

Impact of TOtally transdErmal Sedation in the weaning from remifentanil infusion among critically ill patients undergoing mechanical ventilation: a pilot randomized-controlled Study (The TOES Trial)

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Abstract

Rationale and Background: The choice of the sedation protocol has a massive impact on the duration of mechanical ventilation and the timing of extubation. Many sedation protocols are described in the literature. No data are available about the possibility of using TTS-fentanyl as an alternative to intravenous opioids during the weaning phase from mechanical ventilation and the post-extubation period until the discharge from ICU to the ward. **Objective:** We aim to assess if a TTS fentanyl-based sedation protocol can have an impact on the global Work of Breathing (WOB). Secondary endpoints of the study are the duration of mechanical ventilation, the duration of continuous infusion of opioids, the length of stay in ICU and in hospital. **Methods:** We will perform a 2-arm, single-center, prospective randomized controlled trial. The duration of the study will be approximately one year, for a total of 24 patients. Patients ventilated in pressure support ventilation (PSV) receiving continuous intravenous remifentanyl for more than 5 days will be considered eligible. Eligible patients will be randomized in 2 groups: Group 1 will receive remifentanyl; Group 2 will receive TTS-fentanyl and remifentanyl. Patients will be selected from the population admitted to the adult ICU (a 20-beds unit), the post-operative ICU (a 13-beds unit), and the NeuroICU (a 10-beds unit). An Edi Catheter for diaphragm electrical activity monitoring will be put in place for each patient. **Outcomes:** The primary endpoint is to demonstrate that the area under the curve (AUC) of the work of breathing per minute in the intervention group is not higher than the control group. Secondary endpoints are differences respiratory rate, tidal volume, arterial blood pressure, heart rate, global duration of mechanical ventilation and opioids infusion, length of stay in ICU and in hospital. **Statistical Analysis:** Distribution normality will be assessed with the Kolmogorov-Smirnov test. Continuous variables will be reported expressed as medians (interquartile ranges). Qualitative variables will be reported as frequencies. Analysis on the primary efficacy criterion and other quantitative variables will be assessed with the Wilcoxon-Mann-Whitney test. Categorical outcomes will be compared with the chi-square test, or Fisher's exact test, as appropriate. Cochran-Mantel-Haenszel statistics will be reported for all these results. Two-way analysis of variance (ANOVA) for repeated measures with Bonferroni correction will be used to determine the differences in secondary endpoints. Comparisons between groups regarding these variables at each study time point were performed with the Student's t-test or Mann-Whitney test, as appropriate. Mean difference and 95% confidence interval [CI95%] are reported for most significant results. Two-tail p values ≤ 0.05 Will be considered significant.

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Title	Impact of totally transdermal sedation in the weaning from remifentanil infusion among critically ill patients undergoing mechanical ventilation: a pilot randomized-controlled Study
Protocol ID	2687
Clinical Trials number	NCT04204967
Date	24/02/2020
Center	Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma
PI	Dott. Anselmo Caricato
Collaborators	Dott. Daniele Natalini, Dott. Domenico Luca Grieco, Prof. Massimo Antonelli
Type of financing	internal funding for Interventional Pharmacological Studies
Study type and phase	Monocentric, phase II
Study setting	Neurosurgical intensive care (10 Beds), Adult ICU (20 Beds), Post-operative intensive care (13 Beds)
Length of the study	12 months
Study design	Randomized Controlled Trial. Interventional with drug GROUP 1 : Remifentanil continuous iv infusion GROUP 2:Transdermal fentanyl plus remifentanil
Inclusion criteria	<ul style="list-style-type: none"> • Age > 18 yo • On Pressure Support Ventilation • Negative pregnancy test prior to inclusion in the study • The informed consent form needs to be signed and dated by the patient or a relative/legal guardian before of any procedure related to the study • A patient with prolonged weaning from the mechanical ventilator will be considered eligible • Analgesia provided by continuous infusion of remifentanil lasting five days or more and an intolerance to a dose reduction of 0.025 mcg/kg/min

<p>Exclusion criteria</p>	<ul style="list-style-type: none"> • Hypoxemic respiratory failure (P/F < 200 mmHg); • Haemodynamic instability requiring high doses of inotropes or vasopressors; • Current enrollment or plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 30 days or 5 half-lives of the agent, prior to the baseline visit; • Any condition that may contraindicate the use of remifentanyl or transdermal fentanyl; • Patient admitted for post-operative monitoring after elective surgery; • EAdi catheter contraindicated. • Hypersensitivity to the active substance or any of the excipients; • Hepatic or renal impairment; • Fever (body temperature ≥ 38 °C) or septic shock, hypothermia (body temperature < 35 °C) or presence of active surface cooling systems; • Hypercapnic patients with a PaCO₂ > 45 mmHg; • Delirium state defined as RASS ≥ 3 and CAM-ICU positive; • Patients with a BMI ≥ 35.
<p>Primary Objective</p>	<p>To assess if a transdermal fentanyl-based sedation protocol is at least non-inferior when compared to a totally intravenous remifentanyl infusion protocol. we will compare the global work of breathing (WOB) of the patients randomized to receive transdermal fentanyl vs. remifentanyl alone. We will calculate the area under the curve (AUC) of the work of breathing per minute in the intervention group vs the control group</p>
<p>Secondary Objectives</p>	<p>Main secondary endpoints include differences in respiratory rate, tidal volume, arterial blood pressure, heart rate, global duration of mechanical ventilation, length of stay in ICU and in hospital.</p>
<p>Number of Patients</p>	<p>N = 24</p>

Statistical Analysis	<p>Distribution normality will be assessed with the Kolmogorov-Smirnov test. Continuous variables will be reported expressed as medians (interquartile ranges). Qualitative variables will be reported as frequencies. Analysis on the primary efficacy criterion (AUC of the work of breathing) and other quantitative variables will be assessed with the Wilcoxon-Mann-Whitney sum of rank test. Categorical outcomes will be compared with the chisquare test, or Fisher's exact test, as appropriate: Cochran-Mantel-Haenszel statistics will be reported for all these results. Two-way analysis of variance (ANOVA) for repeated measures with Bonferroni correction will be used to determine the differences in work of breathing per breath, inspiratory effort, delta EAdi, plateau pressure, P 0.1 respiratory rate, tidal volume, arterial blood pressure, heart rate in the two groups. Comparisons between groups regarding these variables at each study timepoint were performed with the Student's t test or Mann-Whitney test, as appropriate. Mean difference and 95% confidence interval [CI95%] are reported for most significant results. Two-tail p values ≤ 0.05 Will be considered significant. Statistical analysis will be performed with SPSS software package (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).</p>
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1. Rationale and Background

Invasive mechanical ventilation is a lifesaving intervention among critically ill patients. However, prolonged ventilation is associated with increased morbidity and mortality. Optimal processes for weaning from ventilation have been studied for many years and have led to evidence-based clinical practice guidelines to facilitate early liberation from invasive mechanical ventilation. It is crucial to avoid prolonged MV, and weaning from the mechanical ventilator should not be delayed to avoid complications as VAP, weakness and atrophy of respiratory muscles, and the need for a tracheostomy (Jeong et al. 2015; Béduneau et al. 2017; Girard et al. 2017; Peñuelas et al. 2011; Perkins et al. 2018).

