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Analgesia-first sedation in critically ill adults: A U.S. pilot, randomized controlled trial

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ABSTRACT

Purpose: To determine the feasibility of conducting a multicenter ICU RCT of AFS compared to either protocol-directed sedation (PDS) or both PDS and daily sedation interruption (DSI) in North America.
Materials and methods: This single-center RCT compared AFS [fentanyl (bolus ± infusions) to reach CPOT ≤2; if RASS ≥1, CPOT ≤2 and additional fentanyl failed to reach RASS goal (−2 to 0), low-dose propofol (up to 6 h) was given] with either PDS or both PDS and DSI daily in adults mechanically ventilated (MV) ≥48 h. Relevant feasibility, safety, and clinical outcomes were defined and evaluated.
Results: 90 of 160 eligible patients were enrolled [AFS = 27; PDS = 28; PDS + DSI = 31]; rate = 3/month. Time from intubation to randomization was 17.5 ± 11.6 h. Study days fully adherent to the study intervention [AFS = 95%; PDS = 99%; PDS + DSI = 96%] and time spent in the first 48 h after randomization without pain (CPOT ≤2) [AFS = 82%; PDS = 78%; PDS + DSI = 77%] and at goal RASS[AFS = 88%; PDS = 83%; PDS + DSI = 95%] were high and similar. Nurse-perceived [median (IQR)] study workload (10-point VAS) was higher with AFS [4(2–6)] than PDS [1(1–3)] or PDS + DSI [2(1–5)]; $p = .002$). Unplanned extubation was rare (AFS = 1; PDS = 0; PDS + DSI = 1). Days [median (IQR)] free of MV in the 28d after intubation [AFS 24(23,26); PDS 24 (20,26); PDS + DSI 24(21,26)] was not different ($p = .62$).
Conclusion: A multicenter RCT evaluating AFS is feasible to conduct in North America.
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1. Introduction

Analgesics and sedatives are routinely administered to mechanically ventilated adults in the intensive care unit (ICU) to optimize comfort and promote safe care [1]. Analgesia-first sedation (AFS) (or analgosedation) promotes the use of analgesics (usually an opioid) rather than a sedative such as propofol or a benzodiazepine [2]. By taking advantage of the analgesic, sedating, and respiratory depressant properties of opioids to optimize pain management and facilitate mechanical ventilation, safety concerns associated with sedatives may be reduced [3].

Multiple, single-center, randomized trials have associated AFS (vs. a traditional sedative-first approach) with a reduction in duration of mechanical ventilation and ICU length of stay and reported no difference in patient self-extubation [4-9]. However, conclusions from these studies are each limited by their enrollment at a single center where the AFS approach was already in use, a frequent and non-protocolized use of non-opioid analgesics, and a control group managed differently between studies [and rarely with either protocol-direction sedation (PDS) or

Abbreviations: ABCDEF, **A**ssess Prevent and Manage Pain, **B**oth Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT), **C**hoice of analgesia and sedation, **D**elirium: assess prevent and manage, **E**arly mobility and Exercise and **F**amily engagement and empowerment; AFS, Analgesia-first sedation; CPOT, Critical Care Pain Observation Tool; DSI, Daily Sedation Interruption; ICDSC, Intensive Care Delirium Screening Checklist; ICU, Intensive Care Unit; IQR, Interquartile Range; IV, Intravenous; PADIS, Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption; PS, Protocolized sedation; RASS, Richmond Agitation Sedation Scale; SBT, Spontaneous breathing trial; SD, Standard deviation; VAS, Visual analog scale.

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daily sedative interruption (DSI)]. Importantly, these trials were all conducted in European ICUs where practices relevant to the efficacy and safety of AFS are different from those in North America [10]. In European ICUs, pre-ICU opioid use is low, remifentanil (an opioid with a far shorter duration of action than fentanyl) use is common, nurse:patient ratios are generally lower, restraint use is rare, respiratory care professionals are generally absent, and mechanical ventilation weaning strategies are different [11,12].

While the use of protocols focused on pain assessment and treatment in North American ICUs have been shown to improve outcomes, none have incorporated an AFS approach [13-16]. AFS practices have been evaluated at two different North American centers but one study focused on AFS use in the Emergency Department [17] and the other compared an AFS approach to propofol [18]. Neither investigation was randomized [17,18]. Given these gaps, the 2018 PADIS guideline provides a conditional rather than a strong recommendation for AFS use in critically ill adults [10].

