Fentanyl versus Hydromorphone as First Line Strategy in Patients on Mechanical Ventilation, a pilot pragmatic cluster randomized superiority clinical trial: the FenHydro Trial

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0. Summary of Changes

October 30th, 2025 (v1.1)

0. Added a retrospective data collection to 30 patients admitted to the ICU prior to trial initiation to compare the accuracy of automated versus manual data extraction (14. Data Collection)

February 2nd, 2026 (v1.2)

1. Added an anonymous survey to gather feedback from health care providers (nurses, advanced practice providers (APPs) and attendings involved in the care of patients during this trial on their experience with fentanyl versus hydromorphone infusions in mechanically ventilated patients. This will be presented as a separate research and it's protocol will be presented elsewhere.

April 6th, 2026 (v1.30)

1. Added to the protocol our institutional approach to analgosedation and recommended doses of each sedative
2. Added a summary of the current interventions to improve adherence of providers to our study
3. Explained in more details the rationale for sample size calculation
4. Clarified if alternate and crossover opioids will be included in the analysis
5. Added a sensitivity analysis for different MME conversion formulas

April 10th, 2026 (v1.31)

1. Harmonized the data analysis by planning to use GLMM for both primary and secondary outcomes to account for random effects

April 14th, 2026 (v1.32)

1. Extended the duration of the trial by 1 week to achieve similar sample sizes between both groups (still within the pre-planned 6 months)

April 22nd, 2026 (v1.33)

1. Explicitly included in the data analysis the adjustment of primary and secondary outcomes for the intraclass correlation coefficients (within-cluster within-period correlation and within-cluster between-period correlation)
2. Corrected the use of GEE instead of GLMM for categorical outcomes.

1. Study Summary

This protocol was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. Any amendment to the protocol after the study is initiated will be registered.

1.11 Title: Fentanyl versus Hydromorphone as First Line Strategy in Patients on Mechanical Ventilation, a pilot pragmatic cluster randomized superiority clinical trial (FenHydro Trial)

1.12 Study Purpose:

The final purpose of this study is to evaluate whether analgosedation of mechanically ventilated patients with fentanyl or hydromorphone infusion as first line strategy will lead to a difference in:

1. daily MME required during mechanical ventilation
2. all-cause mortality at 28 days
3. days alive free of the ICU at 28 days
4. days alive and free of mechanical ventilation at 28 days
5. days alive and free of vasopressors at 28 days
6. ventilatory mechanics during mechanical ventilation
7. daily morphine-milligram equivalent required during the first 28 days
8. incidence of opioid withdrawal
9. daily average number of bowel movements through ICU stay
10. percentage of time without coma and delirium during the ICU stay
11. days alive and free of restraints at 28 days
12. need for tracheostomy during hospital stay

As a pilot study, the trial purpose is also to evaluate:

1. The recruitment rate of patients
2. The contamination rate between the interventions, adherence and compliance to the study protocol
3. Intracluster correlation coefficient
4. Challenges with data collection and follow-up in the setting of a pragmatic trial
5. Other logistics of a pragmatic cluster randomized trial in the ICU

1.13 Overall study design:

We plan to perform a prospective, pragmatic, single center, multiple ICU, cluster randomized, cross-over, open label trial comparing fentanyl to hydromorphone as analgesia in mechanically ventilated patients

1.14 Research question:

Hypothesis: We hypothesize that there is a difference in total morphine-milligram equivalent (MME) between patients receiving fentanyl and those receiving hydromorphone

1.21 Inclusion Criteria

Admitted to a either MICU A, B, C or FICU at Beth Israel Deaconess Medical Center (Boston, MA, USA) requiring mechanical ventilation, and opioid infusion for analgosedation

1.22 Exclusion Criteria

Age < 18 years old, medical team discretion that a specific opioid would be more appropriate for the patient, do not intubate orders, comfort measures or and true immunologic allergy to fentanyl or hydromorphone

1.31 Interventions

Intervention 1: Fentanyl continuous infusion will be the first choice as opioid analgesia for mechanically ventilated patients in the ICU randomized to this intervention group.

Intervention 2: Hydromorphone continuous infusion will be the first choice as opioid analgesia for mechanically ventilated patients in the ICU randomized to this intervention group.

Following 3 months of the intervention, the cluster will be changed to receive the second protocol.

Decision regarding titration, initial dosing, additional boluses of the intervention drug will be at the discretion of the healthcare provider. The study will not impact other sedative medications, additional analgesic medication, weaning of sedation, mechanical ventilation liberation and other ICU management. These will follow-up current guidelines and our ICU policies.

1.41 Sample Size Calculation

There is no trial comparing fentanyl to hydromorphone for analgosedation in critically ill mechanically ventilated patients. One randomized trial performed in Oceania compared morphine and fentanyl. They found that the mean total MME for the morphine group was 747 ± 1131 mg and for the fentanyl group was 1274 ± 1928 mg. Considering a daily MME dose while on mechanical ventilation in the fentanyl group of 270 ± 250 mg and 450 ± 500 mg in the hydromorphone group based on the data from two months of our MICU A, B, C and FICU, group sample sizes of 137 patients would achieve 80% power to detect a difference of 180 MME at a significance level (alpha) of 0.05 using a two sided Mann-Whitney Test. These results are based on 500 Monte Carlo samples from the null distributions: WeibullMS (450 500) and WeibullMS (450 500), and the alternative distributions: WeibullMS (450 500) and WeibullMS (270 250).

Considering eventual losses to follow-up and contamination it will be required a sample size in each group of 150 patients.

Therefore, considering recruitment of 50 patients per month, it will be required 6 months to obtain the sample size.

1.51 Outcomes and Follow-up

Primary Outcome: difference in daily MME during mechanical ventilation

Secondary Outcomes:

- All-cause mortality on day 28
- Days alive and ICU free days at 28 days
- Days alive and free of vasopressors at 28 days
- Days alive and free of ventilator at 28 days
- Requirement of adjunctive analgesia or sedation medications
- Difference in average daily dose of MME required during the first 28 days
- Percentage of days with delirium in the ICU
- Need for tracheostomy
- Incidence of opioid withdrawal
- Daily Average number of Bowel Movements through ICU stay
- Respiratory system mechanics and ventilator synchrony
- Adverse effects

1.61 Follow-up duration: 28 days after enrollment or hospital discharge, whatever comes first

1.71 Planned date of first enrollment: November 3rd, 2025

1.81 IRB approval: The protocol was approved by the institutional review board of the center (IRB 2005P000456), and written informed consent was waived.

1.82 Data Sharing Statement: deidentified data, data dictionary and analytical code will be made available to researchers whose proposed use of the data has been approved by the lead trial investigators for any purpose that facilitates advancement of the field. It will require investigator support and IRB approval, after approval of a proposal, with a signed data access agreement

1.91 Funding: None. This is an investigator initiated study with no trial sponsor and funder

2. Trial Design

This is a cluster randomized, pragmatic, pilot and feasibility superiority clinical trial to compare two standard-of-care analgosedation medications, fentanyl and hydromorphone, in mechanically ventilated patients in the ICU.