The choice of the sedation protocol has certainly a massive impact on the duration of MV and the timing of extubation. Many different sedation protocols are described in the literature and adopted in every day clinical practice. A hypnotic agent, propofol or midazolam, is commonly used in combination with an opioid in infusion, typically remifentanyl, fentanyl or sufentanyl. However, analgesia-based sedation techniques, which focus on patient comfort rather than on patient sedation by catering to the analgesic needs of the patient and adding a sedative only if necessary, are well established in the ICU setting.

1.1 Remifentanyl

Remifentanyl is a selective μ opioid receptor agonist indicated for use during anesthesia and for the provision of analgesia in mechanically ventilated critically patients. Remifentanyl has an onset of 1 min and quickly achieves a steady state. Differently, from other opioids, it is metabolized by non-specific blood and tissue esterases into a clinically inactive metabolite, resulting in an elimination half-life of fewer than 10 minutes and not correlated at all with the infusion duration. The unique pharmacological profile of remifentanyl has proved particularly advantageous in ICU patients (Muellejans et al. 2004). Muellejans et al. randomly compared remifentanyl versus propofol-fentanyl sedation regimen in ICU, showing that remifentanyl alone allowed the adequate provision of optimal sedation and rapid extubation without the need for propofol in the majority of patients. Remifentanyl was associated with less between-patient variability in the mean percentage of time with optimal sedation than was fentanyl. Using conventional opioids such as fentanyl, however, would require constant patient monitoring to avoid over-sedation caused by drug accumulation, resulting in delayed extubation (Muellejans et al. 2004). An RCT published by Akinci et al. comparing remifentanyl to fentanyl infusion in postoperative children confirmed the advantages given by the use of remifentanyl, but the authors suggested that the short elimination time of remifentanyl may also cause some disadvantages. The elevated heart rates, blood pressures, and the increased sedation scores after cessation of remifentanyl probably reflected the short elimination time of remifentanyl. Moreover, a higher incidence of pain was noticed after end of the remifentanyl infusion and probably this could benefit of long-acting analgesic administration before the cessation (Akinci et al. 2005). 23 RCTs with a total of 1905 patients were included in a recent systematic review and meta-analysis comparing remifentanyl infusion with other opioids in mechanically ventilated patients. The results of this meta-analysis suggested that the use of remifentanyl was associated with a reduction in the duration of mechanical ventilation when compared with other opioids, specifically with fentanyl infusion, probably related to the pharmacokinetics and pharmacodynamics of remifentanyl, its rapid onset and offset. Remifentanyl

was associated with reductions in time to extubation after sedation cessation and ICU length of stay but not reductions in hospital length of stay or costs.

Moreover, neurologic assessment is essential for neurosurgical and neurotrauma patients, and the association between remifentanyl and rapid and predictable awakening may be more meaningful in these patients (Zhu et al. 2017). Futier et al. in a retrospective study comparing remifentanyl to sufentanyl suggested that using a short-acting opiate with short context-sensitive half-life in an analgesia-based sedation protocol may significantly decrease the duration of mechanical ventilation and the ICU length of stay even though not significantly in long term sedation, while improving the achievement of sedation goals despite a lower requirement for adjunctive hypnotic agents (Futier et al. 2012). Moreover, remifentanyl is demonstrated to reduce inspiratory muscle effort and improve ventilatory patterns in mechanically ventilated patients with tachypnoea or rapid shallow breathing resulting in an effective choice for patients who remain tachypnoeic during weaning from mechanical ventilation (Natalini et al. 2011).

1.2 TTS-fentanyl

Fentanyl was the first in a class of potent synthetic opioid analgesics developed in the 1960s. Restricted to anesthesia until the 1990s when the development of non-injectable fentanyl formulations was intensively pursued. Nowadays, transdermal fentanyl patches are among the most frequently prescribed strong opioid analgesics. As for remifentanyl, fentanyl is another pure μ opioid receptor agonist. Fentanyl is extensively metabolized, and renal excretion accounts for only 10 % of the dose. Passive Transdermal Therapeutic Systems (TTS) use the matrix technique with the drug dissolved in an inert polymer matrix that controls drug release. Delivery results from the concentration gradient between fentanyl in the patch and the skin. Transdermal fentanyl patches constantly deliver 12.5, 25, 50, 75 or 100 mcg/h over 72 h. The amount delivered is proportional to the surface of the resorption area, fentanyl can be detected in plasma after 1–2 h, but the onset of the full analgesic effect is obtained between 12 and 24 h after patch application and may vary with local conditions such as skin temperature. For example, during fever, fentanyl plasma concentrations can increase by approximately 33 % at body temperatures of 40 C. Transdermally delivered fentanyl is not subject to first-pass metabolism and providing a great bioavailability, near 92% (Newshan 1998; Carter 2003; Lötsch et al. 2013). High doses of TTS-fentanyl is documented to have an effect on the respiratory drive, causing respiratory depression, as a potential danger of any technique maintaining constant blood opioid concentrations, as described in an old study performed on post-operative patients comparing high doses of TTS-fentanyl vs. placebo (Bülow et al. 1995).

1.3 IMP-dose rationale

Different patches delivering different doses of fentanyl are available (12,5 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr). Because we had to choose only one, we decided *a priori* to adopt a TTS-fentanyl patch delivering 25/hr of the active principle. The reason for this choice was that it is more practical for us to titrate the dose. The starting dose will be 50 mcg/hr (two patches) and, based on the PaCO₂ values, can be increased or decreased every 24 hours, adding or removing two (50 mcg/hr) or three patches (75 mcg/hr). According to the study protocol, the maximum achievable dose of fentanyl is 300 mcg/hr. Due to the completely new usage that we are proposing for this drug, there is a lack of information in the literature about which is the maximum dose administrable to patients. In the *Summary of Product Characteristics* of TTS-fentanyl is specified

that: “Some patients may require additional or alternative methods of opioid administration when the TTS-fentanyl dose exceeds 300 mcg/hr”. The conclusion is that we decided not to exceed 300 mcg/hr of transdermal fentanyl.