Pilot studies play a key role in informing the design of large, multicenter, randomized controlled trials, particularly for a relatively complex intervention like AFS not routinely used in North American ICUs [19,20]. We hypothesize AFS, by reducing the amount of non-opioid sedatives administered, will facilitate the liberation from mechanical ventilation faster than patients managed with either PDS or PDS and DSI. We therefore conducted a single-center pilot study to compare AFS with PDS or both PDS and DSI in mechanically ventilated, critically ill adults to establish the feasibility of conducting a future North American AFS multicenter, randomized controlled trial to test our hypothesis.

2. Materials and methods

This three-arm, randomized pilot trial was conducted in a 36-bed medical-surgical ICU at MemorialCare Long Beach Medical Center (LBMC), a 420-bed community teaching hospital in Long Beach, CA. The study was approved by the IRB at LBMH (IRB #2741) and written informed consent was obtained from each subject or their legally authorized representative before randomization. The trial was registered at ClinicalTrials.gov (NCT02219659) before recruitment started.

2.1. Population

Consecutive adults (aged ≥18 years) were screened daily for study participation between 12/2014 and 5/2017 if they were mechanically ventilated (and expected to require it for ≥48 h) and receiving continuous IV midazolam, propofol and/or fentanyl. Exclusion criteria included: cardiac arrest, acute neurologic injury, acute alcohol withdrawal, a condition precluding DSI (e.g., continuous neuromuscular blockade), or use of a continuous IV sedative or opioid ≥24 h. Prior to the study, an AFS approach was rarely used; sedation was titrated by PDS, DSI or a combination of the two. Fentanyl and midazolam use was common, propofol use uncommon, and dexmedetomidine use non-existent.

2.2. Protocol

Patients were randomized to AFS, PDS or PDS + DSI in a 1:1:1 ratio. After study enrollment, all fentanyl, midazolam and propofol orders were stopped. The procedures for the ICU clinical team to manage pain and agitation in the AFS, PDS, and PDS + DSI groups are presented in *E*-Appendix 1–3 and were developed from a review of pertinent ICU trials [2,4-9,18,19,21]. All opioids and sedatives were titrated to maintain patients in a low/no-pain [Critical Care Pain Observation Tool (CPOT) score ≤ 2] and lightly sedated [Richmond Agitation-Sedation Scale (RASS) score − 2 to 0] state [22,23]. Briefly, the AFS group was administered IV fentanyl (boluses ± continuous infusion) to reach a CPOT ≤2. For a RASS ≥1, when the CPOT was ≤2 and additional fentanyl over 30 min failed to reduce it, a propofol infusion was initiated at 5 μg/kg/min and up-titrated by 5 μg/kg/min every 10 min to reach the RASS goal. After a further 6 h, an attempt to wean propofol off was made using additional IV fentanyl as required.

Midazolam (IV bolus ± infusion) was the only sedative used in the PDS and PDS + DSI group to achieve the goal RASS; propofol use was not permitted in either of these groups. Fentanyl (boluses ± infusions) was allowed to treat pain. Dexmedetomidine was not permitted in any of the three study arms. Although the 2013 SCCM PAD guidelines make a weak recommendation to use propofol or dexmedetomidine rather than a benzodiazepine [2], midazolam remained the sedative of choice for mechanically ventilated adults at the study center at the time the study protocol was finalized in early 2014. All patients were managed with a well-established weaning protocol (*E*-Appendix 4). The study intervention was continued until the ICU team deemed continuous IV opioid and/or sedative therapy was no longer warranted, up to 28 days, death in the ICU, or the occurrence of a serious adverse event requiring study removal. For patients requiring re-intubation, the study intervention was resumed.

The randomization sequence was generated using a computerized algorithm with permutated blocks of 15 (i.e., 5 subjects per each group). Randomization was concealed with the use of sealed, opaque, non-re-sealable envelopes numbered 1 through 90. All research personnel, except the research coordinator, were blinded to the study allocation; the ICU clinical team, for obvious reasons, was not.