3. Background

Patients with respiratory failure who require mechanical ventilation are not only at risk of death, but also of complications of prolonged ICU stay [1,2]. Patients may have significant functional decline, impact in quality of life, develop psychiatric disorders and at long-term can lead to significant cost to society [3-5]. Although sedation and analgesia are considered only supportive therapy, several studies have shown that in patients on mechanical ventilation, different approaches can have significant impact on patient centered outcomes [6-8]. However, to date,

randomized clinical trials on critically ill patients have mostly evaluated the sedative agent but not the analgesic agent [9-11]. Although morphine and its derivates are the most common used opioid analgesic agents in the critical care setting [12], only some prospective study compared them head-to-head (ramifentanyl versus morphine and fentanyl versus morphine) [13,14]. Current guidelines recommend choosing the analgesic agent based on pharmacokinectics, physician experience and side-effects profile [15].

3.2 Equipoise Between Approaches, Rationale and Significance for the Study

3.21 Equipoise between approaches

Fentanyl is a synthetic derivate of morphine that is 100 times more potent than morphine, has a great lipid solubility leading to fast onset (one to two minutes), has a short half-life (up to three hours) and limited histamine release [16,17]. It is metabolized by the liver and its excretion is not affected by the kidneys [18]. Those characteristics allow fentanyl to be versatile and be used in many different scenarios in the ICU [15]. Despite those advantages, concerns have been raised regarding adipose tissue accumulation, tachyphylaxis, CYP3A4 interaction and chest wall rigidity, particularly when on high doses [16,19,20].

Hydromorphone is an alternative analgesic agent. It is a semisynthetic morphine derivate that can be five to ten times more potent than morphine [21]. It also has a fast onset (up to 10 minutes), a short half-life (up to three hours) and is less renally excreted than morphine [21]. Some concerns have been raised regarding the accumulation of hydromorphone metabolites including hydromorphone-3-glucuronide, which can lead to neuroexcitatory effects and delirium [22,23]. A few retrospective studies compared fentanyl and hydromorphone in the critical care setting [24,25,26]. Due to the retrospective nature, small size of the studies and several imbalances in the groups, no significant conclusion can be drawn regarding the benefits and risks of fentanyl versus hydromorphone [24,25]. However, the largest and most recent retrospective

study, showed no difference in 28-day mechanical ventilation free days and death during mechanical ventilation [26].

Opioids currently used for analgosedation in mechanically ventilated ICU patients include morphine, fentanyl and hydromorphone. Currently, at BIDMC, fentanyl and hydromorphone represent standard-of-care for providing analgosedation and both are considered by healthcare providers as similar or equal. The selection of a specific agent as standard-of-care is determined by primary ICU team preference and experience. At BIDMC, based on our data, fentanyl is the most commonly used option, due to familiarity. However, the practice varies from institution to institution with hydromorphone is considered as first choice. Although provider experience and unit policy are usually the most common reason to choose one over the other, some clinical characteristics may influence the decision. As mentioned, both medications have fast onset of action, and similar half-lives. Although small differences may affect the decision of one over the other, dosage reduction and close monitoring are used rather than switching to an alternative in most cases [26]. Whether or not either of these agents afford additional meaningful clinical benefits, advantages or contribute to meaningful clinical outcomes has not been fully established in available literature and represents the basis for performing this clinical pilot study. Since the study will not limit the ability of the provider to choose which medication is used for their patient or cross over medications in any situation, the randomization of the unit to a specific opioid agent as the recommended first choice will not add any additional risk to the patients.

We propose to study the use of fentanyl and hydromorphone in the critically ill population on mechanical ventilation due to the paucity of data comparing both medications head-to-head and their widespread use.

3.21 Previous studies comparing Fentanyl versus Hydromorphone

To our knowledge, only three studies [24,25, 26] have compared the use of fentanyl versus hydromorphone in the ICU setting.

Choi et al. performed a single center retrospective study comparing both medications titrated to CPOT [24]. Patients on mechanical ventilation for more than 24 hours from different ICUs (medical, surgical and cardiac) were included. They included 177 patients, 103 in the fentanyl group and 74 in the hydromorphone group. Group imbalances included a higher proportion of patients on neuromuscular blockade on the hydromorphone group (25.68% versus 10.68%), higher levels of sedation in the hydromorphone group and higher use of dexmedetomidine in the fentanyl group. Despite the imbalances, the ICU length of stay was non-statistically significant (seven days, IQR 5 - 11 in the hydromorphone group versus eight days, IQR 4 - 15 in the fentanyl group, $p = 0.11$). The median time on mechanical ventilation was 146.47 hours (IQR 64.55 - 279.69) in the fentanyl group versus 122.33 hours (IQR 70.27 - 204.98) in the hydromorphone group, $p = 0.31$. The study found that the CPOT was different between the two groups (two in the hydromorphone group versus zero in the fentanyl, $p < 0.001$). Also, the need for restraints was statistically higher in the hydromorphone group.

Martin et al. performed a single center retrospective study comparing our intervention medications on patients requiring veno-venous or veno-arterial extracorporeal membrane oxygenation (ECMO) [25]. A total of 52 patients were included in the analysis. In their study, patients on fentanyl were more commonly in veno-venous ECMO (28.1% versus 20%). They also had more prolonged time on ECMO (95.8 hours versus 66 hours) and on mechanical ventilation (seven versus five). They found that subjects receiving hydromorphone had less MME requirement than those on fentanyl (168 mg, IQR 80–281 versus 325 mg, IQR 270–449, p-value <0.01). They also found that patients on hydromorphone had less daily utilization of opioids (94 mg versus 172 mg). This could be explained by the fact that more patients on fentanyl were on veno-venous ECMO, which in their study required more MME than veno-arterial ECMO. Also, it is unclear if this would apply to our study, since it is known that ECMO circuits can sequester medications, particularly fentanyl [27,28].

Finally, one recent study performed at Lahey clinic showed higher dose of opioids used with fentanyl, however with no difference in mechanical ventilation duration (22, 0-25 days in the fentanyl group versus 21, 0-25 days in the hydromorphone group, p = 0.356) [26]. The median days alive and free of mechanical ventilation were also similar among the two groups, with a median of 24 (21-26) days in the fentanyl group and a median of 24 (20.75-26) days in the hydromorphone group (p = 0.751). The cumulative dose of opioids in fentanyl equivalent was higher in the fentanyl group with 4241 (1817-8146) mcg and 2448 (1012-4926) mcg in the hydromorphone group (p < 0.001).

4. Inclusion Criteria

- Admitted to either MICU A, B, C or FICU at Beth Israel Deaconess Medical Center, requiring mechanical ventilation, and opioid infusion for analgosedation

5. Exclusion Criteria

- Age < 18 years old
- Contraindication to fentanyl or hydromorphone (prior true immunological reaction or at medical team discretion)
- Do not intubate orders
- Comfort measures only

6. Study Sites

Participating ICUs included at Beth Israel Deaconess Medical Center

- MICU A and B (Rosenberg 6) - 13 beds
- MICU C (Rosenberg 6) - 8 beds
- FICU (Finard 4) - 14 beds

Both MICU A/B and C are medical ICUs on the same floor of the Rosenberg building (West Campus) but physically separated and run by different teams with no overlap. Physicians, nurses and respiratory therapists do not manage patients in both ICUs during the same shift, except in rare circumstances. FICU is the Finard ICU, a 14 ICU bed with medical, oncological and surgical patients located in other building (East Campus).