Moreover, more considerations need to be done:

- We use TTS-fentanyl to wean the patient from remifentanyl, a much more stronger opioid routinely used in Intensive Care Unit (ICU);
- Patients in ICU are strictly monitored 24 hours a day and mechanically ventilated, so the risks for respiratory depression is minimum;
- Remifentanyl is traditionally infused at rates that may vary from 0.0125 to 0.25 mcg/kg/min. Using tables available for opioid conversion, we can estimate that 300 mcg/hr of transdermal fentanyl corresponds to 180 mg/day of intravenous (IV) morphine and so 1,80 mg of remifentanyl. In a subject of 70 kg, 1,80 mg/day of remifentanyl correspond to 0,0178 mcg/kg/min of infusion rate, a very low dose for ICU standards (see APPENDIX 3).

1.4 EAdi and monitoring of the electrical activity of the diaphragm

Diaphragm dysfunction frequently develops in mechanically ventilated ICU patients and is associated with adverse clinical outcomes, including prolonged mechanical ventilation and mortality. Diaphragm electromyography (EMG) is a technique used to quantify breathing effort in ICU patients. A correlation has been reported between the electrical activity of the diaphragm (EAdi) and trans-diaphragmatic pressure (P_{di}) or esophageal pressure (P_{es}). The $P_{musc}/EAdi$ index (PEI), also known as neuromechanical efficiency, defined as the ratio of the change in airway pressure (ΔP_{aw}) to $\Delta EAdi$ during an end-expiratory occlusion ($PEI_{occl,paw}$), has been used to estimate the inspiratory effort breath by breath. This ratio describes how much pressure can be generated for each microvolt of EAdi signal, in other words, how efficient the diaphragm is in generating pressure for a certain amount of electrical activity (BECK et al. 2001; Bellani et al. 2013; Liu et al. 2010; Jansen et al. 2018). The proportionality between EAdi and the pressure developed by respiratory muscles (P_{musc}) is well described:

$$P_{musc_{EAdi}} = EAdi \cdot PEI_{occl,paw}$$

Bellani and coworkers demonstrated that $PEI_{occl,paw}$ is a good surrogate of the PEI measured during regular tidal ventilation (PEI_{dyn}), thus allowing a clinically valuable estimate of inspiratory effort without the need for P_{es} monitoring. Moreover, Bellani showed that $PEI_{occl,paw}$ is a good estimate of PEI_{dyn} but slightly overestimated probably because of the more favorable condition of the diaphragm in the absence of flow. They deduced that $PEI_{occl,paw}$ needs to be corrected by a factor of 1.25 (Bellani et al. 2013). It is, therefore, possible to obtain a continuous calculation of P_{musc} based on EAdi and $PEI_{occl,paw}$ without knowing the P_{es} value. From $P_{musc_{EAdi}}$ two commonly accepted indexes of inspiratory effort can be obtained: the maximal P_{musc} of the respiratory cycle and the pressure-time product (PTP_{EAdi} , the integral of $P_{musc_{EAdi}}$ during inspiration).

No data are available in the literature about the possibility of using TTS-fentanyl as an alternative

to intravenous opioids during the weaning phase from mechanical ventilation and the post-extubation period until the discharge from ICU to the ward. There is only a case-report documenting the use with success of TTS-fentanyl for a patient who developed central hyperventilation(Adachi et al. 2007).

Our hypothesis is that, due to the intrinsic pharmacokinetics and pharmacodynamic characteristics of TTS formulation of fentanyl, it can have a role in weaning the patient from intravenous opioids, such as remifentanyl, and mechanical ventilation, reducing the duration of MV itself. It can have also an impact on costs allowing the discharge to the ward of patients with an ongoing patch.

2. Study Objectives and Endpoints

2.1 Primary Objective

We aim to assess if a TTS fentanyl-based sedation protocol is at least non-inferior when compared to a totally intravenous remifentanyl infusion protocol. To do that, we will compare the global work of breathing (WOB) of the patients randomized to receive TTS-fentanyl vs. remifentanyl alone.

2.2 Primary Endpoint

To demonstrate that the area under the curve (AUC) of the work of breathing per minute (assessed at 1, 6, 12, 24 hours for the first day after randomization, and every 24 hours for the following days) in the intervention group is not higher than the control group. We will also analyze differences in work of breathing per breath, inspiratory effort, delta EAdi, plateau pressure, driving pressure, transpulmonary driving pressure, pulmonary compliance, P0.1, P/F ratio.

2.3 Secondary Objectives

Secondly, we will assess if a TTS fentanyl-based sedation protocol can have an impact on the duration of mechanical ventilation, as well the duration of continuous infusion of opioids, the length of stay in ICU and hospital compared to a totally intravenous remifentanyl infusion protocol.

2.4 Secondary Endpoints

We will analyze differences in respiratory rate, tidal volume, arterial blood pressure, heart rate, global duration of mechanical ventilation and intravenous remifentanyl infusion, length of stay in ICU and in hospital.

2.5 Safety Endpoints

Main safety endpoints will be hypercapnia ($\text{PaCO}_2 > 45$ mmHg), acidosis ($\text{pH} < 7.35$), hypotension ($\text{SBP} < 90$ mmHg), need for NMBA (neuromuscular blockade agents), need for vasopressors, episodes of $\text{ICP} > 20$ mmHg in neurological patients, need for a tracheostomy, infections.

3. Methods

3.1 Study Design

The aim is to perform a 2-arm, single-center, prospective randomized controlled trial. The duration of the study will be approximately one year, aiming to enroll 12 patients for each arm. An informed consent form will be obtained before randomization.

3.2 Study Population

Eligible patients will be selected from the population admitted to the adult ICU (a 20-beds unit), the post-operative ICU (a 13-beds unit), and the NeuroICU (a 10-beds unit).

3.3 Inclusion and Exclusion Criteria

3.3.1 Criteria for inclusion are:

- Age > 18 yo;
- Negative pregnancy test prior to inclusion in the study;
- The informed consent form needs to be signed and dated by the patient or a relative/legal guardian before of any procedure related to the study; if the patient is initially unable to sign the informed consent form, but later regains the ability to sign it, a new informed consent form will be given to the patient and must be signed and dated;
- Mechanically ventilated in Pressure Support Ventilation, according to the decision to the attending physician;
- A patient with prolonged weaning from the mechanical ventilator will be considered eligible. Prolonged weaning is defined as weaning that is still not terminated 7 days after the first separation attempt from the ventilator (by success or death).

A successful weaning is defined as:

1. For intubated patients: extubation without death or reintubation within 7 days after extubation (whether post-extubation noninvasive ventilation was used or not), or ICU discharge without invasive mechanical ventilation within 7 days, whichever comes first;
 2. For tracheostomized patients: spontaneous ventilation through tracheostomy without any mechanical ventilation during 7 consecutive days or ICU discharge with spontaneous breathing, whichever comes first (Béduneau et al. 2017);
- Analgesia provided by continuous infusion of remifentanil lasting five days or more and an intolerance to a dose reduction of 0.025 mcg/kg/min defined as the presence of at least one of the following criteria: RASS \geq 2, a respiratory rate \geq 35 breaths/minute, a PaCO₂ < 30 mmHg,

a heart rate > 120 bpm, a systolic blood pressure value > 160 mmHg or an increase of Visual Analogue Scale for pain assessment of ≥ 2 points.