After randomization, the appropriate algorithm for AFS, PDS, or PDS + DSI was posted at each subject's bedside. The research coordinator provided baseline education to the ICU team, and at the beginning of each shift, to the bedside nurse about the assigned intervention and other pertinent study procedures. Decisions about the use of physical restraints, non-opioid analgesics, oral/enteral opioid analgesics or sedatives, and all antipsychotics were at the discretion of the ICU team. Non-pharmacologic strategies focused on reducing delirium (e.g., reorientation, mobilization, and eye shades/earplugs at night) were in place throughout the study. While components of the ABCDEF bundle had been implemented prior to the study, the entire bundle itself has yet to be formally implemented [23].

2.3. Measurements

All subjects were evaluated by the bedside nurse for pain (CPOT q4h), level of sedation (RASS q4h), and delirium [Intensive Care Delirium Screening Checklist (ICDSC) q12h] [22,23,25]. Days with coma (RASS ≤ −3) and delirium (ICDSC ≥4) were recorded. Other variables collected during the trial included age, service, severity of illness, pertinent medical history and total daily use of fentanyl, midazolam and propofol. A validated 10-cm VAS [21] was used to evaluate nurse (both day and night shift) and respiratory care practitioner (RCP) (daytime only) perceived workload throughout the ICU stay. Daily clinician compliance (i.e., fully compliant/not fully compliant) to the assigned intervention was recorded. The results of daily SBTs, episodes of extubation failure (i.e., reintubation within 48 h of first extubation), and both ICU and hospital mortality were also collected.

Study feasibility, the primary objective of our trial, was evaluated using nine different outcomes. The success rate for each outcome that denoted feasibility was established a priori through author consensus (Table 1). Unintentional extubation requiring reintubation, patient-directed device removal, and serious adverse events deemed to be related to study participation were the key safety outcomes. The clinical outcomes collected during the study reflect those that would be likely collected in a larger, multicenter, randomized trial. Days spent without mechanical ventilation assistance in the 28 days after randomization was the primary clinical outcome of interest given it might serve as a primary outcome in a future AFS multicenter trial. Data from our pilot study could help inform sample size calculations for such a trial. Secondary outcomes included the SBT pass rate, duration of weaning, time-to-extubation (if extubated within 28 days), use of neuroimaging, physical

Table 1
Feasibility outcomes and a priori-defined benchmarks.

Feasibility outcome	Feasibility benchmark
1. Patients per month meeting all study criteria	10
2. Patients per month meeting all study criteria where physician and legally authorized representative consent to participation	4
3. Time from intubation to study randomization	24 h
4. Baseline patient age, severity of illness (APACHE II score), and admitting service (medicine vs. surgery) between the AFS, PS, and PS + DSI groups	No difference
5. Time AFS group spent free of pain (CPOT ≤2) in the 48 h after randomization	≥ 80%
6. Time AFS group spent at the target sedation goal (RASS = −2 to 0) in the first 48 h after randomization	≥ 80%
7. Proportion of AFS patients requiring a propofol infusion	30%
8. Clinician adherence to the AFS study intervention (% of study days where the complete AFS intervention should have been administered)	≥ 80%
9. Nurse- and respiratory care professional-perceived workload for the AFS (vs. either the PS or PS + DSI) study intervention (based on a VAS − 10 cm scale)	≤ 2 cm higher

APACHE = Acute Physiology and Chronic Health Evaluation; AFS = Analgesia-First Sedation; PS = Protocol-Directed Sedation; DSI = Daily Sedation Interruption; CPOT = Critical Care Pain Observation Tool; RASS = Richmond Agitation Sedation Scale; VAS = Visual Analog Scale.

restraints, vasopressor, or renal replacement therapy, hospital days without coma and/or delirium, and both ICU and hospital length of stay and mortality.

2.4. Statistical analysis

A convenience sample size of 90 patients was chosen given the pilot nature of the study. While a large, multicenter randomized will likely be required to test our primary hypothesis that patients managed with AFS will be liberated faster from mechanical ventilation than patients receiving non-opioid sedative and managed with PDS or PDS and DSI, and rigorously evaluate its safety, we felt that 90 patients (~30 in the AFS arm) would allow us to adequately evaluate each of our feasibility outcomes and provide guidance for sample size calculations for a future multicenter trial.

