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Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol

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ABSTRACT

Introduction: Acute pancreatitis (AP) is a common gastrointestinal disease that is associated with high morbidity and mortality in its most severe forms. Most patients with severe AP require intubation and invasive mechanical ventilation, frequently for more than 7 days, which is associated with worst outcome. Recent increasing evidence from preclinical and clinical studies support beneficial effects of epidural analgesia (EA) in AP, such as increased gut barrier function and splanchnic, pancreatic, renal perfusion, decreased liver damage and inflammatory response, and reduced mortality. Because recent studies suggest that EA might be a safe procedure in the critically ill, we sought to determine whether EA reduced AP-associated respiratory failure and other major clinical outcomes in patients with AP.

Methods and analysis: The Epidural Analgesia for Pancreatitis (EPIPAN) trial is an investigator-initiated prospective multicentre randomised controlled two-arm trial with assessor-blinded outcome assessment. The EPIPAN trial randomises 148 patients with AP requiring admission to an intensive care unit (ICU) to receive EA (with patient-controlled epidural administration of ropivacaine and sufentanil) combined with standard care based on current recommendations on the treatment of AP (interventional group), or standard care alone (reference group). The primary outcome is the number of ventilator-free days at day 30. Secondary outcomes include main complications of AP (e.g., organ failure and mortality, among others), levels of biological markers of systemic inflammation, epithelial lung injury, renal failure, and healthcare-associated costs.

Ethics and dissemination: The study project has been approved by the appropriate ethics committee (*CPP Sud-Est VI*). Informed consent is required. If combined application of EA and standard care proves superior to standard care alone in patients with AP in the ICU, the use of EA may become standard practice in experienced centres, thereby decreasing potential complications related to AP and its burden in critically ill patients.

Trial registration number: NCT02126332.

(Abstract word count: 295)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomised controlled trial to investigate the effects of epidural analgesia on organ failure, mortality and clinical outcomes in critically ill patients with acute pancreatitis enrolled in a total of 11 French, Belgian and Swiss intensive care units.
- Although previous studies have reported good feasibility and safety of epidural analgesia in the intensive care unit setting, this trial will provide valuable data on its safety in critically ill patients.
- In addition, our study includes the constitution of a biobank of plasma and urine sampled over the first week after inclusion, in order to assess the effects of EA on biological markers of inflammation, lung injury and renal failure.
- One limitation of the study is that the physicians are aware of the group of inclusion. However, assessors of study outcomes and biological measures are independent observers who do not know the group of inclusion.
- Another limitation may include poor generalisability of results from this study to unexperienced centres, because EA is a technique that is restricted to experienced anaesthesiologists and intensivists.

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines (supporting file in the appendix).[1]

Acute pancreatitis (AP) is one of the most frequent gastrointestinal diseases, whose incidence in the US reaches 35 per 100,000 population annually. In 2009, AP was responsible for 275,000 hospital admissions in the USA, with a total cost of over US $2,5 billion.[2,3]. AP develops when intracellular protective mechanisms to prevent trypsinogen activation or reduce trypsin activity are overwhelmed[4]. The initiating event may be any insult to the acinar cell that impairs the secretion of zymogen granules, such as alcohol abuse or gallstone migration into the common bile duct. Once the process of cellular injury is initiated, cellular membrane trafficking becomes chaotic, leading to the release of proinflammatory mediators (tumour necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8). These mediators participate to an increase in pancreatic vascular permeability that subsequently favours hemorrhage, oedema and eventually pancreatic necrosis. As these mediators are excreted into the circulation, systemic complications can arise, such as bacteraemia due to gut flora translocation, acute respiratory distress syndrome (ARDS)[5], pleural effusions, gastrointestinal hemorrhage and renal failure.[4,6–9]

The revised Atlanta classification addresses the clinical course and severity of the disease.[10] AP may be divided into two forms, interstitial oedematous pancreatitis, during the first week, and necrotising pancreatitis during a later phase (after 7 days). In approximately 80% of patients, the severity of AP is rather mild and resolves without serious morbidity. However, in up to 20% of patients, AP presents in a more severe form requiring admission to the intensive care unit (ICU) due to persistent organ failure.[10,11] Mortality

rate can reach 20-40% in severe AP because of multiorgan failure (MOF) and pancreatic necrosis.[2,12]

The amplifying effects of inflammatory and oxidative impairment often lead to severe AP-induced complications, which are often regarded as hallmarks of severe AP and herald poor outcome. In a recent French observational study of ICU patients with severe AP, 58% of patients developed acute respiratory failure requiring intubation and invasive mechanical ventilation (MV) (mean duration 15 days, standard deviation (SD) 17 days), and such patients had higher mortality rates than those who were not intubated (34% vs 1.4%).[12] Since respiratory failure is the main cause of death in patients with severe AP, more work is needed for us to prevent and treat AP-associated respiratory failure. Despite recent substantial improvements in the multidisciplinary management of AP (e.g., with regards to fluid therapy, intensive care management, prevention of infectious complications, nutritional support, biliary tract management or necrotising pancreatitis management), the prognosis of severe AP remains poor in patients who develop acute respiratory failure requiring intubation and invasive respiratory support.[4,10,13] Of notes, available therapeutic approaches do not have a direct action on the pancreas itself but aim to attenuate the process of MOF present in the severe form of AP, and no causal treatment has been developed yet.

Epidural analgesia (EA) is one of the most widely and versatile utilized neural deafferentation technique. It is used for analgesia during the perioperative period, but also for obstetrics labour and trauma as well as in the treatment of acute, chronic and cancer-related pain.[14,15] Its objective is not only to block noxious afferent stimuli, but also to induce bilateral selective thoracic sympathetic blockade. In addition to analgesia itself, modulatory effects of thoracic EA could improve organ perfusion with reduced complications in the perioperative period, thus possibly decreasing postoperative complications, shortening hospital stay and improving survival.[15–17]

EA has not yet been extensively assessed in the ICU setting in general, and in critically ill patients with severe AP in particular. Several studies suggest that thoracic EA might be a safe procedure in centres comprising anaesthesiologists with expertise in EA, and thoracic EA has already been used for years to treat pain during AP in critically ill patients in some centres.[18–20] In addition, recent animal studies suggest that thoracic EA may decrease the severity of AP, with reduced respiratory, thromboembolic and abdominal complications.[21–23] EA further decreased the severity of metabolic acidosis and tissue injury in animals, thus preventing the progression from oedematous to necrotising AP.[24] EA may also restore pancreatic hypoperfusion induced by AP through blood flow redistribution from splanchnic to non-perfused pancreatic regions,[25,26] and a recent clinical study suggests that EA could increase pancreatic arterial perfusion and improve clinical outcome in patients with AP.[20] Findings from other experimental studies also support beneficial effects of EA in severe AP, such as increased gut barrier function and renal perfusion, decreased liver damage and inflammatory response, and reduced mortality.[23,25,27,28]

Despite such promising findings from preclinical studies, the effects of thoracic EA on major clinical outcomes have never been specifically assessed and its benefit in critically ill patients with AP remains uncertain.

Objectives

Primary objective

To determine whether the use of thoracic EA combined to standard care is more effective at increasing ventilator-free days (VFD) at day 30 over standard care alone in critically ill patients with AP. The goal of the EPIPAN trial is therefore to test the impact of

thoracic EA on respiratory failure, with the hypothesis that EA could influence survival and/or the need for invasive MV and/or its duration when invasive MV is required.

Secondary objectives

To determine whether in comparison to standard care alone, application of thoracic EA combined with standard care could improve survival, decrease major complications of AP (including sepsis, organ failure), AP-related costs, the need for medical, surgical and radiological interventions, and impact biological markers of systemic inflammation, lung injury and renal failure.

Trial design

The Epidural Analgesia for Pancreatitis (EPIPAN) trial is an investigator-initiated, open-labelled, multicentre randomised controlled two-arm trial.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the EPIPAN trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The EPIPAN study is undergoing in a total of 11 mixed medical and surgical ICUs in France (Clermont-Ferrand (2 ICUs), Montpellier, Nîmes, Cannes, Nancy, Nice, Annecy, Le-Puy-en-Velay), Belgium (Brussels) and Switzerland (Geneva).