Medical teams in the MICU A and B are composed of Critical Care attending, internal/emergency medicine residents and interns, physician assistants or nurse practitioners. MICU A has an average annual admission average of patients requiring mechanical ventilation of 80-100 patients while MICU B has an average annual admission rate of patients requiring mechanical ventilation of 210-250.

Medical teams in the MICU C are composed of a Critical Care attending, a Pulmonary and Critical Care Fellow and internal medicine residents. MICU C has an average annual admission rate of patients requiring mechanical ventilation of 170-200.

The Finard ICU teams are components of a Critical Care attending, a Critical Care Fellow and internal medicine residents. FICU has an average annual admission rate of patients requiring mechanical ventilation of 220-270

7. Study Population

All patients admitted to MICU A, B, C or FICU requiring mechanical ventilation at Beth Israel Deaconess Medical Center during the study period will be enrolled unless they meet any of the exclusion criteria.

We will also assess health care providers' perceptions of continuous fentanyl versus hydromorphone infusions in mechanically ventilated patients by surveying all ICU nurses, APPs and attendings who participated in the care of the patients during the study period.

8. Enrollment

Since this is a cluster randomized trial, all patients requiring mechanical ventilation admitted to the trial ICUs will be included in the study if no exclusion criteria.

Based on previous years, our MICU A, B, C and FICU patients requiring mechanical ventilation comprise an average of 700 to 820 in a year. Therefore, based on our sample size calculation we will need 6 months for a total of 300 patients to be enrolled in the study.

9. Consent

The study satisfies all 4 or 5 conditions required by the U.S. Department of Health and Human Services Office for Human Research Protections:

- The study does not involve additional risk to subjects
- The research could not be carried out practicably without the waiver
- The waiver will not adversely affect the rights and welfare of the subjects
- Where appropriate, the subjects will be provided with additional information about their participation

- The research will not involve identifiable private information or identifiable biospecimens

Fentanyl and hydromorphone intravenous infusions are the most common opioids prescribed for analgesia in mechanically ventilated patients at Beth Israel Deaconess Medical Center. Currently, the choice between them is solely based on provider preference since there is no randomized clinical trial or evidence-based guidelines to recommend one over the other. Expert recommendations [15] defer the choice of the analgesic opioid to the bedside provider based on pharmacokinetics and pharmacodynamics of the drug. We believe that until now, despite small differences, there is clear equipoise between hydromorphone and fentanyl without any current evidence to suggest that one is superior to the other. Since there is no known difference in risks or benefits between both medications a waiver of informed consent was requested. Considering equipoise among interventions, the use of a cluster randomized trial design with waived consent would be the only way to complete this study, allow sufficient recruitment, potentially reduce treatment contamination (since the randomization of the ICU occurs prior to enrolment of the individual patient), improve perceived external validity, potentially decrease bias caused by the open-label nature of the study, increase adherence to the allocated intervention and allow a low implementation costs [29]. The main risk will be inadvertent disclosure of PHI but will be minimized using safeguards for data security and collecting only the minimum necessary information to conduct the study.

10. Randomization

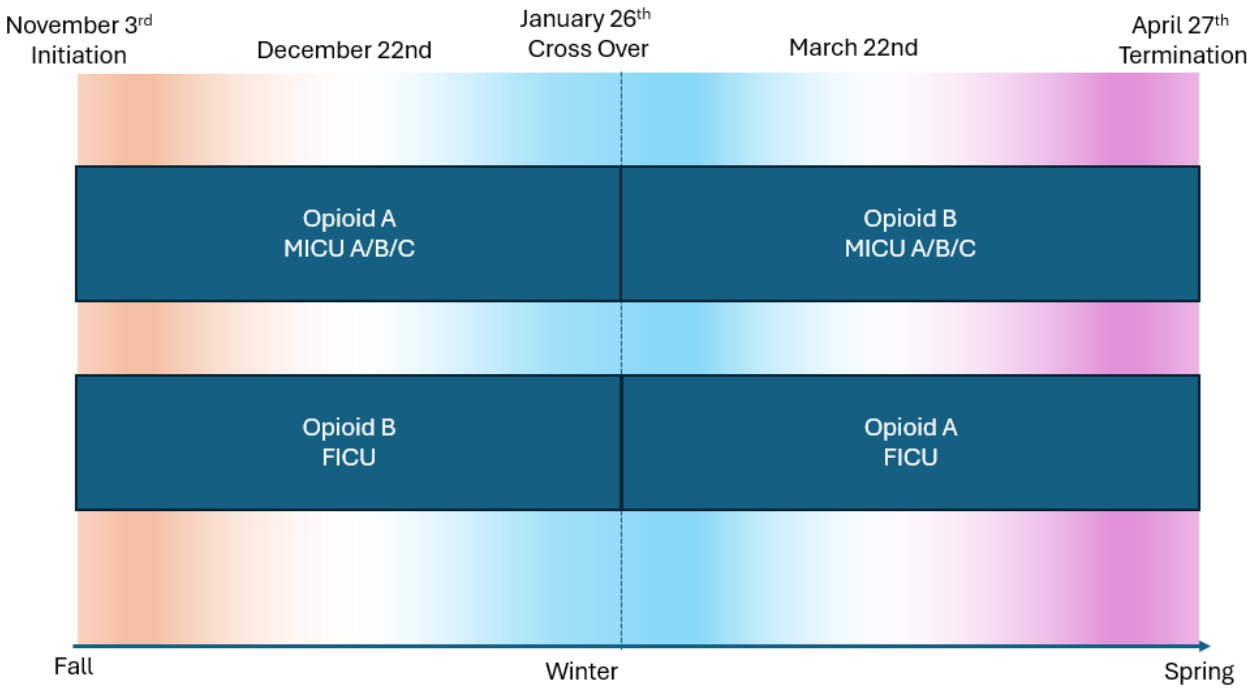
Randomization will occur at the level of the ICU, rather than for each individual patient. Cluster I (MICU A, B, C) and cluster II (FICU) will be randomized to start from a period with fentanyl

or hydromorphone and after 3 months will be crossed over to the other group. Cluster cross-over are planned to be 3 months to avoid seasonal variability. We plan to start enrollment in the middle of a season, so that the clusters have 1.5 months of each season. No washout period is planned.

Table 1. Randomization per ICU, cross-over design

ICU	3 months	3 months
MICU A/B/C	Intervention 1	Intervention 2
FICU	Intervention 2	Intervention 1

Figure 1. Planned Cross-Over according to seasonality



11. Blinding

This will be an open-label study. Due to small differences in pharmacokinetics and pharmacodynamics, an open-label study will be more appropriate regarding safety. The data analyst will be blinded to the intervention groups when performing statistics.