All feasibility, safety and clinical outcomes were collected using an intention-to-treat principle. Continuous variables are presented as mean and standard deviation (SD), or median and interquartile range (IQR). Discrete variables are presented as frequencies and percentages. Student's *t*-test (adjusted for unequal variances when necessary) or Mann-Whitney *U* test were used for continuous data where appropriate. Categorical data were evaluated by using the Pearson's chi-squared test or Fisher's exact test where appropriate. ANOVA testing was used for comparing means between the three groups. Post-hoc, Least Significant Difference (LSD) testing was used given the multiple pairwise comparisons between the three groups. The Kaplan-Meier method was used to estimate and plot the distributions of time to first successful SBT, time to extubation, and time to death in the first 28 days after randomization. Patients were censored at death (if they died before extubation) or transfer (if they were transferred to another institution before 28 days). The two-tailed statistical significance was defined as a $p < .05$. SAS version 9.2 (Cary, NC) was used for all statistical analysis.

3. Results

3.1. Feasibility outcomes

Among 924 consecutive patients screened for study participation, 764 met inclusion criteria and 506 had one or more exclusion criteria (Fig. 1). Among the 258 patients meeting all study criteria (average = 8.6/month), 90 (35%) were enrolled (average = 3/month). The most common reason for non-enrollment was lack of a legally authorized representative to provide consent [102 (61%)]; attending physician refusal for enrollment was uncommon [32 (20%)]. Rate of enrollment