Eligibility criteria

Inclusion criteria

Patients must be admitted to the ICU for AP, whatever the precise reason for admission (e.g., pain management, organ failure).

Exclusion criteria

Patients fulfilling one or more of the following criteria are not included: age <18 years, pregnant or breastfeeding woman, protected person, known or suspected hypersensitivity to study drugs (ropivacaine and sufentanil are administered via the epidural catheter in the EA group, and epidural clonidine can be used as an iterative rescue treatment to achieve analgesia goals), and absolute contraindications to the placement of an epidural catheter: prothrombin time < 60 %, platelet count < 75 G/L^{-1}, curative anticoagulation unless it can be interrupted for at least 8 hours, local infection, active infection of the central nervous system, suspected or confirmed intracranial hypertension, history of back surgery including a dural space procedure, refractory circulatory shock despite adequate resuscitation.

Interventions

Patients eligible for inclusion will be randomly assigned to the interventional group (EA combined with standard care) or to the reference group (standard care alone). Because the trial was primarily designed as a pragmatic trial, all patients will be managed by attending physicians as recommended in recent consensual guidelines on the management of severe AP (standard care): early enteral nutrition when possible, resuscitation measures to correct hypovolemia, maintenance of electrolyte balance, correction of acidosis, early diagnosis and supportive treatment of complications [10,13,29–31] Analgesia goals are the same in both groups, with regular evaluation of pain, at least every 4 hours. In conscious and communicating patients, a visual analogue score (VAS) for pain below 40/100 is targeted and

a behavioural pain scale (BPS) of 3-4 is targeted in non-communicating patients.[32,33] In both groups, a stepped multimodal approach to pain management will be applied based on routine protocols from each participating centre, and combining opioid, non-opioid +/- adjuvant drugs administered through the oral, enteral and/or intravenous routes, as recommended by the World Health Organization's pain relief ladder.[13,34]

The interventional group consists in applying standard care combined with thoracic EA through an epidural catheter placed in an intervertebral space between the 6th and the 9th thoracic vertebra, and administration of a mixed solution of ropivacaine (2 mg.mL^{-1}) and sufentanil (0.5 µg.mL^{-1}), for at least 72 hours. EA will be provided using a patient-controlled epidural analgesia (PCEA) device, with continuous infusion rate of 5 to 15 mL.h^{-1} and *bolus* of 3 to 10 mL every 10 minutes maximum. If the patient is not able to self-administer EA, nurses are encouraged to administer *boli* to achieve analgesia goals if necessary. In addition, iterative epidural administrations of clonidine (1 µg.kg^{-1}) may be used by attending physicians to achieve analgesia goals.[35] The drugs used during EA in this trial will be provided in an unblinded manner by the department of Pharmacy at Clermont-Ferrand university hospital to all participating centres.

Because of insufficient evidence regarding the optimal duration of EA in ICU patients,[18,19,36] total duration of EA will be chosen by participating physicians for each patient, given that it has been administered for at least 72 hours. Weaning of EA and removal of epidural catheter will be conducted accordingly to recommendations and routine protocols from each participating centre.

Outcomes

Primary outcome measures

The primary outcome variable is the number of VFD at day 30, defined as the number of days from day 0 (inclusion) to day 30 after inclusion on which a patient is able to breathe without invasive assistance. A difference in VFD can reflect a difference in mortality, ventilator days, or both.

Secondary outcome measures

Secondary outcomes are the need for and duration of invasive and/or noninvasive MV at day 30, the incidence of AP-related complications at day 30 (death, organ failure, severe sepsis, septic shock,[37] ARDS,[5] acute respiratory failure, abdominal compartment syndrome, intra- or extra-abdominal sepsis, pancreatic necrosis or abscess (infected or not), hemodynamic failure requiring vasopressor therapy, acute kidney injury,[38] requirement for renal replacement therapy, infected intra-abdominal abscesses requiring drainage (radiological, endoscopic or surgical), intolerance to enteral feeding), analgesia scores (VAS, BPS), need for sedation (drugs, doses, level of sedation using the Richmond Agitation-Sedation Scale)[39,40], lengths of stay in ICU and in hospital, the need for ICU readmission within 30 days after inclusion, levels on days 0, 2 and 7 after inclusion of biological markers (as assessed in *duplicate* using commercially available kits) of systemic inflammation (plasma levels of IL-6)[41], lung epithelial injury (plasma levels of the soluble form of the receptor for advanced glycation end-products, sRAGE)[42,43] and acute kidney injury (plasma levels of neutrophil gelatinase-associated lipocalin, NGAL,[44,45], urine levels of tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein7 (IGFBP-7)[46]), and healthcare-related costs at day 30.

The need for antibiotic or antifungal therapy will be assessed. Any minor or major complication that could be attributable to EA and/or epidural catheter will also be rigorously

documented.

Participant timeline

The participant timeline is described in table 1.

Recruitment

Patients are expected to be included during a 3-year inclusion period that has begun in June 2014.

2013-2014: Protocol, approvals from the ethics committee (*CPP Sud-Est VI*) and the French Medicine agency (*Agence Nationale de Sécurité du Médicament,* ANSM); trial tool development (case report form, randomisation system).

2014-2017: Inclusion of patients.

2017: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

A prolongation of the inclusion period will be requested if needed based on observed inclusion rate.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

An electronic, centralised web-based data management system will be used for randomisation (TENALEA, FormsVision BV, the Netherlands). To minimise selection bias, randomisation will be performed in strict sequence, that is, when a subject is confirmed as eligible for randomisation, the next unassigned randomisation number in sequence will be given. Randomisation will be stratified and minimised based on the recruiting centre, the

duration of symptoms (either above or below 48 hours from first symptoms, e.g. abdominal pain, to inclusion) and severity of AP as assessed by the modified Marshall scoring system for organ dysfunction.[10,47] This scoring system has the merit of simplicity, universal applicability across international centres, and the ability to stratify disease severity easily and objectively based on respiratory, renal and/or hemodynamic failure.[48] A score of 2 or more usually defines the presence of organ failure, and 3 strata of severity (scores equal to 0, 1-2 or 3-4) are used to stratify randomisation on the degree of organ failure in the EPIPAN trial.

Blinding

This is an open-label, unblinded trial for patients and physicians in charge of the patients, because of the nature itself of the intervention (placement and maintenance of EA through an epidural catheter). Although some systems may be proposed to ensure, at least, partial blinding to the patient when EA is assessed,[49] such systems were not included in the trial design in order to ensure better feasibility among multiple centres. However, assessors of clinical and biological data in charge of statistical analyses and outcome assessment will be masked as to the subjects' assigned group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Study data are prospectively collected and managed by trained research coordinators and/or investigators from each participating centre, using REDCap electronic data capture tools hosted at Clermont-Ferrand university hospital.[50] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking

data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

The following data are collected and registered at ICU admission and upon inclusion: baseline demographics and characteristics (age, sex, weight, height, body temperature, delay between the onset of AP and ICU admission/study inclusion, comorbidities and coexisting conditions), baseline severity of illness (modified Marshall scoring system, Simplified Acute Physiologic Score (SAPS) II, Sequential Organ Failure Assessment (SOFA)), usual clinical and biological variables that are measured in critically ill patients, organ failure and treatments. From inclusion to day 30 will be assessed: survival status, main complications of AP (e.g., organ failure, sepsis), the need for therapeutic interventions (such as surgery or endoscopic manoeuvres, MV (either invasive or noninvasive), vasopressor support, continuous renal replacement therapy and/or antibiotic therapy), duration of MV if required, length of stay in the ICU/hospital. Biological samples will be collected in each participating centre, prior to shipment of all samples to the department of Medical Biochemistry and Molecular Biology at Clermont-Ferrand university hospital for blinded measurements.