12. Study Procedures

12.1 Groups:

12.1.1 Fentanyl infusion

Fentanyl infusion will be used as first-line therapy for analgosedation, when clinically warranted. The unit automated dispensing cabinet will be loaded with fentanyl, except in circumstances where the provider believes that hydromorphone is the preferred opioid. This will be communicated to the medical teams taking care of patients in this geographic location and study period. ICU pharmacists will also communicate to other ICU pharmacists what the randomized opioid is.

Suggested initial continuous infusion

-Route: Intravenous

-Dose: 0-200 mcg/hr (max 1,440 MME/day)

-Initial dose: 50mcg/hr

-Concentration: 50 mcg/mL

-Bolus: 50-200mcg up to every 5 minutes as needed

-Continuous infusion adjustment: Increase in the continuous infusion if sedation not at goal after 3 bolus doses, increase by 25 mcg/hr every 60 minutes

12.1.2 Hydromorphone infusion

Hydromorphone infusion will be used as first-line therapy for analgosedation, when clinically warranted. The unit automated dispensing cabinet will be loaded with hydromorphone, except in circumstances where the provider believes that fentanyl is the preferred opioid. This will be communicated to the medical teams taking care of patients in this geographic location. ICU pharmacists will also communicate to other ICU pharmacists what the randomized opioid is.

Suggested initial continuous infusion

-Route: Intravenous

-Dose: 0-3 mg/hr (max 1,440 MME/day)

-Initial dose: 0.5mg/hr

-Concentration: 0.2 mg/mL

-Bolus: 0.5-2mg up to every 5 minutes as needed

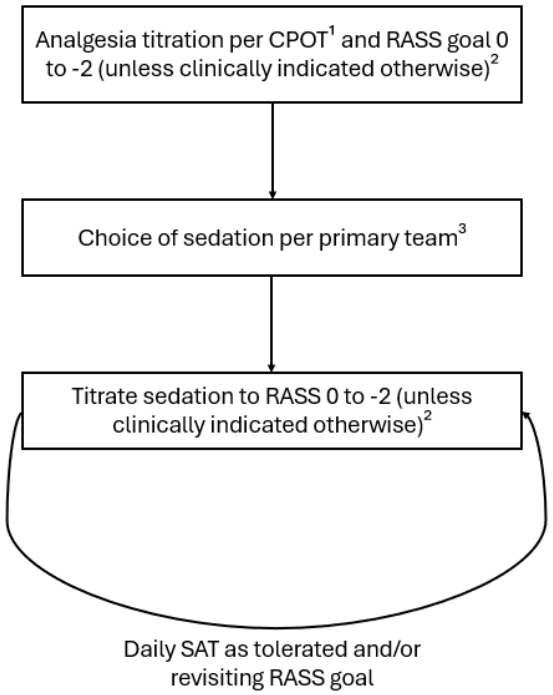
-Continuous infusion adjustment: Increase in the continuous infusion if sedation not at goal after 3 bolus doses, increase by 0.25 mg/hr every 60 minutes

12.2 Patient management correlated with the intervention

Decision regarding titration, initial dosing, additional boluses of the intervention drug will be at the discretion of the healthcare provider. The goal sedation level will be set by the medical team according to patient requirements. The Richmond Analgesia and Sedation Scale (RASS) will be used to titrate sedation. The critical care pain observation tool (CPOT) will be used to titrate pain management.

The study will not impact the use of sedative medications such as dexmedetomidine, propofol, benzodiazepines, antipsychotics and ketamine. Weaning of sedation will be driven per nursing protocol and/or at the discretion of the health care provider. Figure 2 show details of the suggested approach of analgosedation currently used in our institution.

Figure 2. Suggested analgosedation approach



1. Critical-Care Pain Observation Tool
2. Clinical indications for deeper sedation or other RASS goals include, but not limited to: need for neuromuscular blockade, status epilepticus, refractory intracranial hypertension, need for targeted-temperature management, severe refractory patient dyssynchrony, etc.
3. Suggested first line therapies include propofol, dexmedetomidine and/or ketamine

In our instution, the suggested sedation doses are as follows:

12.2.1 Propofol:

Infusion

- Initial dosing allowed: 5-10 mcg/kg/min
- Increase: 5-10 mcg/kg/min every 5 minutes.
- Decrease: 5-10 mcg/kg/min every 5 minutes.

Bolus

- May repeat 10mg every 1 minute x 2 doses. Do not exceed a total of 30mg supplemental dose in any one hour.
- Consider using adjusted body weight in patients with a BMI greater than 30 kg/m2

12.2.2 Ketamine

Infusion

- Usual dosing for Pain/Analgesia: 0.1-0.4 mg/kg/h
- Usual dosing for Sedation: 0.4-2.5 mg/kg/h
- Usual dosing for Generalized Convulsive Status Epilepticus: 1-7 mg/kg/h
- Initial dosing allowed: 0.05 mg/kg/h, 0.1 mg/kg/h, 0.2 mg/kg/h, 1.2mg/kg/h
- Increase: 0.1 mg/kg/h every 30 min
- Decrease: 0.1 mg/kg/h every 30 min

Bolus

- 0.2 mg/kg every 30 minutes PRN if agitation not at goal specified in titration order.

Consider using adjusted or ideal body weight in patients with a BMI greater than 40 kg/m2.

12.2.3 Dexmedetomidine

Infusion

- Usual dosing for Sedation: 0-1.5mcg/kg/h
- Initial dosing allowed: 0.2-0.4 mcg/kg/h
- Increase: 0.2 mcg/kg/h every 30 minutes.
- Decrease: 0.2 mcg/kg/h every 30 minutes.

12.2.4 Midazolam

Infusion

- Usual dosing for Sedation: 0-5 mg/h
- Initial dosing allowed: 0.5-2mg/h
- Increase: If not still at goal after 3 bolus doses, increase by 0.5 mg/hr every 60 minutes.
- Decrease: 50% of the current hourly infusion rate every 60 minutes.

Bolus

- Administer whichever is greater, 2 mg or 50% of current continuous infusion rate Q5min PRN agitation not at goal specified in titration order.
- Must give at least 3 boluses within 60 minutes before increasing the infusion rate. If patient requires 3 boluses within 30 minutes, contact provider.

Liberation from mechanical ventilation will be driven per respiratory therapist and nursing protocols or at discretion of the health care provider. Spontaneous breathing trials (SBT) will be performed per protocol with 0 to 8 cmH2O of inspiratory pressure augmentation and 0 to 5 cmH2O of PEEP. Variations on the SBT will be allowed at discretion of the health care provider.

Once a patient is liberated from mechanical ventilation, the study intervention medication will be discontinued. However, if at any time during the study period, the patient will receive the drug assigned to the cluster at the time of the first institution of mechanical ventilation, if possible. Enrolled patients who remain in the ICU through the crossover time will continue with the same drug intervention.