3.3.2 Criteria for exclusion are:

- Hypersensitivity to the active substance or any of the excipients;
- Hepatic or renal impairment;
- Fever (body temperature ≥ 38 °C) or septic shock, hypothermia (body temperature < 35 °C) or presence of active surface cooling systems;
- Hypoxemic respiratory failure (P/F < 200 mmHg);
- Hypercapnic patients with a PaCO₂ > 45 mmHg;
- Hemodynamic instability requiring high doses of inotropes or vasopressors;
- Delirium state defined as RASS ≥ 3 and CAM-ICU positive;
- Any condition that may contraindicate the use of remifentanil or TTS-fentanyl;
- Patient admitted for postoperative monitoring after elective surgery;
- Patients with a BMI ≥ 35 ;
- Current enrollment or plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 30 days or 5 half-lives of the agent, prior to the baseline visit;
- EAdi catheter contraindicated.

4. Study Periods, Visits and Assessments

An overview of the study periods and “visits” is provided below.

4.1 Screening Period

The subject will be evaluated for eligibility for the study based on the inclusion and exclusion criteria. A pregnancy test for females in fertile age and an informed consent will be obtained from the subject or proxy, and/or a third party and signed by the investigator, prior to performing any assessment that is considered to be specifically mandated by the study.

Patients considered eligible for the study will be randomized in two arms. An EAdi Catheter, which is a standard nasogastric tube for enteral nutrition, will be positioned and connected to a mechanical ventilator provided with an EAdi module (Servo-U ventilator, Maquet). EAdi, flow, and Paw waveforms will be acquired from the Servo-U ventilator via a RS232 serial port connected to a laptop with dedicated software (SERVO Tracker SCI, version 1.0, Maquet Critical Care 2017). Baseline data will be collected before randomization.

4.2 Treatment Period

The treatment period starts immediately with the baseline assessments.

In Group 1, in which remifentanyl infusion is administered alone, the infusion rate will be increased or decreased according to the study protocol based on PaCO₂ value resulting from the Arterial Blood Gases sample (ABG) collected at each visit.

In Group 2, TTS-fentanyl will be administered with a starting dose of 50 mcg/hr simultaneously with the preexistent remifentanyl continue infusion. Remifentanyl infusion rate will be increased or decreased based on PaCO₂ value resulting from the Arterial Blood Gases sample (ABG) collected at each visit. After randomization, the TTS-fentanyl dose can be modified every 24 hours according to the study protocol to achieve the desired effect in terms of PaCO₂ value resulting from the Arterial Blood Gases sample (ABG) collected.

A priori we will not exceed 0,2 mcg/kg/min for remifentanyl infusion in both arms.

4.3.1 Visits

Visits will be performed at the baseline and every 4 hours for the first 24 hours, every 6 hours for day 2 and day 3.

At each visit we will record:

- An Arterial Blood Gases (ABG) sample will be collected and ABG parameters recorded (pH, PaCO₂, PaO₂, HCO₃⁻, Lactates, SaO₂);
- Glasgow Coma Scale, RASS (see APPENDIX 1-2), the dosage of remifentanyl and TTS-fentanyl;
- Respiratory parameters: Ventilation mode, Pressure Support, Respiratory Rate (RR), Tidal Volume (V_t), peep, FiO₂, EtCO₂, SpO₂; if patient is spontaneously breathing: FiO₂, RR, SpO₂.
- Hemodynamic parameters (Heart Rate, SBP/DBP/MAP, need for vasopressors, inotropes).

A baseline 1-hour recording of EAdi, flow, and Paw waveforms will be performed, as well as after 1, 6, 12, 24 for the first day from the time of randomization and every 24 hours for the following days until the end of the observation period for the primary endpoint. Each recording will last one hour for patients mechanically ventilated, 10 minutes for patients weaned from the mechanical ventilator.

Four different situations are possible:

- For patients connected to the mechanical ventilator in pressure support ventilation (PSV), we will perform an expiratory pause maneuver and an inspiratory pause maneuver (both lasting enough to have 2 or 3 spontaneous breaths) with an interval of one minute between each maneuver. The maneuvers will be performed after 30 and 60 minutes from the start of recording.
- If in the meantime the patient is weaned from the mechanical ventilator and spontaneously breathing through a tracheostomy, we will temporarily reconnect the patient to the mechanical ventilator, in PSV mode, with zero peep (ZEEP), we will perform an expiratory

pause maneuver and an inspiratory pause maneuver (both lasting enough to have 2 or 3 spontaneous breaths) with an interval of one minute between each maneuver. In these weaned patients, the maneuvers will be performed after 5 and 10 minutes from the start of recording that will last only 10 minutes;

- If in the meantime the patient is weaned from the mechanical ventilator, extubated, spontaneously breathing and able to cooperate, the patient will be asked to inspire in a close system connected to a pneumotachograph to estimate P_{aw} . The maneuver will be performed after 5 and 10 minutes from the start of recording that will last only 10 minutes;
- If in the meantime, the patient is weaned from the mechanical ventilator, extubated, spontaneously breathing, and unable to cooperate we will use as a surrogate the neuromechanical efficiency calculated when the patient was connected to the ventilator. The recording will last only 10 minutes.

We will calculate $PEI_{occl,paw}$, the $P_{musEAdi}$ waveform, and the two most validated indexes of inspiratory effort: ΔP_{mus} and the PTP_{EAdi} (a good indicator of the metabolic work of breathing). We will analyze the dynamic transpulmonary driving pressure, corresponding to the sum of the pressure support level and $P_{mus_{dyn}}$, and representing a surrogate of dynamic stress that takes into account the chest wall elastance. Moreover we will measure the plateau pressure, the positive end-expiratory pressure (PEEP), and we will calculate the driving pressure and the static compliance of the respiratory system.

4.3.2 Spontaneous Breathing Trial (SBT) and Extubation/Disconnection

When PaO_2/FiO_2 is no lower than 200 mm Hg at $PEEP \leq 8$ cmH₂O, the patient will be considered to have an acceptable gas exchange on 8-5 cmH₂O of PEEP and will be deemed capable to tolerate this setting.