Statistical methods

Sample size Estimation

According to previous studies from the literature,[12,20] we have estimated that a sample size of n = 74 patients per group would provide 80% statistical power to detect an absolute between-group difference of 7 days (with a SD of ± 15) in the primary outcome, i.e. in the number of VFD at day 30 after randomization (expected number of VFD at day 30: 20 ± 15 vs. 13 ± 15), for a two-sided type I error of 5%.

Given theoretical concerns related to possible adverse effects of EA in ICU patients, an interim safety analysis will be performed after data for 74 patients are collected. The independent Data and Safety Monitoring Board (DSMB) will recommend that the trial be stopped if it is found that the conduct of the trial compromises patient safety (a between-group difference in mortality or VFD at day 30).

Statistical analysis

A predefined statistical analysis plan will be followed. Statistical analyses will be conducted using Stata software (version 14, StataCorp, College Station, USA). A two-sided p-value of less than 0.05 will be considered to indicate statistical significance.

Concerning the primary outcome, the comparison between interventional and reference groups will be analysed using Student's t-test or Mann-Whitney's test if assumptions of t-test are not met. Normality will be studied by the Shapiro-Wilk test and homoscedasticity using the Fisher-Snedecor test. Results will be expressed as effect-sizes and 95% confidence intervals. Intention to treat (ITT) analysis of data from all randomised patients (except patients who withdraw their consent and those who do not meet the inclusion criteria), including those from the interventional group who do not receive EA for at least 72 hours, will be considered for the primary analysis. Then, the analysis of the primary outcome will be completed by multivariate analysis using a linear mixed model to take into account: (1) fixed effects covariates determined according to univariate results and to clinical relevance (duration of symptoms (either above or below 48 hours from first symptoms, e.g. abdominal pain, to inclusion) and severity of AP as assessed by the modified Marshall scoring system for organ dysfunction) and (2) centre as random-effects (to measure between and within centre variability). The normality of residuals will be studied as described previously. Results will be expressed as regression coefficients and 95% confidence intervals.

Other continuous endpoints (e.g., level of sedation using the Richmond Agitation-Sedation Scale, analgesia scores, doses of drugs, length of stay in ICU/hospital, levels and kinetics of biological markers, duration of MV, and healthcare-related costs at day 30) will be analysed in the same way.

Categorical parameters (death, organ failure, severe sepsis, septic shock, ARDS, the need for MV, acute respiratory failure, abdominal compartment syndrome, intra- or extra-abdominal sepsis, pancreas necrosis (infected or not) as assessed by computed tomography, hemodynamic failure requiring vasopressor support, acute kidney injury, the need for renal replacement therapy, intra-abdominal collection requiring radiological, surgical or endoscopic drainage) will be analysed using Chi-squared or Fisher's exact tests for univariate analysis and generalized linear mixed model (logistic for dichotomous dependent endpoint or Poisson if more appropriate) for multivariate analysis. Type I error will be adjusted using the Hochberg method if appropriate. Results will be expressed as relative risks and 95% confidence intervals. These data will also be analysed as censored data, when appropriate; survival analyses will be performed with the Kaplan-Meier estimator and differences between groups will then be assessed using the log-rank test. The assumption of log-linearity of risk and the proportional hazards will be checked beforehand. Results will be expressed as hazard ratios and 95% confidence intervals. The tolerance of enteral nutrition and/or the incidence of signs of gastrointestinal intolerance (nausea, vomiting, and ileus) will be analysed similarly.

Longitudinal analyses of repeated measures (levels on days 0, 2 and 7 after inclusion of biological markers of systemic inflammation, lung epithelial injury and acute kidney injury will be studied using random-effect models (linear or generalized linear), to take into account patients as random-effect (slope and intercept), nestled in centre random-effect.

According to clinical relevance and to CONSORT recommendations, subgroup analyses depending on the presence or the absence of epidural analgesia will be proposed after the study of subgroup x randomisation group interaction in regression models.

Per-protocol analyses will also be conducted after intention-to-treat analysis is performed. Results from per-protocol analyses will be compared to those from intention-to-treat analyses. A particular focus will be given to safety and patients who are lost to follow-up. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). According to this study, the most appropriate approach to the imputation of missing data will be proposed (maximum bias (e.g., last observation carried forward vs. baseline observation carried forward) or estimation proposed by Verbeke and Molenberghs for repeated data).

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICU attended formal training sessions on the study protocol and data collection.

The physicians, clinical research nurses and/or clinical research assistants are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data. Patients who are admitted to the ICU with AP but who are not included, and the reasons why they are not included, will be recorded anonymously into a screening log in each centre.

Data monitoring and quality control will be conducted at least annually in all participating centres by official representatives from the study promoter, i.e. from the department of Clinical Research and Innovation at Clermont-Ferrand university hospital.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with EA.

Given potential theoretical concerns related to possible adverse effects of EA in ICU patients, an interim safety analysis will be performed after data for 74 patients have been obtained using the Lan and DeMets method (East software, Cytel Inc., Cambridge, MA, USA). The independent Data and Safety Monitoring Board (DSMB) will recommend that the trial be stopped if it is found that the conduct of the trial compromises patient safety (a between-group difference in mortality or VFD at day 30).

All adverse events thought to be related to the trial will be reported to the trial coordinating centre. According to the French Public Health Code, all suspected unexpected serious adverse events will be reported to the ANSM. In addition, this information will be submitted to the DSMB.

Auditing

An independent DSMB, composed of three experts (Prs. Hervé Dupont, Thomas Lescot and Philippe Montravers) will monitor the safety of the trial. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

ETHICS AND DISSEMINATION

Research ethics approval

The EPIPAN study is conducted in accordance with the declaration of Helsinki and was registered at http://www.clinicaltrial.gov on April 11, 2014 with trial identification number NCT02126332. The trial was approved by the ethics committee *CPP Sud-Est VI* in June, 2014 (approval number AU1090) and ANSM (approval number 131557A-32) in January, 2014. Approvals from appropriate authorities were also obtained for Belgian and Swiss centres. Any change to eligibility criteria, outcomes, analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

Consent or assent

Three methods of consent will be used, as required by the Institutional Review Board in accordance with the 2013 Declaration of Helsinki. Whenever possible, the patient will be included after written informed consent. However, the patient may be unable to provide informed consent because of the severity of illness (e.g., altered mental status, use of sedation). These patients will be included after written informed consent is provided by the next of kin, or using an emergency procedure (investigator signature, countersigned by an independent physician) if the next of kin is not present. When available, and as soon as possible after recovery, patients will be retrospectively asked for written consent to continue the trial.

Confidentiality

Data will be handled in a confidential and anonymous manner, according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Clermont-Ferrand university hospital, Clermont-Ferrand, France. There is no industry support or involvement in the trial.

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Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

Severe acute pancreatitis requiring ICU admission is associated with high morbidity and mortality, especially in patients who need intubation and invasive ventilation.[10,12]

Optimising the management of critically ill patients with AP is therefore of particular importance, especially in those with, or at risk of, acute respiratory failure requiring intubation/prolonged ventilation, death, or both. However, and despite recent improvement in ICU practice in general, current guidelines on the management of severe AP only include supportive measures such as early enteral nutrition, hemodynamic resuscitation, maintenance of electrolyte balance, correction of acidosis, and early diagnosis and treatment of complications (e.g., with appropriate use of anti-infectious drugs, radiologic drainage, endoscopic manoeuvres and/or elective surgery in selected patients).[10,13,29–31]

EA is primarily an analgesic technique that is used by anaesthesiologists to treat pain in the perioperative period, for obstetrical analgesia and after severe chest trauma.[51] There has been recent interest in the use EA as a therapy for AP, and growing evidence from experimental studies now support beneficial effects of EA that include augmented ileal mucosal capillary perfusion, restored pancreatic microcirculation, increased gut barrier function and renal perfusion, decreased severity and improved survival.[21–23,25,27,28,52]. However, only one small recent randomised pilot study in 35 patients with AP was found to translate such promising preclinical findings into the clinical settings.[20] In this study, the median duration of EA was 5.7 days, and no complications of the epidural procedure were reported; an improvement in perfusion of the pancreas was observed in 43% of measurements in the EA group versus 7% in the control group (P=0.0025), but although analgesia was better when EA was used, there was no significant between-group differences in other clinical outcomes (e.g., the need for necrosectomy, length of stay in hospital and mortality), probably due to a lack of statistical power.[20] The EPIPAN trial is the first randomised controlled study powered to investigate the effectiveness of thoracic EA combined with standard care on major clinical outcomes in critically ill patients with EA, with specific emphasis on respiratory outcomes and survival.[21]