12.3 Interventions to improve adherence

Our records show that fentanyl is the more prevalently analgosedation opioid used in our units, however hydromorphone is used in around 20-25% of patients. Given the potential for contamination, we implemented several strategies to minimize accidental crossover:

1. Randomization at the building level rather than by individual ICU
2. Weekly email reminders to ICU intensivists and nocturnists
3. Weekly announcements during multidisciplinary rounds specifying the assigned opioid of the unit
4. Signage indicating the randomized opioid in easily accessible locations, including on the automated dispensing cabinets
5. Patients who had been assigned an opioid within 28 days prior to crossover and remained in the unit continued on the same opioid unless a clinical change was deemed necessary by the primary team

Table 2. Participant timeline: Schedule of enrollment, interventions, and assessments

	STUDY PERIOD							
	Enrollment	During Study						Termination
TIMEPOINT	*Initiation of MV and opioid for analgosedation*	*MV day 1*	*MV day 2*	*MV day 3*	*...*	*Extubation*	*Floors*	*Discharge or 28 days*
ENROLLMENT:	X							
Eligibility screen	X							
INTERVENTIONS								
Hydromorphone	X	X	X	X	X			
Fentanyl	X	X	X	X	X			
ASSESSMENTS:								
Baseline and demographics	X							
Opioid receipt and dose	X	X	X	X	X	X	X	X
Invasive support (vasopressors, RTT, etc.)	X	X	X	X	X	X	X	
Laboratory work-up	X	X	X	X	X	X	X	
Ventilator Mechanics	X	X	X	X	X	X		
Bowel Movements		X	X	X	X	X	X	
CAM-ICU		X	X	X	X	X		
COWS		X	X	X	X	X	X	
Clinical outcomes								X

12.4 Pragmatic Intervention Approach

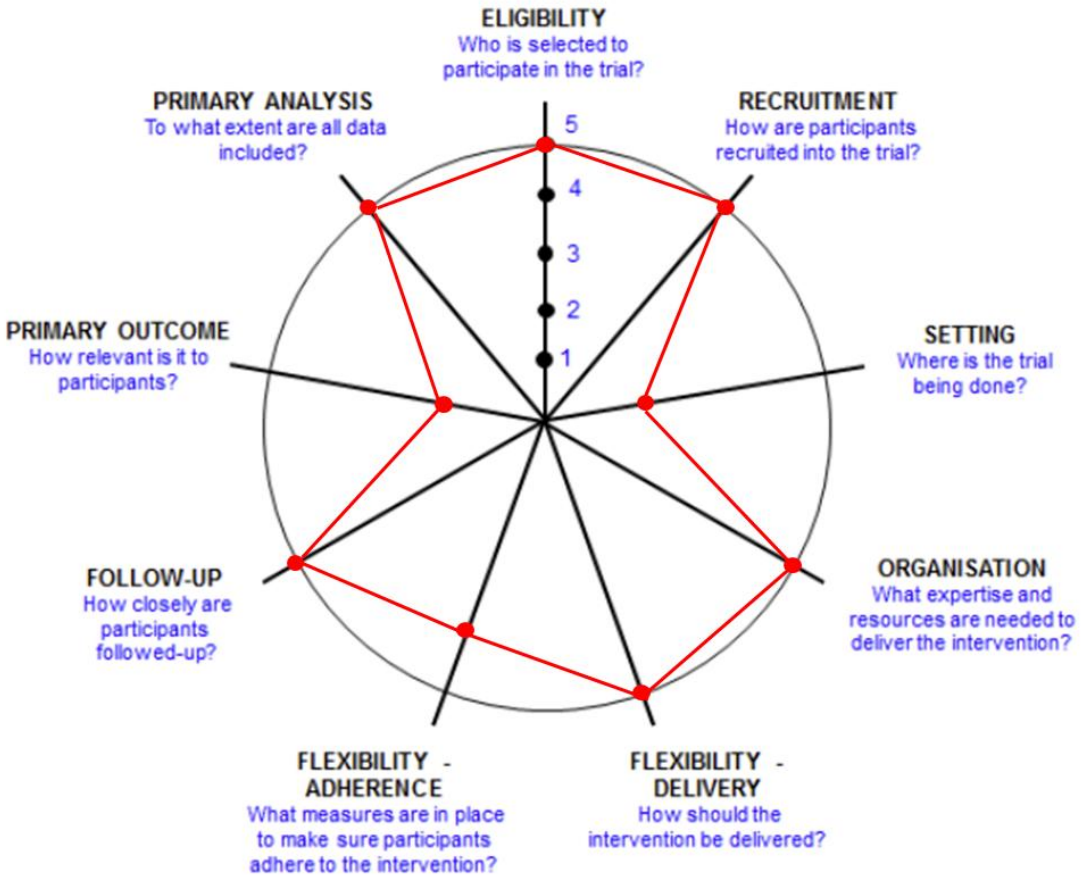
The goal of the trial is to evaluate fentanyl versus hydromorphone as a first line strategy for analgosedation in mechanically ventilated patients in a pragmatic randomized trial. We decided to perform a feasibility and pilot trial in order to understand not only clinical outcomes but also improve and obtain outcomes regarding the logistics of such a type of study. To evaluate and aid with the trial development we performed the PRECIS-2 prior to the trial initiation. The PRECIS-2 is a tool developed to aid trialists to evaluate whether design decisions match their intended purpose.

Table 3. PRECIS-2 evaluation

#	Domain	Score	Rationale
1	Eligibility	5	Inclusion criteria: "Admitted to either MICU A, B, C or FICU at Beth Israel Deaconess Medical Center, requiring mechanical ventilation, and opioid infusion for analgosedation" Very broad inclusion criteria with appropriate safety exclusion (medical team discretion, contraindication to the agent, DNI, CMO)
2	Recruitment Path	5	No specific recruitment limitation. All patients are admitted to the ICU on MV, both medical and mixed (medical and surgical) ICU. We are not excluding transfers within the hospital neither from outside hospitals.
3	Setting	2	Since this is single center academic tertiary hospital, we reduced the score by 3. This may limit generalizability to smaller or secondary hospitals.
4	Organization	5	Care will not change among two interventions except by the medication themselves. All decisions will follow usual care. No extra training of staff will be required since both medications are routinely used in the ICU.

5	Flexibility of experimental intervention – Delivery	5 for both	The delivery of the randomized medication follows our regular ICU policy (developed years prior to the trial) and dosing, titration can be changed at any moment by preference of the team.
6	Flexibility of experimental intervention – Adherence	Individual: NA Cluster: 4	Individual Intervention: Patients are sedated and participants do not need to adhere to the trial. Cluster intervention: we provided signage to ICU team and meetings to remind them about the trial, but always making them aware that the decisions are defined by the primary team. Cross-over was allowed without restriction.
7	Follow-up	5	No additional follow-up than usual care and no additional data collection than usual care
8	Outcome	2	The use of daily MME during ICU stay, although not patient-centered, it is a useful surrogate. Also, the measurement of outcome is pragmatic, not requiring any additional measurement.
9	Analysis	5	Intention-to-treat analysis including all patients in the trial

Figure 3. PRECIS-2



13. Safety Monitoring

Assuring patient safety is primordial for this protocol. Although patients would already require an opioid infusion for analgesia if not participating in the trial, the protocol will address safety through:

- Exclusion of patients with any contraindication to the intervention drugs, as determined by the medical team
- Since this study is performed in the ICU, all patients will be monitored with telemetry, SpO2, mechanical ventilator monitor, and a high level of laboratory monitoring. Patients will also have a high number of medical staff required in the ICU including nurses, respiratory therapists, pharmacists and physicians.

