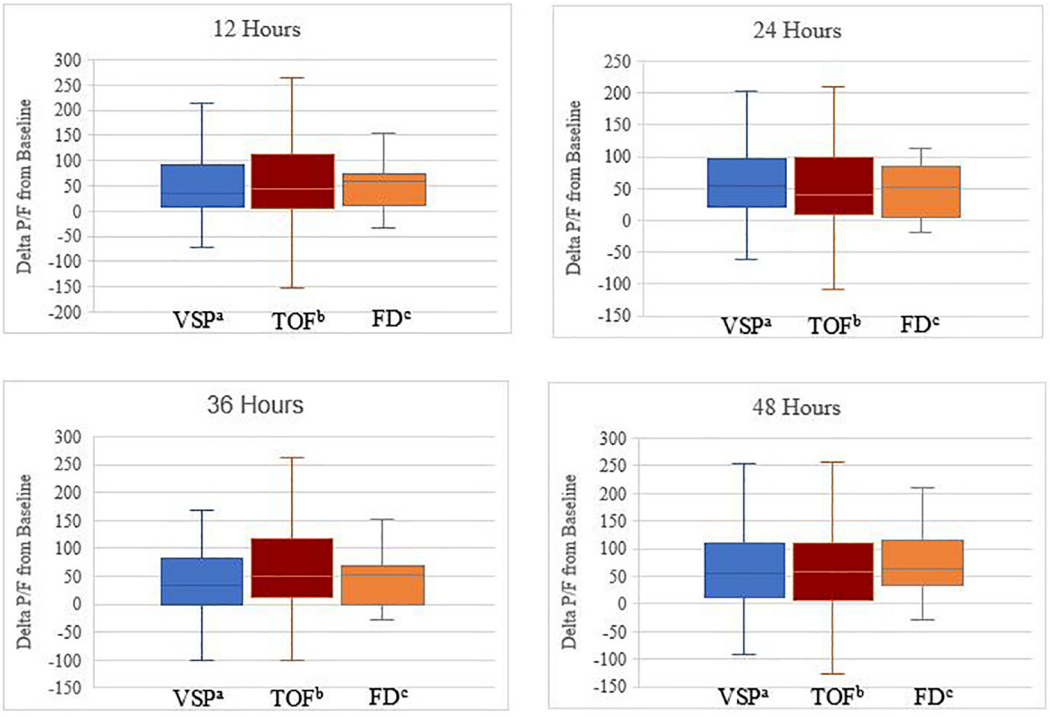

Fig. 2. Change in PaO_2/FiO_2 ratio from Time zero to 48 h. A comparison of changes in P/F ratio at 12, 24, 36 and 48 h from baseline. Box and whisker plots demonstrate median, interquartile range, and range (exclusive of outliers). The results of the *t*-test of equivalence demonstrated equivalence in change in P/F at all time points between all groups; $p < 0.005$.
*S/F substitutions were used for the calculation of P/F ratio in 20%, 25%, 35% and 34% of recordings at time point 12, 24, 36 and 48 h, respectively.

Table 4
Patient outcomes.

Outcome	Ventilator synchrony (n = 69)	Train-of-four (n = 99)	Fixed dose (n = 21)	p-value
ICU LOS, days	14 (11 to 22)	16 (9 to 31)	13 (10 to 17)	0.244
Hospital LOS, days	21 (14 to 30)	22 (11 to 34)	17 (12 to 26)	0.611
MV Time, days	13 (9 to 16)	12 (8 to 17)	9 (7 to 11)	0.064
Mortality	33 (48)	44 (44%)	8 (38)	0.73

Data reported as median (IQR) or N (%).
ICU = Intensive care unit; LOS = Length of stay; MV = Mechanical ventilation; COD = Cause of death; ARDS = Acute respiratory distress syndrome.

physiological efficacy as measured by P/F ratio and OI at four distinct time points.

Despite the numerous strengths of this evaluation, we appreciate the limitations. First, our retrospective design led to the inability to control the number of patients assigned to each group. We acknowledge the low number of patients included in our FD arm which may have led to differences in certain baseline characteristics. However, we completed a multivariate linear regression analysis to control for differences between the groups, and dosing strategy remained a strongly significant predictor of cumulative drug. Secondly, we were unable to standardize the timing of arterial blood gas collection, causing some patients to not be evaluated at each time point. However, we did utilize the S/F to overcome this limitation and improve inclusion at each time point. Thirdly, details of MV parameters and airway pressures were not consistently recorded across the cohorts, limiting our ability to further analyze these data. Fourthly, there was limited information available in the electronic medical record detailing the site of TOF monitoring, or timing and duration of prone ventilation. Additionally, we recognize that using spontaneous respiratory rate greater than ventilator set rate in our VSP as the main titration parameter is an over-simplification of the term "ventilator synchrony". However, this was a pragmatic protocol designed to allow for a nurse-driven titration guideline with physician oversight, and we feel that it is an appropriate appellation. Lastly, lack of information on VSP and TOF titration compliance was another important limitation.

5. Conclusion

Without impacting efficacy of gas exchange, a protocol using ventilator synchrony for CIS titration required significantly less drug compared to TOF-based titration and a fixed dosing regimen. Further prospective research is needed to explore the therapeutic benefits of these results.

Author statement

All authors have seen and approved the final version of the manuscript being submitted. JNB contributed to the methodology, investigation, visualization, writing, preparation and revision of the manuscript. RMR contributed to the methodology, validation, formal analysis, data curation, and drafting and revision of the manuscript. BJM, PEL, and MPD contributed to conceptualization, methodology, writing and revising of the manuscript and supervision of the project. LMG contributed to the conceptualization, methodology, investigation, data curation, writing, revision and supervision of the project in addition to ensuring that the descriptions are accurate and agreed by all authors.

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Conflicts of interest

There are no conflicts of interest to disclose for any author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.07.012.

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