This study may have some limitations. First, no strict definition for severe AP is used to enrol patients. Instead, all patients admitted to the ICU with AP is eligible whatever the precise reason for admission (e.g., pain management, development of organ failure). However, we believe that randomisation, as stratified on modified Marshall scoring system (thus distinguishing patients with absent, moderate and severe organ failure), among other parameters, should ensure similar distribution of the severity of AP in both arms. Second, we acknowledge that the EPIPAN trial does not include precise (sub)protocols addressing every single aspect of the management of patients with AP (e.g., enteral feeding, its initiation, route of administration and dose), because it was believed that it would have hamper inclusions of patient and the feasibility of this pragmatic study. Instead, current guidelines for the management of AP are actively encouraged among study participants.[10,13,29–31] Although the implementation of consensual recommendations will not be specifically assessed while the study is still ongoing, and as it may impact the findings and their interpretation, adherence of physicians from participating centres to these guidelines will be analysed after study completion. Third, this trial, whatever its results, will not address the question of the selection of patients with AP who may best benefit of EA. However, analyses of clinical and biological subphenotypes of patients included in the trial, and their responses to EA, should possibly inform on how to better select patients for future studies. Fourth, another limitation may include the limited generalizability of the results obtained from this study because EA is a technique that is restricted to experienced anaesthesiologists and intensivists. Finally, some could highlight potential risks associated with EA in critically ill patients with hyperinflammatory conditions such as AP[36,53,54], although previous studies suggest good feasibility and safety of EA in this setting. Findings from the EPIPAN trial will undoubtedly provide new data on both the efficacy and the safety of EA during clinical AP.

This study also has several strengths. First, it is to our knowledge the largest randomised controlled trial in critically ill patients with AP. Even in case of "negative" results, data from this trial will contribute to a better understanding of the characteristics, management and prognosis of ICU patients with AP. Second, it is the first trial powered to specifically assess the effects of EA on major patient outcomes such as respiratory outcomes and 30-day mortality. In addition, other strengths are the inclusions performed around the clock, nights and weekend included as a routine clinical practice. Third, this study includes the constitution of a biobank of plasma and urine sampled over the first week after inclusion, in order to assess biological markers of inflammation, lung injury and renal failure and the effects of EA on such markers. Finally, and despite an open-label design, one strength of the study is that final assessors of clinical and biological data who will be in charge of statistical analyses and outcome assessment, remain masked as to the subjects' assigned group, thus limiting bias.

In conclusion, the EPIPAN trial is an investigator-initiated pragmatic multicentre randomised controlled trial powered to test the hypothesis that adding thoracic EA to standard care in comparison to standard care alone may improve respiratory outcomes, i.e. increase the number of ventilator-free days at day 30, in critically ill patients with AP. The EPIPAN trial will also assess the effects of combined EA and standard care on main complications of AP and other major patient outcomes.

AUTHORS CONTRIBUTIONS TO THE STUDY

SB is involved in the conception, hypotheses delineation, preparation and design of the study, in writing the article and in its revision prior to submission.

BP is involved in the conception, hypotheses delineation, preparation and design of the study and of statistical analyses, in writing the article and in its revision prior to submission.

EC is involved in the preparation and design of the study, in writing the article and in its revision prior to submission.

EI is involved in the conception, hypotheses delineation, preparation and design of the study, in writing the article and in its revision prior to submission.

LR is involved in the preparation and design of the study and of biological analyses, and in the revision of this manuscript prior to submission.

LB is involved in the preparation of the study, in the preparation of drugs used in this study and in the revision of this manuscript prior to submission.

LB is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

CH is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

SJ is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

JYL is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

RC is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

PMB is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

PFL is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

PG is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

PED is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

EE is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

AS is involved in the conception, preparation and design of the study, and in the revision of this manuscript prior to submission.

DM is involved in the preparation and design of the study, in writing the article and in its revision prior to submission.

VS is involved in the preparation and design of the study and of biological analyses, and in the revision of this manuscript prior to submission.

JMC is involved in the conception, hypotheses delineation, preparation and design of the study, in writing the article and in its revision prior to submission.

MJ is involved in the conception, hypotheses delineation, preparation and design of the study and of statistical analyses, in writing the article and in its revision prior to submission. MJ takes responsibility for the content of the manuscript.

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FIGURE LEGENDS

FIGURE 1. CONSORT diagram of the EPIPAN trial illustrating the randomisation and flow of patients in the study.

TABLE

	Inclusion (day 0)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 15	Day 30
Informed consent	X									
Eligibility: check inclusion and exclusion criteria	X									
Randomisation	X									
Filling of case report forms (including data on EA in the interventional group)	X	X	X	X	X	X	X	X	X	X
Sampling of blood and urine specimens	X		X					X		
Complications of acute pancreatitis and survival status									X	X
End of study										X

Table 1. Participant timeline

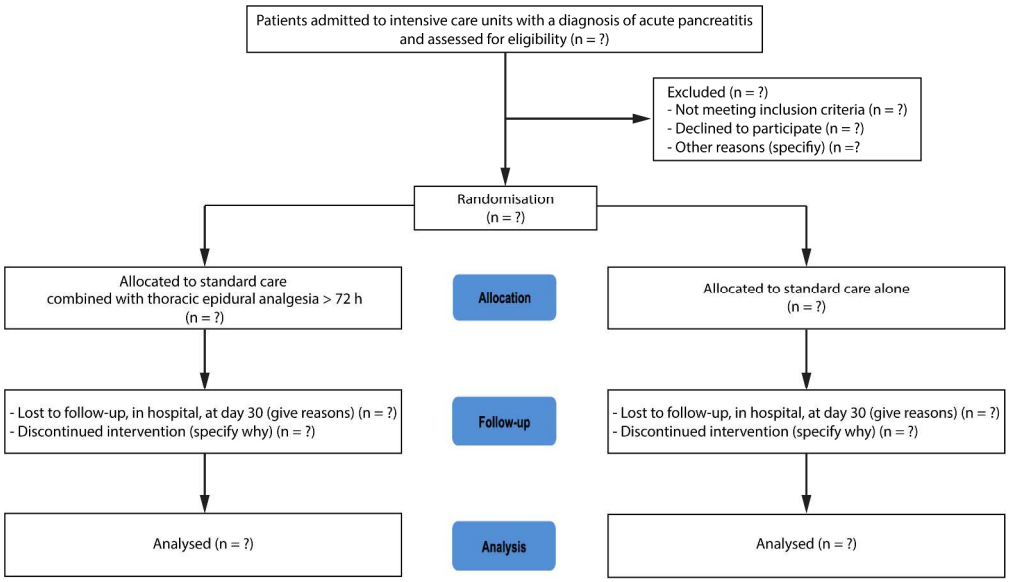

FIGURE 1. CONSORT diagram of the EPIPAN trial illustrating the randomisation and flow of patients in the study.