Since both interventions are standard of care and our protocol does not involve any additional change in our hospital policy, the IRB waived the need for a Data Safety Monitoring Board.

Routine monitoring of adverse events will be performed during intensive care department, nursing leadership and pharmacy meetings.

14. Data Collection

14.1 Preliminary data collection validation

Data will be collected from the patient's electronic medical record using SQL. The automated data Extraction will be compared to the manual data extraction by two independent team members prior to the trial initiation. Data will be collected from 30 patients to achieve at least 10% of the predicted sample size and at the same time enough power to obtain an expected intraclass correlation coefficient of 0.95 and a minimum accepted of 0.99. Data that cannot be extracted

using SQL will be collected manually for the study data set. The accuracy of the data collection will be published elsewhere.

The data collected will be entered into REDcap, an online and secure database.

Our study will not require any additional studies besides the ones required for medical care and the decision to order the studies will be at discretion of the medical ICU team.

14.2 Data Collection at the time of enrollment

For laboratory, radiographic, and vital signs, we will consider data available up to 12 hours prior to 12 hours after enrollment, if more than one value available, we will prioritize the one prior to randomization. We present the data that will be collected, but not restricted to:

- Medical Record Number (only for initial identification, patients will be assigned a study number and data for analysis will be unidentified)
- Admission date (MM/DD/YYYY and time in military system), admission indication, ICU admission date (MM/DD/YYYY and time in military system), location when inclusion criteria met (ED, floor, ICU), ICU indication
- Transfer from outside hospital or other within system ICU
- Intubation date (MM/DD/YYYY and time in military system)
- Demographic data
    - Age (years)
    - Sex assigned at birth (Male or Female)
    - Race (Caucasian, Hawaiian, African American, Asian, American Indian, Alaska Native, not defined)
    - Height (cm)
    - Measured Weight (kg)

    - Ideal Weight (men = 50 kg + 2.3 * [height (in) – 60], women = 45.5 kg + 2.3 * [height (in) – 60])
    - Body mass index (BMI, kg/m²)
- Comorbidities
- Laboratory results (creatinine, estimated GFR, BUN, sodium, potassium, chloride, glucose, bicarbonate, lactic acid, ALT, AST, alkaline phosphatase, WBC, hemoglobin, hematocrit, platelet count, INR)
- Vital signs including
    - Heart rate (bpm)
    - Blood pressure (mmHg)
    - Temperature (°C)
    - SpO2 (%)
    - Respiratory Rate (rpm)
- Support therapy including:
    - Vasopressors (norepinephrine, vasopressin, phenylephrine, angiotensin 2, epinephrine, dobutamine), rates (data collected in usual rate presentation, but will be adjusted to norepinephrine equivalents, when possible), daily total dose
    - Sedation medication (propofol, ketamine, midazolam, dexmedetomidine) and rates (data collected in usual rate presentation, but will be adjusted to propofol equivalents, when possible), daily total dose
    - Neuromuscular blockade (cisatracurium or rocuronium) (Y/N), daily total dose
    - Mechanical ventilation settings (PEEP [cmH2O], inspiratory pressure [cmH2O], tidal volume [mL], inspiratory time [s], driving pressure [cmH2O], peak pressure [cmH2O], resistive pressure [cmH2O], plateau pressure [cmH2O], respiratory rate [ipm], minute ventilation [L/min], FiO2 [%])

- Prior to randomization intervention medication rate (fentanyl or hydromorphone) converted to MME and total MME received
- SOFA (PaO_2, FiO_2, need for mechanical ventilation, platelets, glasgow coma scale, bilirubin, mean arterial pressure, creatinine)

14.3 Data Collection during the time of intervention

The data collection during intervention will be performed daily. For numerical data, the lowest, the highest and the morning (7:00 am) values will be collected. For continuous interventions such as presence or absence of mechanical ventilation, use of vasoactive drugs, neuromuscular blockade, continuous renal replacement therapy and others we will consider as “Yes” if the intervention was present at 7:00 am and “No” if absent. For laboratory work-up we will consider the closest value to 7:00 am, on the same day.

- Patient alive (Y/N)
- Daily Laboratory results (creatinine, estimated GFR, BUN, sodium, potassium, chloride, glucose, bicarbonate, lactic acid, ALT, AST, alkaline phosphatase, WBC, hemoglobin, hematocrit, platelet count, INR)
- Venous blood gas or arterial blood gas if available (pH, pCO_2, pO_2).
- Daily vital signs. We will consider the highest value for temperature, heart rate, respiratory rate and the lowest value for blood pressure and oxygen saturation.
    - Heart rate (bpm)
    - Blood pressure (mmHg)
    - Temperature (°C)
    - SpO_2 (%)
    - Respiratory Rate (rpm)
- Days requiring mechanical ventilation, accidental extubation (Y/N), planned extubation (Y/N)

- Daily mechanical ventilation settings (PEEP [cmH2O], inspiratory pressure [cmH2O], tidal volume [mL], inspiratory time [s], driving pressure [cmH2O], peak pressure [cmH2O], resistive pressure [cmH2O], plateau pressure [cmH2O], respiratory rate [ipm], minute ventilation [L/min], FiO2 [%]) and tracings, if possible.
- Fluid net, intakes and outputs (in mL)
- Number of daily bowel movements
- Sedation medication (propofol, ketamine, midazolam, dexmedetomidine) and rates (data collected in usual rate presentation, but will be adjusted to propofol equivalents, when possible), daily total dose
- Daily RASS
- Intervention medication rate (fentanyl or hydromorphone) and MME.
- Vasopressors and inotropes (Y/N), type (norepinephrine, vasopressin, phenylephrine, angiotensin 2, epinephrine, dobutamine) and rates (data collected in usual rate presentation, but will be adjusted to norepinephrine equivalents, when possible), daily total dose
- Neuromuscular blockade (Y/N), type and rate
- Renal replacement therapy (Y/N)
- Presence of delirium in the day (as diagnosed by the medical team, from the primary team note, or CAM-ICU positive by nurse evaluation) (Y/N)
- Presence of opioid withdrawal (as diagnosed by the medical team, from the primary team note or COWS by nurse evaluation) (Y/N)
- Need for tracheostomy (Y/N and time to event - MM/DD/YYYY and time in military system)
- Additional analgesic medication used (Y/N and type), rate and/or dose
- Daily need for restraints
- Adverse Events as explained in “17. Benefits and possible Risks”

14.4 Data at the time of termination

At termination of the patient inclusion we will collect

- Patient alive at 28 days (Y/N)
- Patient is discharged from the ICU at 28 days (Y/N), ICU transfer date (MM/DD/YYYY and time in military system)
- Patient is discharged from the hospital at 28 days (Y/N), hospital discharge date (MM/DD/YYYY and time in military system)