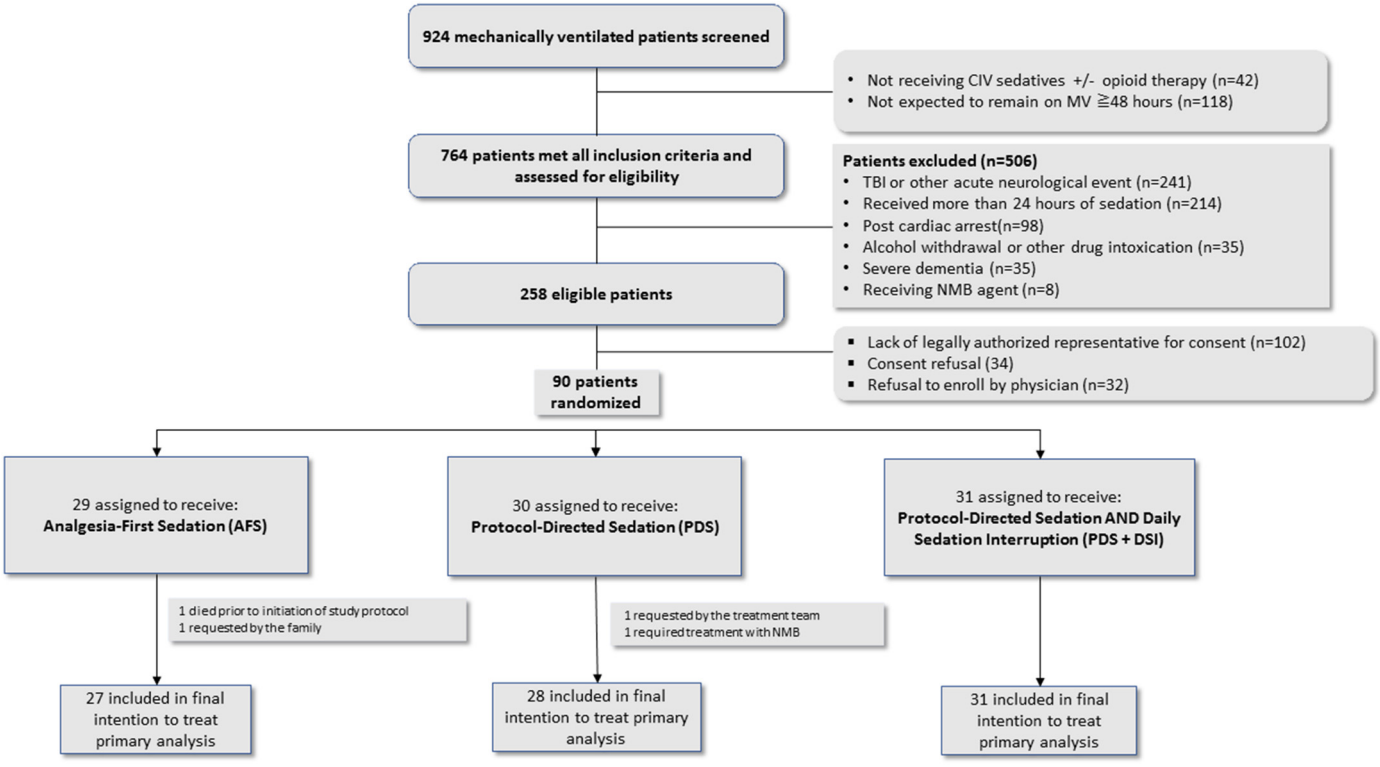

Fig. 1. Patient screening, recruitment, and randomization.

was reasonably close to the prespecified benchmarks. Time from intubation to study randomization was surprisingly fast (17.5 ± 11.6 h).

Patient characteristics were similar between the three groups (Table 2) except a medical (vs. a surgical) diagnosis was more common in the AFS (92.6%) and PDS (89.3%) groups than the PDS + DI group (64.5%; $p = .02$). Overall, 87% of patients were receiving midazolam infusions and 90% were receiving fentanyl infusions at the time of randomization. Time spent in the 48-h after randomization without pain (CPOT ≤2) (AFS 82%; PDS 78%; PDS + DIS 77%; $p = .88$) and at goal RASS (−2 to 0) (AFS 89%; PDS 88%; PDS + DIS 95%; $p = .93$) was high and did not differ between the three groups.

Adherence to the study intervention (across all study days) was high, exceeded the feasibility benchmark, and did not differ between the three groups (AFS 95%; PDS 99%; PDS + DSI 96%; $p = .24$). Data surrounding fentanyl, midazolam, and propofol use are summarized in Table 3. One of the AFS patients was accidently started on a midazolam infusion at night; the 7-h infusion (a total of 11 mg was administered) was stopped in the morning. Only 5 (19%) AFS group patients required propofol, a lower proportion than predicted. Only one of these patients could not be weaned off propofol within 6 h after reaching the goal RASS. During the dayshift, nurse-reported workload was significantly lower in the PDS group (vs. either the AFS or the PDS + DSI groups); at night PDS and PS + DSI were each associated with significantly lower reported workload than the AFS. Respiratory care practitioners reported higher work load with AFS ($p = .003$) (Table 4). (All workload comparisons are presented in an *E*-Table.) While perceived AFS workload exceeded the feasibility benchmark for nurses, it did not for RCPs.

3.2. Safety outcomes

None of the patients experienced a serious adverse event related to their participation in the study. Incidence of unintentional extubation was low (2.2%; 2/90) and similar between the three groups (AFS 3.7%; PDS 0%; PDS + DSI 3.2%; $p = .76$]. Both cases of self-extubation required reintubation within 48 h. No study patient removed a device (other than their endotracheal tube). Two AFS patients were withdrawn from the study after randomization [one died shortly after randomization and before the AFS intervention could be initiated; the other was withdrawn at family request because of worsening critical illness and a lack of interest in continuing research] (Fig. 1).

3.3. Clinical outcomes

The [median (IQR)] days free of mechanical ventilation in the 28 days after randomization was not different among the three groups [AFS 24.0 (23,26); PDS 23.5 (20,26); PDS + DI 24 (21,26) ($p = .62$)] (Table 5). Neither the average weaning time and duration of mechanical ventilation nor the time to the first successful SBT was different (e-

Table 2
Baseline characteristics.