A 30-120 minute spontaneous breathing trial (SBT) will be initiated as the following criteria are met and whether a patient tolerated fully assist ventilation with $PEEP \leq 8$ cmH₂O for at least 4 hours without experiencing hypoxemia ($SpO_2 < 88\%$ or $PaO_2/FiO_2 < 150$ mmHg):

- improvement or resolution of the underlying cause of acute respiratory failure;
- correction of arterial hypoxemia ($PaO_2 \geq 60$ mmHg at a $FiO_2 \leq 0.4$ with $PEEP \leq 8$ cmH₂O);
- absence of fever (≥ 38 °C) or sepsis;
- blood hemoglobin concentration of 7 g/dL or more;
- hemodynamic stability without cardiac ischemia or arrhythmias (norepinephrine < 0.1 gamma/kg/min).

Success of the spontaneous breathing trial will be defined as presence of the following criteria:

- respiratory rate < 35 /min;
- arterial oxygen saturation $\geq 90\%$;
- heart rate < 120 /min;

- systolic blood pressure > 90 and < 160 mmHg;
- adequate cough.

If the spontaneous breathing trial is successful, the patient will be extubated or disconnected from the mechanical ventilator if tracheostomized. In case of SBT failure, mechanical ventilation will be resumed (with any PEEP levels accepted, according to the strategies described above)

Data about extubation/deconnection will be collected immediately before extubation and 20 minutes following extubation. The need for a tracheostomy will be recorded in the CRF as well as the incidence of adverse events, i.e., the need for reintubation, infection rate, death. After the discharge from ICU, the enrolled patients will be followed until discharge from the hospital.

4.4 Observation period for the primary endpoint

This period covers the interval over which the subject may qualify for the primary endpoint of the study. It starts with the randomization and ends 72 hours after randomization. After this period the treatment duration will be dependent on the subject's clinical course and the investigator's judgment on the perceived need to continue the study drug. The use of TTS-fentanyl will not be allowed in remifentanyl alone group even after the end of the observation period for the primary outcome.

4.5 24-hour safety follow-up period

This period starts with the permanent discontinuation of the study drug (TTS-fentanyl) and ends 24 hours later. Subjects must not be discharged from the hospital until the end of this period.

New Adverse Events occurring in this period are recorded in the case report form (CRF).

4.6 End of Study (EOS) visit (individual subject)

This visit occurs at the discharge from the intensive care unit or in case of death after the observation period for the primary endpoint and is defined as the last visit performed by an individual subject for the study. This visit may occur earlier for subjects who prematurely withdraw from the study.

In this visit we will record:

- An Arterial Blood Gases (ABG) sample will be collected and ABG parameters recorded (pH, PaCO₂, PaO₂, HCO₃⁻, Lactates, SaO₂);
- Glasgow Coma Scale, RASS;
- Respiratory parameters: Ventilation mode, Pressure Support, Respiratory Rate, Tidal Volume, peep, FiO₂, EtCO₂; if patient is spontaneously breathing: FiO₂, RR, SpO₂;
- Hemodynamic parameters (Heart Rate, SBP/DBP/MAP);
- Data on the global duration of opioid therapy/length of stay (LOS) in hospital and ICU.

4.7 Last Visit Last Patient (LVLP)

This visit or time point occurs when the last subject randomized into the study completes his/her last visit

The overall study design is depicted in Figures 1, 2, 3, 4, and table 1.

5. Previous and Concomitant therapy

5.1 Definitions

For this study, a previous therapy is defined as any treatment for which the end date is prior to the signature of the informed consent form. A study-concomitant therapy is defined as any treatment that is ongoing or initiated after the signature of the informed consent form or initiated up to 24 hours post-study drug discontinuation. A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period until the time of permanent study drug discontinuation.

5.2 Allowed concomitant therapy

The usual standard of care for each patient is allowed except for those therapies listed in the “forbidden concomitant therapy” section and must be documented in the medical chart.

5.3 Forbidden concomitant therapy

The following medications/therapies are forbidden due to their potential to interfere with the evaluation of efficacy or safety, or due to the potential for a drug to drug interaction with study drug (TTS-fentanyl):

- Monoamine Oxidase Inhibitors (MAOI): TTS-fentanyl is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported. Therefore, TTS-fentanyl should not be used within 14 days after discontinuation of treatment with MAOIs;
- Serotonergic medicinal products: Co-administration of fentanyl with serotonergic medicinal products, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition;
- Concomitant use of mixed opioid agonists/antagonists: The concomitant use of buprenorphine, nalbuphine, or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonize the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid-dependent patients;
- The concomitant use of CYP3A4 inhibitors and inducers and TTS-fentanyl is not recommended because it can interfere with the drug concentrations and with the evaluation of efficacy or safety. The following substances may increase fentanyl concentrations and should be avoided: amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, nefazodone, ritonavir, verapamil,

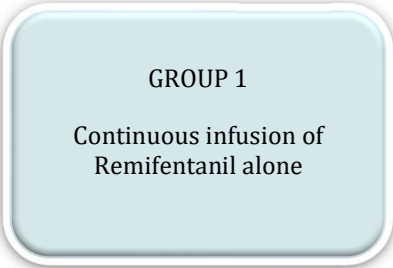
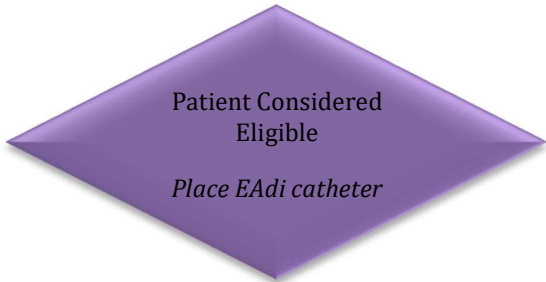
and voriconazole. The following substances may decrease fentanyl concentrations and should be avoided: carbamazepine, phenobarbital, phenytoin, and rifampicin;

- Techniques of haemofiltration and haemodiafiltration can interfere with fentanyl serum concentrations causing a potential bias in the study;
- Techniques of extracorporeal circulation can interfere with fentanyl serum concentrations causing a potential bias in the study;
- Noradrenaline infusion rates more or equal than 0.1 mcg/kg/min or Inotropes should be avoided as they can have an impact on fentanyl transdermal absorption altering microcirculation resulting in unpredictable fentanyl serum concentrations causing a potential bias in the study.

5.4 Reporting of previous/concomitant therapy in the CRF

All previous and study-concomitant therapies taken/administered less than or equal to 24 hours prior to randomization into the study will be recorded in the CRF. All medications administered randomization and up to 24 hours post-study drug discontinuation will also be recorded in the CRF. The generic name, start/end dates and times of administration, route, dose regimen, and indication will be recorded.