Table 3. Retrospective Data Collection timepoints details

Data	Enrollment	Daily Routine	Extubation day	ICU discharge	Day 28 or Discharge
Demographic data	X				
Comorbidities	X				
Intubation data	X				
SOFA	X				
APACHE	X				
Intervention total dose (type and daily MME)	X	X			
Other sedatives *type and dose)	X	X	X	X	X
Other analgesics (type and dose)	X	X	X	X	X
Neuromuscular		X			

blockade (Y/N)					
Vital Signs and Is/Os	X	X			
Bowel Movements (Y/N and n)		X			
Vasopressors (type, total dose)	X	X			
RRT (Y/N)		X			
Mechanical Ventilation Data	X	X			
Adverse Events (type and Y/N)		X			
COWS (Y/N)		X	X	X	
Extubation data (day and time)			X		
Tracheostomy (Y/N)					X
Use of opioids (daily MME)	X	X			X
CAM-ICU (Y/N)		X	X	X	
Mechanical Ventilation Day (Y/N)		X			X
ICU Day (Y/N)		X			X
Death (Y/N)		X		X	X

15. Outcomes Measures

15.1 Primary Outcome:

- Difference in daily MME dose received during mechanical ventilation period. The daily MME dose will be calculated using all the opioid doses received during the day. The outcome will be obtained from the days patients were on mechanical ventilation. It will include not only the intervention medication, but also the additional boluses and alternate opioids, including cross-over drug. The doses will be converted into MME [30].

15.2 Secondary Outcomes:

- All cause mortality on day 28 - patients who were discharged prior to 28 days will be assumed to be alive. If they are readmitted to our hospital system before day 28, we will use the that admission information
- Days alive and free of MV at day 28 (VFD) - the ventilator free days will be counted as 28 minus the duration of mechanical ventilation in days for those patients who survived the 28 days. Patients discharged prior to 28 days will be assumed to be free of mechanical ventilation. Patients who died before 28 days will be assumed to have zero VFD.
- Days alive and free of ICU at day 28: counted as 28 minus the days alive in the ICU. Patients discharged prior to 28 days will be assumed to be out of the ICU. Patients who died before 28 days will be assumed as zero ICU free days.
- Days alive and free of vasopressors at day 28: counted as 28 minus the days alive with intravenous vasopressors. Patients discharged prior to 28 days will be assumed to be off of vasopressors. Patients who die before 28 days will be assumed as zero vasopressors free days.
- Days alive and free of hospitalization at day 28: counted as 28 minus the days alive in hospital. Patients discharged prior to 28 days will be assumed to be out of the hospital. Patients who die before 28 days will be assumed as zero hospital free days.

- Total morphine-milligram equivalent doses required: will be calculated based on total dose at 28 days of the intervention drug and other opioids received during hospital admission [30]. The dose of opioids used on the comfort measures period for those patients that were transitioned to comfort measures will not be considered for the outcome analysis.

- Difference in average daily dose of morphine milligram equivalent required during hospital stay. Will be calculated based on total dose at 28 days of the intervention drug and other opioids received during hospital admission. The dose of opioids used on the comfort measures period for those patients that were transitioned to comfort measures will not be considered for the outcome analysis. Patients discharged prior to 28 days of enrollment will be considered to have 0 morphine milligram equivalent per day after discharge.

- Difference in total daily dose of vasopressor in norepinephrine equivalents. Calculated based on total dose at 28 days of all the vasopressors (norepinephrine, epinephrine, dobutamine, vasopressin, angiotensin II, phenylephrine). Patients discharged prior to 28 days of enrollment will be considered to have 0 dose per day after discharge.

- Requirement of adjunctive analgesia or sedation medications: total dose and medications used at 28 days in propofol equivalent dose

- Patient-ventilator mechanics, measure by weighted average of the following outcomes: PEEP, plateau, driving pressure and compliance through the first 3 and 7 days

- Incidence of opioid withdrawal: using daily COWS measure during 28 hospital days or until discharge

- Daily Average number of Bowel Movements through ICU stay: Will be measured by the number of bowel movements per day during the ICU stay. In patients with rectal tube, 1 bowel movement will be considered to have least 50mL and a maximum of 250mL of stools.

- Percentage of time without coma and delirium during the ICU stay: assessed daily by RASS and CAM-ICU by nurses at the bedside. A positive day for coma is RASS of -3 or less and delirium is

considered as RASS of 3 or more or positive CAM-ICU. The value obtained will be divided by the number of days in the ICU.

- 28 day free of restraints: counted as 28 minus the days alive with need for restraints. Patients discharged prior to 28 days will be assumed to be off of restraints. Patients who die before 28 days will be assumed as zero restraints free days.
- Need for tracheostomy during hospital stay
- Mean difference in total MME dose received during the first 24 hours, first 3 days, 7 days and total hospital stay

16. Statistical Analysis Plan

To enhance transparency and reproducibility, the statistical analysis plan will be available, pre-specified and every update will be time-marked.

16.1 Sample Size Calculation

There is no trial comparing fentanyl to hydromorphone for analgosedation in critically ill mechanically ventilated patients. Considering a daily MME dose while on mechanical ventilation in the fentanyl group of 270 ± 250 mg and 450 ± 500 mg in the hydromorphone group based on the data from two months of our MICU A, B, C and FICU, group sample sizes of 137 patients would achieve 80% power to detect a difference of 180 MME at a significance level (alpha) of 0.05 using a two sided Mann-Whitney Test. These results are based on 500 Monte Carlo samples from the null distributions: WeibullMS (450 500) and WeibullMS (450 500), and the alternative distributions: WeibullMS (450 500) and WeibullMS (270 250). Considering eventual losses to follow-up and contamination it will be required a sample size in each group of 150 patients.

Therefore, considering a recruitment of 50 patients per month, it will require 6 months to obtain the sample size.

Considering post-COVID-19 data, since 2022 our average number of patients on mechanical ventilation was:

- MICU A had an average of 100 patients on mechanical ventilation per year
- MICU B had an average of 250 patients on mechanical ventilation per year
- MICU C had an average of 200 patients on mechanical ventilation per year
- FICU had an average of 270 patients on mechanical ventilation per year

There are no published estimates of intra-cluster coefficient (ICC) or within-/between-period correlations for opioid consumption (MME) in ICU settings and using retrospective data to obtain ICC is likely to be biased as treatment choice is influenced by clinical factors. To account for ICC, as previously recommended, we chose to:

- Inflate the sample size by about 10% to account for potential clustering effects.
- Additionally evaluate the sample size under alternative modeling assumptions (including mixed-effects modeling), which resulted in a similar magnitude of inflation (~10%).
- Use our anticipated enrollment rate (50–70 patients/month) conservatively based on the lower bound, making it likely that the final sample size will exceed the minimum required, further mitigating potential loss of power.

Importantly, the true ICC in this study is likely to be small, as the two clusters (ICUs) are highly comparable in terms of patient population, staffing structure, clinical protocols and care environment. Also, our crossover accounts for season (fall, winter and spring) variability to decrease between-periods variation. Thus, any clustering effect is expected to be decreased.