275x157mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **– PAGE 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **– PAGES 6 and 21**
	2b	All items from the World Health Organization Trial Registration Data Set **– PAGE 21**
Protocol version	3	Date and version identifier **– PAGE 21**
Funding	4	Sources and types of financial, material, and other support **– PAGES 22-23**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **– PAGES 1, 2 and 27**
	5b	Name and contact information for the trial sponsor **– PAGES 1 and 22**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **– PAGES 22-23**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **– PAGES 20-21**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **– PAGES 7-8-9**
	6b	Explanation for choice of comparators **– PAGES 8-9**
Objectives	7	Specific objectives or hypotheses **– PAGES 9-10**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **– PAGE 10**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **– PAGE 11**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **– PAGE 11**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **– PAGES 11-12-13**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **– PAGES 21-22**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **– PAGES 12-25-26**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **– PAGES 11-12-13**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **– PAGES 13-14**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **– PAGES 14 and Table 1**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **– PAGE 14**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **– PAGES 14-15**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **– PAGE 16**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **– PAGE 16**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **– PAGE 16**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **– PAGE 16**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **– PAGE 16**

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **– PAGE 17**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **– PAGE 17**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **– PAGE 17**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **– PAGES 18-19**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **– PAGES 18-19**

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **– PAGES 18-19**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **– PAGES 21-22**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **– PAGES 18 and 21**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **– PAGES 21-22**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **– PAGES 21-22**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **– PAGE 23**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **– PAGE 23**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **– PAGE 23**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **– PAGE 23**

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **– PAGES 23-24**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **– PAGE 24**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **– PAGE 24**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **– PAGE 23**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **– PAGE 24**
	31b	Authorship eligibility guidelines and any intended use of professional writers **– PAGE 24**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **– PAGE 24**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **– Appendix**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **– Table 1**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol

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Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol

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ARTICLE FOCUS

Acute pancreatitis (AP) is a major gastrointestinal disease that is associated with high mortality rates in its most severe forms. Recent preclinical and clinical data suggest that epidural analgesia (EA), a technique primarily aimed at decreasing pain, might improve clinical outcome through anti-inflammatory effects or enhanced splanchnic and pancreatic blood flow.

We therefore designed a prospective multicentre randomised controlled trial to study the impact of EA on patient outcome after AP, as assessed by ventilator-free days at day 30, serving as a composite surrogate for death, respiratory failure requiring invasive mechanical ventilation and duration of invasive mechanical ventilation when needed.

KEY MESSAGES

To our knowledge, this large ongoing prospective multicentre randomised controlled trial is the first trial aimed at assessing the effects of EA on major clinical outcomes in critically ill patients with AP.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This is the first randomised controlled trial to investigate the effects of EA on organ failure, mortality and clinical outcomes in critically ill patients with AP enrolled in a total of 11 French, Belgian and Swiss intensive care units.

Other strengths are the inclusions performed around the clock, nights and weekend included as a routine clinical practice.

In addition, our study includes the constitution of a biobank of plasma and urine sampled over the first week after inclusion, in order to assess the effects of EA on biological markers of inflammation, lung injury and renal failure.

One limitation of the study is that the physicians are aware of the group of inclusion. However, assessors of study outcomes and biological measures are independent observers who do not know the group of inclusion.

Another limitation may include poor generalisability of results from this study to unexperienced centres, because EA is a technique that is restricted to experienced anaesthesiologists and intensivists.

Finally, some could highlight potential risks associated with EA in critically ill patients with hyperinflammatory conditions such as AP, although previous studies have reported good feasibility and safety of EA in this setting. This trial will provide additional data on the safety of EA in ICU patients.

ABSTRACT

Introduction: Acute pancreatitis (AP) is associated with high morbidity and mortality in its most severe forms. Most patients with severe AP require intubation and invasive mechanical ventilation, frequently for more than 7 days, which is associated with worst outcome. Recent increasing evidence from preclinical and clinical studies support beneficial effects of epidural analgesia (EA) in AP, such as increased gut barrier function and splanchnic, pancreatic, renal perfusion, decreased liver damage and inflammatory response, and reduced mortality. Because recent studies suggest that EA might be a safe procedure in the critically ill, we sought to determine whether EA reduced AP-associated respiratory failure and other major clinical outcomes in patients with AP.

Methods and analysis: The Epidural Analgesia for Pancreatitis (EPIPAN) trial is an investigator-initiated prospective multicentre randomised controlled two-arm trial with assessor-blinded outcome assessment. The EPIPAN trial randomises 148 patients with AP requiring admission to an intensive care unit (ICU) to receive EA (with patient-controlled epidural administration of ropivacaine and sufentanil) combined with standard care based on current recommendations on the treatment of AP (interventional group), or standard care alone (reference group). The primary outcome is the number of ventilator-free days at day 30. Secondary outcomes include main complications of AP (e.g., organ failure and mortality, among others), levels of biological markers of systemic inflammation, epithelial lung injury, renal failure, and healthcare-associated costs.

Ethics and dissemination: The study was approved by the appropriate ethics committee (*CPP Sud-Est VI*). Informed consent is required. If combined application of EA and standard care proves superior to standard care alone in patients with AP in the ICU, the use of EA may become standard practice in experienced centres, thereby decreasing potential complications

related to AP and its burden in critically ill patients. The results will be disseminated in a peer-reviewed journal.

Trial registration number: NCT02126332.

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INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines (supporting file in the appendix).[1]

Acute pancreatitis (AP) is one of the most frequent gastrointestinal diseases, whose incidence in the US reaches 35 per 100,000 population annually. In 2009, AP was responsible for 275,000 hospital admissions in the USA, with a total cost of over US $2,5 billion.[2,3]. AP develops when intracellular protective mechanisms to prevent trypsinogen activation or reduce trypsin activity are overwhelmed[4]. The initiating event may be any insult to the acinar cell that impairs the secretion of zymogen granules, such as alcohol abuse or gallstone migration into the common bile duct. Once the process of cellular injury is initiated, cellular membrane trafficking becomes chaotic, leading to the release of proinflammatory mediators (tumour necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8). These mediators participate to an increase in pancreatic vascular permeability that subsequently favours hemorrhage, oedema and eventually pancreatic necrosis. As these mediators are excreted into the circulation, systemic complications can arise, such as bacteraemia due to gut flora translocation, acute respiratory distress syndrome (ARDS)[5], pleural effusions, gastrointestinal hemorrhage and renal failure.[4,6–9]

The revised Atlanta classification addresses the clinical course and severity of the disease.[10] AP may be divided into two forms, interstitial oedematous pancreatitis, during the first week, and necrotising pancreatitis during a later phase (after 7 days). In approximately 80% of patients, the severity of AP is rather mild and resolves without serious morbidity. However, in up to 20% of patients, AP presents in a more severe form requiring admission to the intensive care unit (ICU) due to persistent organ failure.[10,11] Mortality

rate can reach 20-40% in severe AP because of multiorgan failure (MOF) and pancreatic necrosis.[2,12]

The amplifying effects of inflammatory and oxidative impairment often lead to severe AP-induced complications, which are often regarded as hallmarks of severe AP and herald poor outcome. In a recent French observational study of ICU patients with severe AP, 58% of patients developed acute respiratory failure requiring intubation and invasive mechanical ventilation (MV) (mean duration 15 days, standard deviation (SD) 17 days), and such patients had higher mortality rates than those who were not intubated (34% vs 1.4%).[12] Since respiratory failure is the main cause of death in patients with severe AP, more work is needed for us to prevent and treat AP-associated respiratory failure. Despite recent substantial improvements in the multidisciplinary management of AP (e.g., with regards to fluid therapy, intensive care management, prevention of infectious complications, nutritional support, biliary tract management or necrotising pancreatitis management), the prognosis of severe AP remains poor in patients who develop acute respiratory failure requiring intubation and invasive respiratory support.[4,10,13] Of notes, available therapeutic approaches do not have a direct action on the pancreas itself but aim to attenuate the process of MOF present in the severe form of AP, and no causal treatment has been developed yet.