- Age > 18 yo
- Pregnancy test (-) if female in fertile age
 - Obtain Informed Consent
- Remifentanil infusion lasting > or = 5 days
 - On Pressure Support Ventilation



BASELINE VISIT

- ABG (pH, PaCO₂, PaO₂, HCO₃⁻, Lactates, SaO₂);
- GCS, RASS, the dosage of remifentanil;
- Respiratory parameters;
- Haemodynamic parameters;
- 1-hour recording of EAdi, flow and Paw

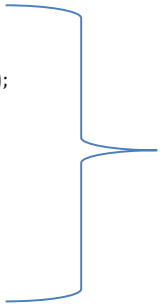


Fig 1. Screening Period

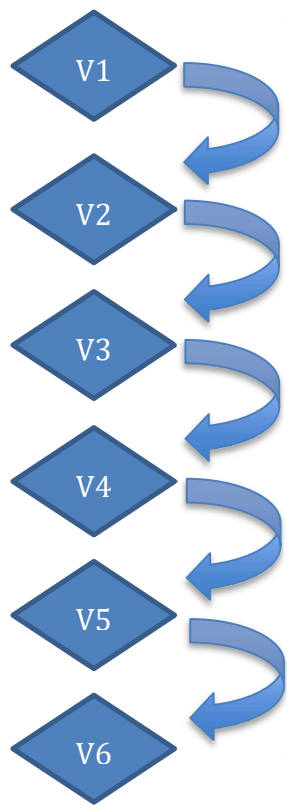
GROUP 1
Remifentanyl iv alone

At each visit we will record:

- An Arterial Blood Gases (ABG) sample will be collected
- Glasgow Coma Scale, RASS, the dosage of remifentanyl;
- Respiratory parameters: Ventilation mode, Pressure Support, Respiratory Rate, Tidal Volume, peep, FiO₂, EtCO₂, SpO₂; if spontaneously breathing: FiO₂, RR, SpO₂
- Haemodynamic parameters

EAdi, flow and Paw waveforms will be recorded 1, 6, 12, 24 hours from the time of randomization for day 1 and every 24 hours for the following days.

4 Hours

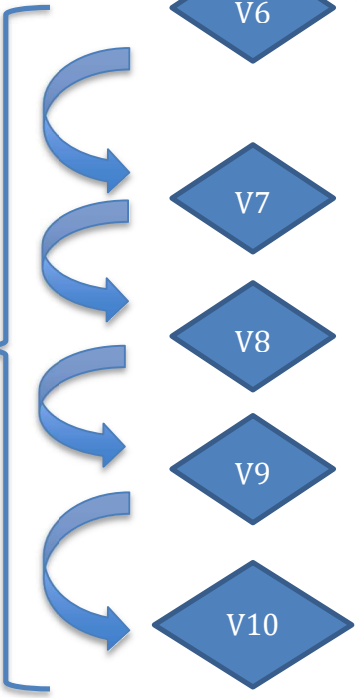


Day 1
Visits every 4 hours

- If PaCO₂ > 45 mmHg ↓ 0.025 mcg/kg/min
- If PaCO₂ 40-45 mmHg ↓ 0.0125 mcg/kg/min
- If PaCO₂ 35-40 mmHg ≈ no changes
- If PaCO₂ 30-35 mmHg ↑ 0.0125 mcg/kg/min
- If PaCO₂ < 30 mmHg ↑ 0.025 mcg/kg/min

Day 2 and 3
Visits every 6 hours

- If PaCO₂ > 45 mmHg ↓ 0.025 mcg/kg/min
- If PaCO₂ 30-45 mmHg ↓ 0.0125 mcg/kg/min
- If PaCO₂ < 30 mmHg ↑ 0.0125 mcg/kg/min



GROUP 2

Starts TTS fentanyl 50 mcg/hr and maintain remifentanyl iv

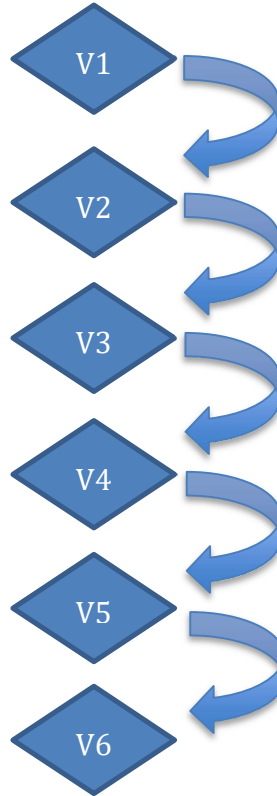
EVERY 24 HOURS

- If PaCO₂ >45 mmHg remove TTS-fentanyl 25 mcg/hr
- If PaCO₂ 35-45 mmHg don't add or remove tts fentanyl
- If PaCO₂ 30-35 mmHg add TTS-fentanyl 50 mcg/hr
- If PaCO₂ <30 mmHg add TTS-fentanyl 75 mcg/hr

At each visit we will record:

- An Arterial Blood Gases (ABG) sample will be collected
- Glasgow Coma Scale, RASS, the dosage of remifentanyl and TTS-fentanyl;
- Respiratory parameters: Ventilation mode, Pressure Support, Respiratory Rate, Tidal Volume, peep, FiO₂, EtCO₂, SpO₂; if spontaneously breathing: FiO₂, RR, SpO₂
- Haemodynamic parameters

4 Hours



Day 1

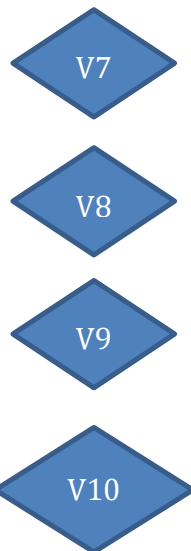
Visits every 4 hours

- If PaCO₂ >45 mmHg ↓0.025 mcg/kg/min
- If PaCO₂ 40-45 mmHg ↓0.0125 mcg/kg/min
- If PaCO₂ 35-40 mmHg ≈ no changes
- If PaCO₂ 30-35 mmHg ↑0.0125 mcg/kg/min
- If PaCO₂ <30 mmHg ↑0.025 mcg/kg/min

Day 2 and 3

Visits every 6 hours

- If PaCO₂ >45 mmHg ↓0.025 mcg/kg/min
- If PaCO₂ 30-45 mmHg ↓0.0125 mcg/kg/min
- If PaCO₂ <30 mmHg ↑0.0125 mcg/kg/min



EAdi, flow and Paw waveforms will be recorded 1, 6, 12, 24 hours from the time of randomization for day 1 and every 24 hours for the following days.