Characteristic	Analgesia-first sedation $N = 27$	Protocol-directed sedation $N = 28$	Protocol-directed sedation and daily sedation interruption $N = 31$
Age	65.6 ± 15.8	64.1 ± 18.4	66.0 ± 16.4
Medical (vs. Surgical) admission (%)[b]	93	89	65
APACHE II[a, c]	26 (20, 32)	27 (19, 30)	23 (19, 27)
Male, n (%)	62	39	64
Mechanically ventilated, n (%)	100	100	100
BMI	31.5 ± 9.9	31.2 ± 10.1	30.3 ± 10.3
SOFA[a, d]	10 (6, 12)	11 (8, 12)	8 (5, 10)
Chronic conditions and substance use prior to ICU admission, n (%)[f]			
Respiratory	7 (26)	7 (25)	4 (13)
Neurologic	4 (15)	6 (21)	9 (29)
Renal dysfunction	3 (11)	7 (25)	1 (3)
Liver	3 (11)	2 (7)	0 (0)
Psychiatric	4 (15)	8 (29)	3 (10)
Non-prescribed psychoactive drug use	4 (15)	1 (4)	3 (10)
Nicotine use	4 (15)	4 (14)	3 (10)
Alcohol use	5 (19)	7 (25)	7 (22)
Primary ICU admission diagnosis[e], n (%)			
Respiratory	11 (41)	15 (54)	14 (45)
Sepsis	8 (30)	8 (29)	4 (13)
Gastrointestinal	4 (15)	1 (4)	2 (6)
Post-operative	2 (7)	1 (4)	4 (13)
Other	2 (8)	3 (11)	7 (23)
Fentanyl infusion before randomization, n (%)	22 (81)	27 (96)	28 (90)
Midazolam infusion before randomization, n (%)	25 (93)	26 (93)	27 (87)
RASS score at time of randomization, n (%)			
≥ 1	3 (11)	0 (0)	3 (10)
0 or − 1	7 (26)	7 (25)	14 (45)
-2 to −3	16 (59)	15 (54)	14 (45)
-4 or − 5	1 (4)	6 (21)	0 (0.0)

Plus-minus values are mean ± standard deviation.
Abbreviations: RASS: Richmond Agitation and Sedation Scale; APACHE II: Acute Physiology and Chronic Health Evaluation; BMI: body mass index (calculated as weight in kilograms divided by the square of the height in meters); ICU: intensive care unit; MV: mechanical ventilation; IQR: interquartile range; SOFA: Sequential Organ Failure Assessment.
[a] Median (Interquartile range).
[b] Surgical refers to direct admissions from an operating room or postoperative recovery area.
[c] Scores on the APACHE II score range from 0 to 71, with higher scores indicating greater disease severity.
[d] The total SOFA score ranges from 0 to 20 points, with higher scores indicating more severe dysfunction.
[e] Diagnoses in this category are mutually exclusive. The most frequent diagnoses are listed, and the remainders are categorized as "other."
[f] Pre-ICU conditions are listed in descending frequency: Respiratory condition: chronic obstructive pulmonary disease, emphysema, asthma, recurrent infections; Neurologic condition defined as stroke, seizure disorder, dementia, neuromuscular disease, Parkinson's disease; Renal dysfunction defined as chronic renal failure with creatinine level >2 mg/dL 1or chronic dialysis; Psychiatric condition includes depression, bipolar disorder, schizophrenia, anxiety disorder, or other psychiatric condition; Liver disease defined as Child Pugh Grade C or known esophageal varices; Non-prescribed psychoactive drug use includes opioids, cocaine, amphetamines, hallucinogens; Nicotine use refers to daily use; Alcohol use refers to an average chronic intake of ≥2 drinks/day.

Table 3
Fentanyl, midazolam and propofol use.

Medication	Analgesia-first sedation N = 27	Protocol-directed sedation N = 28	Protocol-directed sedation and daily sedation interruption *N* = 31
Fentanyl			
Use of infusion, n (%)	26 (96)[a]	27 (96)	29 (94)
Days of infusion	3 (1, 8)	2 (1, 7)	2 (1, 6)
Daily dose administered (mcg/d)	500 (300, 1300)	460 (189, 945)	410 (160, 876)
Midazolam			
Use of infusion, n (%)	1 (4)[b]	28 (100)	31 (100)
Days of infusion	0[b]	3.5 (1, 6)	1 (1, 5)
Daily dose administered (mg/d)	0[b]	30 ± 39	32 ± 57
Propofol			
Use of infusion, n (%)	5 (19)[c]	0 (0)	0 (0)
Days of infusion	0.3 (0.3, 0.4)[c]	0	0
Infusion rate (mcg/kg/min)	8 ± 23[c]	0	0

Days of infusion [presented as a median (IRQ)] includes all ICU days where an infusion was administered. Daily dose administered includes all fentanyl (and midazolam) that was administered by either IV bolus or continuously infused. Only ICU days where the medication was administrated is included in the average. Data is presented as a median (IQR) for fentanyl and a mean ± SD for midazolam. The propofol infusion rate (presented as a mean ± SD) represents the average infusion rate/patient for only those hours that propofol was administered.