Epidural analgesia (EA) is one of the most widely utilized neural deafferentation technique. It is used for analgesia during the perioperative period, but also for obstetrics labour and trauma as well as in the treatment of acute, chronic and cancer-related pain.[14,15] Its objective is not only to block noxious afferent stimuli, but also to induce bilateral selective thoracic sympathetic blockade. In addition to analgesia itself, modulatory effects of thoracic EA could improve organ perfusion with reduced complications in the perioperative period, thus possibly decreasing postoperative complications, shortening hospital stay and improving survival.[15–17]

EA has not yet been extensively assessed in the ICU setting in general, and in critically ill patients with severe AP in particular. Several studies suggest that thoracic EA might be a safe procedure in centres comprising anaesthesiologists with expertise in EA, and thoracic EA has already been used for years to treat pain during AP in critically ill patients in some centres.[18–20] In addition, recent animal studies suggest that thoracic EA may decrease the severity of AP, with reduced respiratory, thromboembolic and abdominal complications.[21–23] EA further decreased the severity of metabolic acidosis and tissue injury in animals, thus preventing the progression from oedematous to necrotising AP.[24] EA may also restore pancreatic hypoperfusion induced by AP through blood flow redistribution from splanchnic to non-perfused pancreatic regions,[25,26] and a recent clinical study suggests that EA could increase pancreatic arterial perfusion and improve clinical outcome in patients with AP.[20] Findings from other experimental studies also support beneficial effects of EA in severe AP, such as increased gut barrier function and renal perfusion, decreased liver damage and inflammatory response, and reduced mortality.[23,25,27,28]

Despite such promising findings from preclinical studies, the effects of thoracic EA on major clinical outcomes have never been specifically assessed and its benefit in critically ill patients with AP remains uncertain.

Objectives

Primary objective

To determine whether the use of thoracic EA combined to standard care is more effective at increasing ventilator-free days (VFD) at day 30 over standard care alone in critically ill patients with AP. The goal of the EPIPAN trial is therefore to test the impact of

thoracic EA on respiratory failure, with the hypothesis that EA could influence survival and/or the need for invasive MV and/or its duration when invasive MV is required.

Secondary objectives

To determine whether in comparison to standard care alone, application of thoracic EA combined with standard care could improve survival, decrease major complications of AP (including sepsis, organ failure), AP-related costs, the need for medical, surgical and radiological interventions, and impact biological markers of systemic inflammation, lung injury and renal failure.

Trial design

The Epidural Analgesia for Pancreatitis (EPIPAN) trial is an investigator-initiated, open-labelled, multicentre randomised controlled two-arm trial.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the EPIPAN trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The EPIPAN study is undergoing in a total of 11 mixed medical and surgical ICUs in France (Clermont-Ferrand (2 ICUs), Montpellier, Nîmes, Cannes, Nancy, Nice, Annecy, Le-Puy-en-Velay), Belgium (Brussels) and Switzerland (Geneva).

Eligibility criteria

Inclusion criteria

Patients must be admitted to the ICU for AP, whatever the precise reason for admission (e.g., pain management, organ failure).

Exclusion criteria

Patients fulfilling one or more of the following criteria are not included: age <18 years, pregnant or breastfeeding woman, protected person, known or suspected hypersensitivity to study drugs (ropivacaine and sufentanil are administered via the epidural catheter in the EA group, and epidural clonidine can be used as an iterative rescue treatment to achieve analgesia goals), and absolute contraindications to the placement of an epidural catheter: prothrombin time < 60 %, platelet count < 75 G/L^{-1}, curative anticoagulation unless it can be interrupted for at least 8 hours, local infection, active infection of the central nervous system, suspected or confirmed intracranial hypertension, history of back surgery including a dural space procedure, refractory circulatory shock despite adequate resuscitation.

Interventions

Patients eligible for inclusion will be randomly assigned to the interventional group (EA combined with standard care) or to the reference group (standard care alone). Because the trial was primarily designed as a pragmatic trial, all patients will be managed by attending physicians as recommended in recent consensual guidelines on the management of severe AP (standard care): early enteral nutrition when possible, resuscitation measures to correct hypovolemia, maintenance of electrolyte balance, correction of acidosis, early diagnosis and supportive treatment of complications.[10,13,29–31] In particular, criteria for intubation are based on current recommendations and include any of the following major clinical events:

respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, massive aspiration, persistent inability to clear respiratory secretions, heart rate of less than 50/min with loss of alertness, and severe hemodynamic instability without response to fluid and vasoactive drugs. When invasive mechanical ventilation is needed, the use of a low-tidal-volume protective ventilatory strategy and recommendations on weaning from mechanical ventilation are strongly encouraged at each participating centre.[32,33] Analgesia goals are the same in both groups, with regular evaluation of pain, at least every 4 hours. In conscious and communicating patients, a visual analogue score (VAS) for pain below 40/100 is targeted and a behavioural pain scale (BPS) of 3-4 is targeted in non-communicating patients.[34,35] In both groups, a stepped multimodal approach to pain management will be applied based on routine protocols from each participating centre, and combining opioid, non-opioid +/- adjuvant drugs administered through the oral, enteral and/or intravenous routes, as recommended by the World Health Organization's pain relief ladder.[13,36]

The interventional group consists in applying standard care combined with thoracic EA through an epidural catheter placed in an intervertebral space between the 6^{th} and the 9^{th} thoracic vertebra, and administration of a mixed solution of ropivacaine (2 $mg.mL^{-1}$) and sufentanil (0.5 $\mu g.mL^{-1}$), for at least 72 hours. In the study protocol, there is no strict time interval between ICU admission, enrolment in the study and placement of the epidural catheter. EA will be provided using a patient-controlled epidural analgesia (PCEA) device, with continuous infusion rate of 5 to 15 $mL.h^{-1}$ and *bolus* of 3 to 10 mL every 10 minutes maximum. If the patient is not able to self-administer EA, nurses are encouraged to administer *boli* to achieve analgesia goals if necessary, e.g. prior to possibly painful nursing procedures. In addition, iterative epidural administrations of clonidine (1 $\mu g.kg^{-1}$) may be used by attending physicians to achieve analgesia goals.[37] The drugs used during EA in

this trial will be provided in an unblinded manner by the department of Pharmacy at Clermont-Ferrand university hospital to all participating centres.

Because of insufficient evidence regarding the optimal duration of EA in ICU patients,[18,19,38] total duration of EA will be chosen by participating physicians for each patient, given that it has been administered for at least 72 hours. Weaning of EA and removal of epidural catheter will be conducted accordingly to recommendations and routine protocols from each participating centre.

Outcomes

Primary outcome measures

The primary outcome variable is the number of VFD at day 30, defined as the number of days from day 0 (inclusion) to day 30 after inclusion on which a patient is able to breathe without invasive assistance. A difference in VFD can reflect a difference in mortality, ventilator days, or both.

Secondary outcome measures

Secondary outcomes are the need for and duration of invasive and/or noninvasive MV at day 30, the incidence of AP-related complications at day 30 (death, organ failure, severe sepsis, septic shock,[32] ARDS,[5] acute respiratory failure, abdominal compartment syndrome, intra- or extra-abdominal sepsis, pancreatic necrosis or abscess (infected or not), hemodynamic failure requiring vasopressor therapy, acute kidney injury,[39] requirement for renal replacement therapy, infected intra-abdominal abscesses requiring drainage (radiological, endoscopic or surgical), intolerance to enteral feeding), analgesia scores (VAS, BPS), need for sedation (drugs, doses, level of sedation using the Richmond Agitation-Sedation Scale)[40,41], lengths of stay in ICU and in hospital, the need for ICU readmission

within 30 days after inclusion, levels on days 0, 2 and 7 after inclusion of biological markers (as assessed in *duplicate* using commercially available kits) of systemic inflammation (plasma levels of IL-6)[42], lung epithelial injury (plasma levels of the soluble form of the receptor for advanced glycation end-products, sRAGE)[43,44] and acute kidney injury (plasma levels of neutrophil gelatinase-associated lipocalin, NGAL,[45,46], urine levels of tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein7 (IGFBP-7)[47]), and healthcare-related costs at day 30. The need for antibiotic or antifungal therapy will be assessed. Any minor or major complication (e.g., epidural hematoma or infection) that could be attributable to EA and/or epidural catheter will also be rigorously documented.

Participant timeline

The participant timeline is described in table 1.

Recruitment

Patients are expected to be included during a 3-year inclusion period that has begun in June 2014. This duration was estimated based on the number of admissions for AP at each participating centre during a 5-year period (2009-2014).