16.1.2 Definitions

Intention-to-treat analysis: patients will be included in the intention-to-treat analysis if

- Meeting inclusion criteria for the study
- Are in an ICU randomized and assigned to an intervention group

Patients readmitted to the ICU within the study period will only have the index admission considered for outcomes perspective.

16.2 Data Analysis Plan

16.2.1 Descriptive Statistics

As recommended by CONSORT guidelines, patient flow information will be presented. Patients screened, randomized, excluded, those who received the intervention, withdraws, loss to follow-up, death and hospital discharge will be presented. Patients randomized will be described as overall baseline characteristics for both interventions. Continuous data will be described as median and interquartile range, while categorical variables will be present as frequency and percentage. We will not perform statistical testing for baseline differences.

16.2.2 Methods of Analysis

Categorical variables will be described as number and percentage. Continuous variables will be described as median and interquartile ranges (IQR).

Primary Outcome

We will use intention-to-treat analysis. Our primary outcome, the daily MME requirement during mechanical ventilation, will be analyzed within the framework of cluster analysis. Therefore, we will use Generalized Linear Mixed Models (GLMM) where the cluster will be treated as a random effect. Intraclass correlation coefficients will be estimated to assess within-cluster correlation over time to guide if more random-effects are needed to be added to the GLMM. The final link function

will be determined based on the daily MME distribution (linear for normally distributed, log link for skewed continuous data, log transformation or GLMM assuming a Gamma distribution with log link). For the MME calculation we will use all the MME received during the MV period, including alternate and crossover opioids.

Secondary Outcomes

For 28 day vasopressor free day, 28 day ICU free day, 28 day VFD, requirement of adjunctive sedation, requirement of adjunctive analgesia, percentage of time without coma and delirium, 28 day restraints free days and daily average bowel movements we will use GLMM.

For our 28-day mortality, we will use Kaplan-Meier curves and log-rank tests and censor patients at time of death. We will consider the time 0 as the time of enrollment.

For categorical variables we will use GEE.

Multiple Comparisons

No adjustment will be made for multiple comparisons when examining pre-defined secondary outcomes as recommended [31]. However, caution will be used to interpret results by noting the number of significant tests that would occur by chance alone.

16.3 Missing Data

We do not expect missing data to be present for our primary outcome. However, considering that it may occur for the primary outcome and also secondary outcomes, missing data will be imputed via multiple imputation methods.

16.4 Prespecified Subgroup and Sensitivity Analysis

We will include the following as prespecified subgroup/sensitivity analysis:

- Different sedative medications (e.g., propofol, ketamine, midazolam, dexmedetomidine)
- Patients with sepsis on ICU admission
- Patients requiring vasopressors
- Patients with ARDS
- Patients with acute or chronic liver failure (liver dysfunction)
- Per ICU site (MICU A, B and C versus FICU)
- Per type of admission (medical or surgical)
- Patients with acute kidney injury and/or chronic kidney injury
- Patients requiring renal replacement therapy
- Patients on previous opioid infusion prior to randomization
- Patients on neuromuscular blockade agents
- Excluding patients admitted from outside hospital ICU and/or within system ICU
- Previous opioid exposure for more than 24 hours
- Excluding patients with < 48 hours or > 14 days of mechanical ventilation
- Patients on ECMO
- Per protocol analysis and evaluating different cut-offs for definition of cross-over (25%, 50%)
- We will also perform sensitivity analyses using multivariable regression to adjust for imbalances in baseline factors. For 28 day ventilation free days, 28 day ICU free days and 28 day vasopressor free days we will use linear regression and for time-to-event outcomes such as 28 day mortality we will use Cox regression.
- We will perform a sensitivity analysis using different MME conversion for hydromorphone and fentanyl
- We will perform a Bayesian

17. Benefits and Possible Risks

17.1 Benefits

To date, there are no well established benefits related to the selection of fentanyl or hydromorphone for mechanically ventilated patients. The differences in pharmacokinetics and pharmacodynamics and its clinical implications to critically ill population are unknown. One small phase II randomized clinical trial comparing remifentanil with morphine showed potential benefit with remifentanil regarding mean percentage on optimal sedation. There was also a small reduction in mechanical ventilation duration of 4 hours (18.1 ± 3.4 hours versus 14.1 ± 2.8 hours) [13]. A cluster randomized trial comparing fentanyl with morphine showed a 0.79 (95% CI, 0.31–1.28) day reduction in days alive and free of mechanical ventilation at 28 days. There was also a statistically significant decrease in ICU-free days at day 28 and a non-statistically significant decrease in hospital-free day at day 28 and day-28 mortality [14]. However, it is unclear if these benefits would apply to a larger population and different interventions (fentanyl versus hydromorphone).

17.2 Risks

A potential risk to the study patients involves data collection of personal information. Multiple steps will be taken to avoid associated risks such as:

- Data collected to database will be de-identified
- Minimize data necessary to conduct the study
- Data will be collected in a secure database

Risks to the exposure to fentanyl and hydromorphone include bradypnea, apnea, delirium, oversedation, hypotension, altered mental status, nausea, vomiting, ileus, urinary retention, pruritus, constipation, withdrawal and opiate induced hyperalgesia. Since patients would receive an opioid infusion even if not participating in the trial, the additional risk of the study regarding

opioid side effects are not different. To avoid unnecessary risk exposure to fentanyl or hydromorphone side effects based on pharmacodynamics and pharmacokinetics we will exclude patients with contra-indications to either of them. To mitigate risks adverse events will be monitored (**13. Safety Monitoring**).

18. Study Withdrawal and Discontinuation

The patients can be withdrawn from the study by the investigators for safety reasons, if the patient or family requests to be withdrawn. The reason for withdrawal will be recorded in the patient's study chart.

19. Privacy

19.1 Data Security

Patient identities will not be revealed. The patient identifier to their specific data will be destroyed as soon as possible. The data from the electronic medical record will be uploaded to an online secure (password-protected) database behind a firewall. On that database, patients will have a unique study number, which will be erased as soon as possible.

19.2 Dissemination of Research Results

Once the results of the study are available and published we will make it available at the Beth Israel Deaconess Medical Center portal and website.

20. Study Chart Retention

Patient data will be stored in MIMICs database and in our online secure (password-protected) REDcap database. The information will be stored for an indefinite period of time for future reference and possible subsequent post-hoc analysis. However, the patient identifier to their specific data will be destroyed as soon as possible.

21. Roles and Responsibilities

Trial Steering Committee: EMHP, AW, MH, DF, AS, AG, MAA, ENBK

Trial Management Group: EMHP, AS, AG, MAA

Data Monitoring Committee: Not Required by IRB

Endpoint adjudication Committee: NA

Data management team: EMHP, AW, AN, KN, SH, GC, KC, VN

Other individuals or groups overseeing the trial: VMBG, KC, DT

22. Funding

None. This is an investigator initiated study with no trial sponsor and funder.

23. Conflicts of Interest

Dr. David M. Furfaro: One-time advisory board member for InflaRx Pharmaceuticals in 4/2024, no longer ongoing.

Other authors have no conflict of interest to declare.

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