Figure 3. Treatment Period Group 2

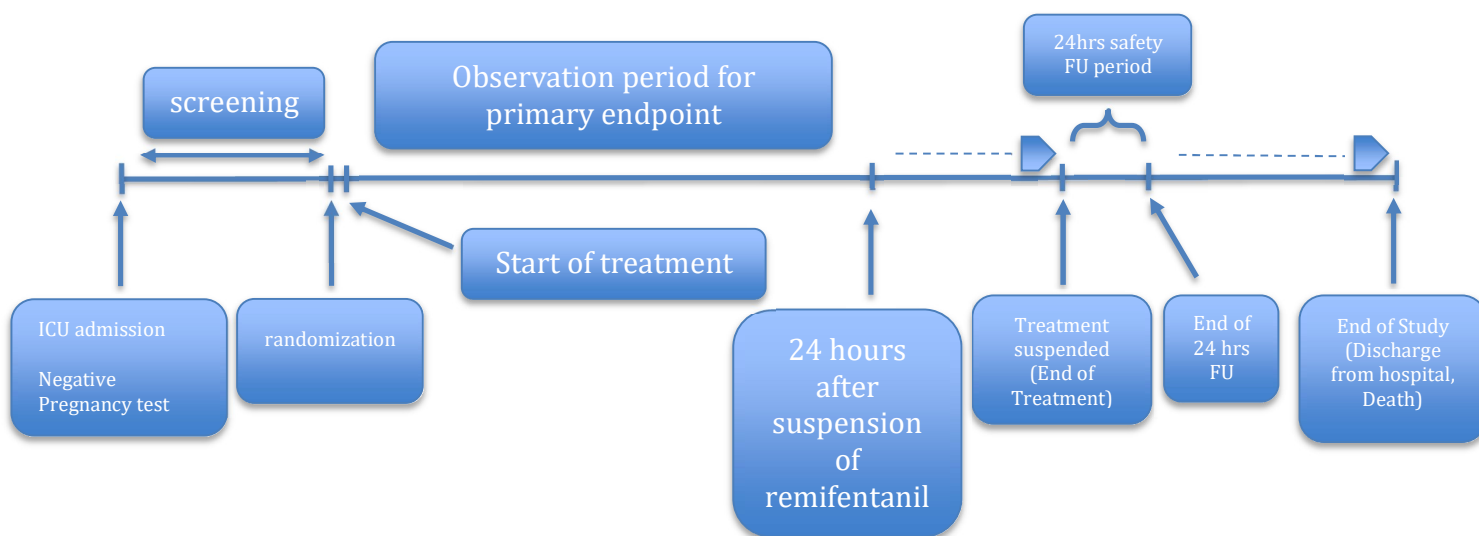


Figure 4. Study Design

Screening Period	Verify inclusion/exclusion Criteria, Obtain Pregnancy test and Informed consent
Patient Enrolled	Baseline: ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanyl at inclusion, 1-hour recording of EAdi, flow, and Paw
Treatment period	Randomization (group 1 remifentanyl alone, group 2 remifentanyl + TTS-fentanyl)
1 hour*	Recording of EAdi, flow, and Paw
4 hours* (Visit 1)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanyl and TTS-fentanyl
6 hours*	Recording of EAdi, flow, and Paw
8 hours* (visit 2)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanyl and TTS-fentanyl
12 hours* (visit 3)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanyl and TTS-fentanyl, Recording of EAdi, flow, and Paw

16 hours* (visit 4)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
20 hours* (visit 5)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
24 hours* (visit 6)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl, Recording of EAdi, flow, and Paw
30 hours* (visit 7)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
36 hours* (visit 8)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
42 hours* (visit 9)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
48 hours* (visit 10)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl, Recording of EAdi, flow, and Paw
54 hours* (visit 11)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
60 hours* (visit 12)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
66 hours* (visit 13)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl
72 hours* (visit 14)	ABG sample, respiratory and hemodynamic parameters, GCS, RASS, dosage of remifentanil and TTS-fentanyl, Recording of EAdi, flow, and Paw
End of observation period for the primary endpoint	72 hours after randomization

Treatment suspended	The treatment duration will be dependent on the subject's clinical course and the investigator's judgment on the perceived need to continue the study drug
Safety FU period	Permanent discontinuation of TTS-fentanyl: start of 24 hours of Safety Follow up Period (any adverse event will be recorded on the CRF)
End of Study Visit	This visit occurs at the discharge from the ICU or in case of death after the observation period for the primary endpoint ABG sample, respiratory and hemodynamic parameters, GCS, RASS, Data on the global duration of opioid therapy/length of stay (LOS) in hospital and ICU

*Hours from randomization

Table 1. Study visits and assessments

6. Statistical analysis

Distribution normality will be assessed with the Kolmogorov-Smirnov test. Continuous variables will be reported expressed as medians (interquartile ranges). Qualitative variables will be reported as frequencies.

Analysis of the primary efficacy criterion (AUC of the work of breathing) and other quantitative variables will be assessed with the Wilcoxon-Mann-Whitney sum of rank test. Categorical outcomes will be compared with the chi-square test, or Fisher's exact test, as appropriate: Cochran-Mantel-Haenszel statistics will be reported for all these results. Two-way analysis of variance (ANOVA) for repeated measures with Bonferroni correction will be used to determine the differences in work of breathing per breath, inspiratory effort, delta EAdi, plateau pressure, P 0.1 respiratory rate, tidal volume, arterial blood pressure, heart rate in the two groups. Comparisons between groups regarding these variables at each study time point will be performed with the Student's t-test or Mann-Whitney test, as appropriate. Mean difference and 95% confidence interval [CI95%] are reported for most significant results.

Two-tail p values ≤ 0.05 Will be considered significant. Statistical analysis will be performed with SPSS software package (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

6.1 Sample size calculation

As said previously, the primary endpoint is to demonstrate that the area under the curve (AUC) of the work of breathing per minute (assessed at 1, 6, 12, 24, 48, and 72 hours) in the intervention group is not higher than the control group. Data on the work of breathing of ICU patients undergoing mechanical ventilation while on remifentanyl continuous infusion are lacking. However, there are studies suggesting that a sample of 10 patients is adequate to draw significant conclusions on the physiological endpoints related to respiratory mechanics and work of breathing among patients with respiratory failure (Delorme et al. 2017; Lellouche et al. 2002; Prat et al. 2003; LHer et al. 2005). Thus, for this phase II, pilot, randomized trial, using a conservative approach and considering an attrition rate lower than 10%, we planned to enroll 12 patients per group, for a total sample of 24 patients in 12 months. Julius et al., in their study published on pharmaceutical statistics in 2005 confirmed that a minimum 12 subjects per group are enough for a pilot randomized trial (Julious et al. 2005).

7. Premature withdrawal from the study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die within the observation period for the primary endpoint, or are lost to follow up. If a subject withdraws consent, no further data will be collected in the CRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if he/she believes that continued participation in the study would be contrary to the best interests of the subject.

The reason for premature withdrawal from the study must be recorded in the CRF.

7.1 Premature termination or suspension of the study

The Sponsor has the right to close the study (or, if applicable, individual segments (e.g. treatment arms; dose steps; centers)) at any time, which may be due, but not limited to, the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example: Safety findings from this study (e.g. SAEs)
- If the study conduct (recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame and a proper quality status.