[a] One AFS patient was managed with only intermittent IV fentanyl.

[b] One AFS patient was accidently started on a midazolam infusion at 3 am by the clinical team. The infusion was stopped at 7:30 am after 9 mg of midazolam was administered.

[c] Among the 5 AFS patients who ever required a propofol infusion, 4 required just one propofol infusion and were weaned off it within 6 h after reaching the goal RASS. One patient required a propofol infusion on two different days. On one of these days, propofol was administered for a total of 11 h.

Fig. 1). Days spent in the ICU ($p = .96$) and duration of hospital stay ($p = .88$) were not different. Use of neurological imaging, application of physical restraints, incidence of tracheostomy, and mortality in the ICU and at 28-day were also not different between the three groups. Over 28 days, the adjusted time to death remained similar between the three groups (e-Fig. 2). Days spent free of both delirium and coma were not different.

4. Discussion

A multicenter study comparing AFS to other sedation strategies (PDS + DSI and PDS) in North America appears feasible to conduct. Screening, consenting, and randomization after intubation is possible in less than the 24 h we predicted. While our enrollment rate of 3 patients per month was less than the 4/month feasibility benchmark it was still strong. Intensivists at the study center were supportive of study enrollment suggesting that clinical equipoise towards AFS exists. Adherence to the AFS intervention was very high indicating ICU clinicians, and most notably, the bedside nurse was able to capably manage patients AFS after receiving only basic education. The lower than expected use of propofol, in the context of a higher than predicted proportion of patients reaching protocolized pain and sedation goals and a very low incidence of severe agitation-related events, suggests that the ICU clinicians were able to effectively use IV fentanyl, as it was protocolized in the AFS intervention, to safely manage their patients.

The three groups were well-matched except for an imbalance in the number of medical patients. A future, multicenter trial should be designed to account for a potential allocation differences such as this given that response to AFS might be different between medical and surgical populations. While nurses and respiratory care practitioners perceived AFS-related workload to be higher than with either PDS or PS + DSI, adherence to AFS intervention was still very high. Moreover, the fact that target RASS and CPOT goals were each attained >80% of the time in the AFS group suggests that the bedside nurse was able to overcome the additional perceived workload of AFS when delivering care.

Importantly, AFS, as it was administered in trial and in only 27 patients, appears to be safe to further investigate in a future, multicenter, randomized trial. The rate of patient self-extubation was low and similar between the AFS and two non-AFS arms. No AFS patient removed a device or line or had to be removed from the study because of a safety concern. While not evaluated in our trial, any potential deleterious effect of fentanyl on respiratory drive appears to be low given that time to first successful SBT, weaning time, and time-to-extubation were not different between the AFS and two sedation groups. Other opioid-associated safety concerns (e.g. constipation), while not evaluated in our pilot investigation, will be important to evaluate in future trials.

Management of pain in the critical care setting is the first component of the ABCDEF bundle (i.e., A = assess, prevent, and manage pain), a quality improvement bundle shown to improve both ICU and post-ICU outcomes [24]. Prior data supports analgosedation strategies as a method to optimize pain management [2,18]. While PDS and PDS + DSI, when accompanied by protocolized SBT use are accepted strategies for optimizing patient comfort and facilitating extubation [18,21], all SBT and weaning-related outcomes were similar between the three groups. The effects of AFS on SBT screening requires further investigation.

Our study has potential limitations. Important feasibility-related outcomes may not have been evaluated. The high use of midazolam in the PDS and PDS + DSI arms is not reflective of sedative practices at many North American centers nor guideline recommendations [2,10]. While bedside clinicians were not blinded, the logistics of blinding clinicians to an AFS intervention would be complex. The high proportion of patients in the PDS and PDS + DSI groups receiving fentanyl infusions

Table 4
Comparison of Nurse and Respiratory Care Practitioner Perceived Workload.