2013-2014: Protocol, approvals from the ethics committee (*CPP Sud-Est VI*) and the French Medicine agency (*Agence Nationale de Sécurité du Médicament,* ANSM); trial tool development (case report form, randomisation system).

2014-2017: Inclusion of patients.

2017: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

A prolongation of the inclusion period will be requested if needed based on observed inclusion rate.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

An electronic, centralised web-based data management system will be used for randomisation (TENALEA, FormsVision BV, the Netherlands). To minimise selection bias, randomisation will be performed in strict sequence, that is, when a subject is confirmed as eligible for randomisation, the next unassigned randomisation number in sequence will be given by the TENALEA system. Randomisation will be stratified and minimised based on the recruiting centre, the duration of symptoms (either above or below 48 hours from first symptoms, e.g. abdominal pain, to inclusion) and severity of AP as assessed by the modified Marshall scoring system for organ dysfunction.[10,48] This scoring system has the merit of simplicity, universal applicability across international centres, and the ability to stratify disease severity easily and objectively based on respiratory, renal and/or hemodynamic failure.[49] A score of 2 or more usually defines the presence of organ failure, and 3 strata of severity (scores equal to 0, 1-2 or 3-4) are used to stratify randomisation on the degree of organ failure in the EPIPAN trial.

Blinding

This is an open-label, unblinded trial for patients and physicians in charge of the patients, because of the nature itself of the intervention (placement and maintenance of EA through an epidural catheter). Although some systems may be proposed to ensure, at least,

partial blinding to the patient when EA is assessed,[50] such systems were not included in the trial design in order to ensure better feasibility among multiple centres. However, assessors of clinical and biological data in charge of statistical analyses and outcome assessment will be masked as to the subjects' assigned group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Study data are prospectively collected and managed by trained research coordinators and/or investigators from each participating centre, using REDCap electronic data capture tools hosted at Clermont-Ferrand university hospital.[51] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

The following data are collected and registered at ICU admission and upon inclusion: baseline demographics and characteristics (age, sex, weight, height, body temperature, delay between the onset of AP and ICU admission/study inclusion, comorbidities and coexisting conditions), baseline severity of illness (modified Marshall scoring system, Simplified Acute Physiologic Score (SAPS) II, Sequential Organ Failure Assessment (SOFA)), usual clinical and biological variables that are measured in critically ill patients, organ failure and treatments. From inclusion to day 30 will be assessed: survival status, main complications of AP (e.g., organ failure, sepsis), the need for therapeutic interventions (such as surgery or

endoscopic manoeuvres, MV (either invasive or noninvasive), vasopressor support, continuous renal replacement therapy and/or antibiotic therapy), duration of MV if required, length of stay in the ICU/hospital. Biological samples will be collected in each participating centre, prior to shipment of all samples to the department of Medical Biochemistry and Molecular Biology at Clermont-Ferrand university hospital for blinded measurements.

Statistical methods

Sample size Estimation

According to previous studies from the literature,[12] we have estimated that a sample size of n = 74 patients per group would provide 80% statistical power to detect an absolute between-group difference of 7 days (with a SD of ± 15) in the primary outcome, i.e. in the number of VFD at day 30 after randomization (expected number of VFD at day 30: 20 ± 15 vs. 13 ± 15), for a two-sided type I error of 5%.

Given theoretical concerns related to possible adverse effects of EA in ICU patients, an interim safety analysis will be performed after data for 74 patients are collected. The independent Data and Safety Monitoring Board (DSMB) will recommend that the trial be stopped if it is found that the conduct of the trial compromises patient safety (a between-group difference in mortality or VFD at day 30).

Statistical analysis

A predefined statistical analysis plan will be followed. Statistical analyses will be conducted using Stata software (version 14, StataCorp, College Station, USA). A two-sided p-value of less than 0.05 will be considered to indicate statistical significance.

Concerning the primary outcome, the comparison between interventional and reference groups will be analysed using Student's t-test or Mann-Whitney's test if

assumptions of t-test are not met. Normality will be studied by the Shapiro-Wilk test and homoscedasticity using the Fisher-Snedecor test. Results will be expressed as effect-sizes and 95% confidence intervals. Intention to treat (ITT) analysis of data from all randomised patients (except patients who withdraw their consent and those who do not meet the inclusion criteria), including those from the interventional group who do not receive EA for at least 72 hours, will be considered for the primary analysis. Then, the analysis of the primary outcome will be completed by multivariate analysis using a linear mixed model to take into account: (1) fixed effects covariates determined according to univariate results and to clinical relevance (duration of symptoms (either above or below 48 hours from first symptoms, e.g. abdominal pain, to inclusion) and severity of AP as assessed by the modified Marshall scoring system for organ dysfunction) and (2) centre as random-effects (to measure between and within centre variability). The normality of residuals will be studied as described previously. Results will be expressed as regression coefficients and 95% confidence intervals. Other continuous endpoints (e.g., level of sedation using the Richmond Agitation-Sedation Scale, analgesia scores, doses of drugs, length of stay in ICU/hospital, levels and kinetics of biological markers, duration of MV, and healthcare-related costs at day 30) will be analysed in the same way.

Categorical parameters (death, organ failure, severe sepsis, septic shock, ARDS, the need for MV, acute respiratory failure, abdominal compartment syndrome, intra- or extra-abdominal sepsis, pancreas necrosis (infected or not) as assessed by computed tomography, hemodynamic failure requiring vasopressor support, acute kidney injury, the need for renal replacement therapy, intra-abdominal collection requiring radiological, surgical or endoscopic drainage) will be analysed using Chi-squared or Fisher's exact tests for univariate analysis and generalized linear mixed model (logistic for dichotomous dependent endpoint or Poisson if more appropriate) for multivariate analysis. Type I error will be adjusted using the

Hochberg method if appropriate. Results will be expressed as relative risks and 95% confidence intervals. These data will also be analysed as censored data, when appropriate; survival analyses will be performed with the Kaplan-Meier estimator and differences between groups will then be assessed using the log-rank test. The assumption of log-linearity of risk and the proportional hazards will be checked beforehand. Results will be expressed as hazard ratios and 95% confidence intervals. The tolerance of enteral nutrition and/or the incidence of signs of gastrointestinal intolerance (nausea, vomiting, and ileus) will be analysed similarly.

Longitudinal analyses of repeated measures (levels on days 0, 2 and 7 after inclusion of biological markers of systemic inflammation, lung epithelial injury and acute kidney injury will be studied using random-effect models (linear or generalized linear), to take into account patients as random-effect (slope and intercept), nestled in centre random-effect.

According to clinical relevance and to CONSORT recommendations, subgroup analyses depending on the presence or the absence of epidural analgesia will be proposed after the study of subgroup x randomisation group interaction in regression models.

Per-protocol analyses will also be conducted after intention-to-treat analysis is performed. Results from per-protocol analyses will be compared to those from intention-to-treat analyses. A particular focus will be given to safety and patients who are lost to follow-up. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). According to this study, the most appropriate approach to the imputation of missing data will be proposed (maximum bias (e.g., last observation carried forward vs. baseline observation carried forward) or estimation proposed by Verbeke and Molenberghs for repeated data).

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICU attended formal training sessions on the study protocol and data collection.

The physicians, clinical research nurses and/or clinical research assistants are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data. Patients who are admitted to the ICU with AP but who are not included, and the reasons why they are not included, will be recorded anonymously into a screening log in each centre.

Data monitoring and quality control will be conducted at least annually in all participating centres by official representatives from the study promoter, i.e. from the department of Clinical Research and Innovation at Clermont-Ferrand university hospital.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with EA.

Given potential theoretical concerns related to possible adverse effects of EA in ICU patients, an interim safety analysis will be performed after data for 74 patients have been obtained using the Lan and DeMets method (East software, Cytel Inc., Cambridge, MA, USA). The independent Data and Safety Monitoring Board (DSMB) will recommend that the trial be stopped if it is found that the conduct of the trial compromises patient safety (a between-group difference in mortality or VFD at day 30).