7.2 Medical care of subjects after withdrawal from the study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s)/medical care is necessary and available according to local regulations. Such care may include the use of drugs that were forbidden during concomitant study treatment administration.

8. Safety definitions and reporting requirements

8.1 Safety definitions

8.1.1 Definition of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the study, whether or not considered by the investigator as related to the study treatment.

AEs include

- Exacerbation of a pre-existing disease if considered medically relevant;
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition;
- Disease or medical condition detected or diagnosed during the study even though it may have been present before the start of the study;
- Continuous persistent disease or symptoms present at study start that worsen following the signing of the informed consent form;
- Laboratory test abnormalities if they represent a clinically significant finding (symptomatic or not), which was not present at study start or worsened during the course of the study as per investigator's judgment, or led to interruption or permanent discontinuation of study treatment.

8.1.2 Definition of adverse drug reaction (ADR)

Considering the new usage that is proposed in this study for TTS-fentanyl and that the therapeutic dose is not well established, all noxious and unintended responses to TTS-fentanyl related to any dose should be considered adverse drug reactions.

8.1.3 Definition of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least 1 of the following criteria:

- Fatal;
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe;
- Requiring prolongation of hospitalization;
- Resulting in persistent or significant disability or incapacity;
- Congenital anomaly or birth defect;
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered medically significant based upon appropriate medical judgment, as they may jeopardize the subject, and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

8.2 Reporting of adverse events

All AEs with an onset date and time from study drug initiation up to 24 hours after study treatment discontinuation (i.e., the 24-hour safety follow-up period) must be recorded on specific AE forms of the CRF. Those AEs occurring from the signature of the informed consent form until End of Study will also be recorded on an AE form in the CRF if they are believed to be related to a protocol-mandated procedure.

Information to be collected in an AE form in the CRF includes date and time of onset, action taken with the study treatment, outcome of AE, date of resolution (if applicable) and PI's assessment of seriousness and intensity, and relationship to study treatment, study design or protocol mandated procedures. For AEs related to cardiac rhythm abnormalities, additional ECG parameters may be collected.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE form. If the AE lessens in intensity, no change in the severity is required to be reported.

For AEs ongoing at the start of study treatment, the worsening of the AE after the start of study treatment will be recorded as a separate AE with the new intensity.

Follow-up information on any ongoing AEs obtained after the subject's EOS visit will not be collected in the CRF.

9. Risk-Benefit Assessment

In an ICU setting, in which patients are continuously monitored 24 hours a day and mechanically ventilated, it can be stated that the risks related to the use of TTS-fentanyl are few. There is obviously a consistent risk of developing an opioid addiction, already present using remifentanyl, that compared to fentanyl is stronger and short-acting. Respiratory depression is easily and early detected. On the other hand, an alternative and "needle-free" route of administration of an opioid,

fentanyl, that is different from a pharmacokinetic point of view if compared to remifentanyl, could help in IV opioids weaning, it can reduce the length of mechanical ventilation, and length of stay in ICU, decreasing the risks related to the stay in an ICU setting as infections rate and increases in costs. Moreover, TTS-fentanyl could theoretically be exported out from the ICU to the medical wards, allowing more gradual and physiological weaning from opioids.

10. Data handling

The investigator is responsible for ensuring the accuracy, completeness, and timely reporting of subject data. All source documents should be completed in a neat, legible manner to ensure accurate interpretation and traceability of the data. Data reported in the CRF derived from source documents must be consistent with the source documents.

The investigator must ensure that data confidentiality is maintained. On CRF or other documents, subjects must be identified only by a number and never by their name or initials, date of birth, hospital numbers, or any other personal identifier. The investigator must keep a subject identification code list at the site, showing the subject number, the subject's name, date of birth, and address or any other accepted identifiers. Documents identifying the subjects (e.g., signed informed consents) must be kept in strict confidence by the investigator.

10.1 Archiving

The Principal Investigator must ensure the archiving of the essential documents of the study as specified by the GCP and in compliance with the applicable legislation. The Principal Investigator or his/her delegates must adopt all the necessary measures to avoid accidental or premature destruction. Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital (25 years). Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

10.2 Direct access to original documents

The Principal Investigator and/or his delegates must allow the Regulatory Authorities and individuals delegated by the Independent Ethics Committee to have free access to and to conduct the relevant verification of all the original documentation of the study, including the informed consent forms signed by the patients enrolled into the study, the relevant patient files and/or out-patient files. Those individuals who are given free access to the documentation must take every reasonable precaution to keep the identity of the patients as reserved information, in accordance with applicable legislation.

10.3 Data Protection

We will follow Art. 13 GDPR (UE/2016/679) about normative regarding data protection.

11. Publication policies and communication of results

The scientific director of the study will undertake to draw up a final report and a scientific article and to make the results public at the end of the study. The data will be made public anonymously and presented as requested in an aggregate manner.

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APPENDIX 1. RASS SCORE

RASS score			CAM-ICU
Richmond Agitation & Sedation Scale			
Score	Description		
+4	Combative	Violent, immediate danger to staff	RASS ≥ -2 Proceed to CAM-ICU assessment
+3	Very agitated	Pulls at or removes tubes, aggressive	
+2	Agitated	Frequent non-purposeful movements, fights ventilator	
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous	
0	Alert & calm		
-1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 secs)	Voice
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 secs)	
-3	Moderate sedation	Movement or eye-opening to voice (no eye contact)	Touch
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	
-5	Un-rousable	No response to voice or physical stimulation	
			RASS < -2 STOP Recheck later

APPENDIX 2. GLASGOW COMA SCALE

Glasgow Coma Scale		
Response	Scale	Score
Eye Opening Response	Eyes open spontaneously	4 Points
	Eyes open to verbal command, speech, or shout	3 Points
	Eyes open to pain (not applied to face)	2 Points
	No eye opening	1 Point
Verbal Response	Oriented	5 Points
	Confused conversation, but able to answer questions	4 Points
	Inappropriate responses, words discernible	3 Points
	Incomprehensible sounds or speech	2 Points
	No verbal response	1 Point
Motor Response	Obeys commands for movement	6 Points
	Purposeful movement to painful stimulus	5 Points
	Withdraws from pain	4 Points
	Abnormal (spastic) flexion, decorticate posture	3 Points
	Extensor (rigid) response, decerebrate posture	2 Points
	No motor response	1 Point
Minor Brain Injury = 13-15 points; Moderate Brain Injury = 9-12 points; Severe Brain Injury = 3-8 points		

APPENDIX 3. TABLES OF OPIOID CONVERSION

- <https://opioidcalculator.practicalpainmanagement.com/conversion.php>
- Arnold R, Weissman DE. Calculating Opioid Dose Conversions, 2nd Edition. Fast Facts and Concepts. July 2005; 36. Available at:
http://www.eperc.mcw.edu/EPEC/FastFactsIndex/ff_036.htm.