Clinician and shift	Analgesia-first sedation *N* = 27	Protocol-directed sedation *N* = 28	Protocol-directed sedation and daily sedation interruption *N* = 31	*P-value*
Nurse daytime workload[A]	4 (2, 6)	1 (1, 3.5)	2 (1, 5)	0.004*
Nurse nighttime workload[A]	5 (2, 7)	1 (1, 2.5)	2 (1, 4)	0.0003*
Respiratory care practitioner daytime workload[A]	6 (5, 7)	5 (4, 6)	5 (4, 5)	0.003*

Reported in cm using a validated, self-administered, 10 cm Visual Analog Scale[18].

* *P*-value was considered significant for all comparisons when independent sample tests were used to compare distribution of variables between the three groups. All results presented as median (IQR).

Table 5
Comparison of clinical outcomes.

Clinical outcome	Analgesia-first sedation N = 27	Protocol-directed sedation N = 28	Protocol-directed sedation and daily sedation interruption N = 31	*P-value*
Days free of mechanical ventilation in the 28 days after randomization	24 (23, 26)	23.5 (20, 26)	24 (21, 26)	0.62
Days to first successful SBT	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.81
Days from first successful SBT to extubation	2 (1, 4)	2 (1, 6)	2 (1, 5)	0.81
Duration of first intubation (d)	4 (2, 5)	5 (2, 8)	4 (2, 7)	0.62
SBT pass rate, n (%)	22 (82)	23 (85)	29 (94)	0.36
Reintubation rate, n (%)	5 (19)	3 (11)	8 (26)	0.33
RASS at time of first successful SBT				
Nurse-reported	−1 (−1, 0)	-1 (−2, 0)	0 (−1.5, 0)	0.64
Respiratory care-reported	0 (−1, 0)	0 (−1, 0)	-1 (−2, 0)	0.09
Neurologic imaging, n (%)	13 (48)	14 (50)	12 (39)	0.64
Physical restraint use, n (%)	27 (100)	23 (85)	30 (97)	0.07
Neuromuscular blocker use, n (%)	0 (0)	1 (3.57)	0 (0)	0.64
Renal replacement therapy, n (%)	1 (4)	5 (18)	3 (10)	0.25
Vasopressor(s) use, n (%)	16 (59)	15 (54)	12 (39)	0.26
Duration of ICU stay (d)	7 (4, 14)	7 (3, 15)	8 (3, 15)	0.96
Duration of hospital stay (d)	13 (7, 22)	11 (8, 21)	14 (6, 19)	0.88
Days without coma or delirium during hospitalization	11 (6, 19)	10 (6, 22)	11 (5,18)	0.86
ICU mortality, n (%)	7 (26)	5 (18)	3 (10)	0.27
28-day mortality, n (%)	8 (30)	6 (21)	4 (13)	0.29

Data is presented as a median (IQR) unless indicated otherwise noted.
Abbreviations: d, day; RASS: Richmond Agitation and Sedation Scale; SBT: Spontaneous breathing trial; ICU, intensive care unit; IQR, interquartile range.

may have obscured outcome differences with the AFS group. Potential safety concerns with fentanyl administration were not well evaluated although the incidence of these effects have not been observed to be higher in other single-center AFS studies [9,15,26].

While our study establishes the feasibility of conducting a large, multicenter AFS study in North America, further consideration should be given as to whether days-free of mechanical ventilation in the 28 days after randomization is the ideal primary outcome for such an investigation. It remains unclear how important this outcome is to mechanically ventilated, critically ill adults. Moreover, this outcome was nearly identical between the AFS and the two comparator groups in our pilot trial suggesting that AFS may not influence liberation from mechanical ventilation when patients are managed to a light sedation goal and with an established SBT protocol. With PDS and PDS and DSI are both recommended as strategies to maintain patient wakefulness in the ICU [10], a future multicenter AFS study may not need to separately control for the use of each strategy. Wakefulness strategies should be applied to both the AFS and control arms given the high use of fentanyl infusions in the AFS arm of our pilot study. Finally, a future multicenter RCT where benzodiazepine exposure is minimized in the control arm, may result in clinical outcomes that are quite different from the trends observed in our pilot investigation.

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Author contributions

M.T. takes full responsibility for the content of the manuscript, including the data and analysis. M. T., H.M.N, H·P, and J.W.D., had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. M. T., H.M.N, H·P, S.M., S.K.E., F.Y., A. B., G.F., R. S., A. S., J.L. and J.W.D contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Other contributions

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