All adverse events thought to be related to the trial will be reported to the trial coordinating centre. According to the French Public Health Code, all suspected unexpected

serious adverse events will be reported to the ANSM. In addition, this information will be submitted to the DSMB.

Auditing

An independent DSMB, composed of three experts (Prs. Hervé Dupont, Thomas Lescot and Philippe Montravers) will monitor the safety of the trial. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

ETHICS AND DISSEMINATION

Research ethics approval

The EPIPAN study is conducted in accordance with the declaration of Helsinki and was registered at http://www.clinicaltrial.gov on April 11, 2014 with trial identification number NCT02126332. The trial was approved by the ethics committee *CPP Sud-Est VI* in June, 2014 (approval number AU1090) and ANSM (approval number 131557A-32) in January, 2014. Approvals from appropriate authorities were also obtained for Belgian and Swiss centres. Any change to eligibility criteria, outcomes, analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

Consent or assent

Three methods of consent will be used, as required by the Institutional Review Board in accordance with the 2013 Declaration of Helsinki. Whenever possible, the patient will be included after written informed consent. However, the patient may be unable to provide informed consent because of the severity of illness (e.g., altered mental status, use of sedation). These patients will be included after written informed consent is provided by the next of kin, or using an emergency procedure (investigator signature, countersigned by an independent physician) if the next of kin is not present. When available, and as soon as possible after recovery, patients will be retrospectively asked for written consent to continue the trial.

Confidentiality

Data will be handled in a confidential and anonymous manner, according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Clermont-Ferrand university hospital, Clermont-Ferrand, France. There is no industry support or involvement in the trial. The principal investigators have no financial or other competing interests.

Funding

This trial is supported by grants from the *Société Française d'Anesthésie et de Réanimation* (*Contrat de Recherche* SFAR 2015) and from Clermont-Ferrand university

hospital (*Appel d'Offre Interne* 2014, CHU Clermont-Ferrand). The funders have no influence in the study design, conduct, and analysis or in the preparation of this article.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

Severe acute pancreatitis requiring ICU admission is associated with high morbidity and mortality, especially in patients who need intubation and invasive ventilation.[10,12] Optimising the management of critically ill patients with AP is therefore of particular importance, especially in those with, or at risk of, acute respiratory failure requiring intubation/prolonged ventilation, death, or both. However, and despite recent improvement in ICU practice in general, current guidelines on the management of severe AP only include supportive measures such as early enteral nutrition, hemodynamic resuscitation, maintenance of electrolyte balance, correction of acidosis, and early diagnosis and treatment of complications (e.g., with appropriate use of anti-infectious drugs, radiologic drainage, endoscopic manoeuvres and/or elective surgery in selected patients).[10,13,29–31]

EA is primarily an analgesic technique that is used by anaesthesiologists to treat pain in the perioperative period, for obstetrical analgesia and after severe chest trauma.[52] There has been recent interest in the use EA as a therapy for AP, and growing evidence from

experimental studies now support beneficial effects of EA that include augmented ileal mucosal capillary perfusion, restored pancreatic microcirculation, increased gut barrier function and renal perfusion, decreased severity and improved survival.[21–23,25,27,28,53]. However, only one small recent randomised pilot study in 35 patients with AP was found to translate such promising preclinical findings into the clinical settings.[20] In this study, the median duration of EA was 5.7 days, and no complications of the epidural procedure were reported; an improvement in perfusion of the pancreas was observed in 43% of measurements in the EA group versus 7% in the control group (P=0.0025), but although analgesia was better when EA was used, there was no significant between-group differences in other clinical outcomes (e.g., the need for necrosectomy, length of stay in hospital and mortality), probably due to a lack of statistical power.[20] The EPIPAN trial is the first randomised controlled study powered to investigate the effectiveness of thoracic EA combined with standard care on major clinical outcomes in critically ill patients with EA, with specific emphasis on respiratory outcomes and survival.[21]

This study may have some limitations. First, no strict definition for severe AP is used to enrol patients. Instead, all patients admitted to the ICU with AP is eligible whatever the precise reason for admission (e.g., pain management, development of organ failure). However, we believe that randomisation, as stratified on modified Marshall scoring system (thus distinguishing patients with absent, moderate and severe organ failure), among other parameters, should ensure similar distribution of the severity of AP in both arms. Second, we acknowledge that the EPIPAN trial does not include precise (sub)protocols addressing every single aspect of the management of patients with AP (e.g., enteral feeding, its initiation, route of administration and dose), because it was believed that it would have hamper inclusions of patient and the feasibility of this pragmatic study. Instead, current guidelines for the management of AP are actively encouraged among study participants.[10,13,29–31]

Although the implementation of consensual recommendations will not be specifically assessed while the study is still ongoing, and as it may impact the findings and their interpretation, adherence of physicians from participating centres to these guidelines will be analysed after study completion. Third, this trial, whatever its results, will not address the question of the selection of patients with AP who may best benefit of EA. However, analyses of clinical and biological subphenotypes of patients included in the trial, and their responses to EA, should possibly inform on how to better select patients for future studies. Fourth, another limitation may include the limited generalizability of the results obtained from this study because EA is a technique that is restricted to experienced anaesthesiologists and intensivists. Fifth, the expected between-group difference in primary endpoint, as extrapolated from the study from Jung et al.[12], may be debatable and considered as too optimistic. Although we acknowledge that this choice is debatable, we believe that it is an acceptable compromise between study feasibility and clinical relevance, while ensuring the building of the largest cohort of critically ill patients with acute pancreatitis to date. Finally, some could highlight potential risks associated with EA in critically ill patients with hyperinflammatory conditions such as AP[38,54,55], although previous studies suggest good feasibility and safety of EA in this setting. Findings from the EPIPAN trial will undoubtedly provide new data on both the efficacy and the safety of EA during clinical AP.

This study also has several strengths. First, it is to our knowledge the largest randomised controlled trial in critically ill patients with AP. Even in case of "negative" results, data from this trial will contribute to a better understanding of the characteristics, management and prognosis of ICU patients with AP. Second, it is the first trial powered to specifically assess the effects of EA on major patient outcomes such as respiratory outcomes and 30-day mortality. In addition, other strengths are the inclusions performed around the clock, nights and weekend included as a routine clinical practice. Third, this study includes

the constitution of a biobank of plasma and urine sampled over the first week after inclusion, in order to assess biological markers of inflammation, lung injury and renal failure and the effects of EA on such markers. Finally, and despite an open-label design, one strength of the study is that final assessors of clinical and biological data who will be in charge of statistical analyses and outcome assessment, remain masked as to the subjects' assigned group, thus limiting bias.

In conclusion, the EPIPAN trial is an investigator-initiated pragmatic multicentre randomised controlled trial powered to test the hypothesis that adding thoracic EA to standard care in comparison to standard care alone may improve respiratory outcomes, i.e. increase the number of ventilator-free days at day 30, in critically ill patients with AP. The EPIPAN trial will also assess the effects of combined EA and standard care on main complications of AP and other major patient outcomes.

AUTHORS CONTRIBUTIONS TO THE STUDY

MJ takes responsibility for the content of the manuscript. MJ, SB, EI, BP, EC, DM and JMC were involved in the conception, hypotheses delineation, and design of the study, acquisition and analysis of the data, in writing the article and in its revision prior to submission.

All other authors were involved in the design of the study, acquisition and analysis of the data, in writing the article and in its revision prior to submission.

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FIGURE LEGENDS

FIGURE 1. CONSORT diagram of the EPIPAN trial Illustrating the randomisation and flow of patients in the study.

TABLE

	Inclusion (day 0)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 15	Day 30
Informed consent	X									
Eligibility: check inclusion and exclusion criteria	X									
Randomisation	X									
Filling of case report forms (including data on EA in the interventional group)	X	X	X	X	X	X	X	X	X	X
Sampling of blood and urine specimens	X		X					X		
Complications of acute pancreatitis and survival status									X	X
End of study										X

Table 1. Participant timeline

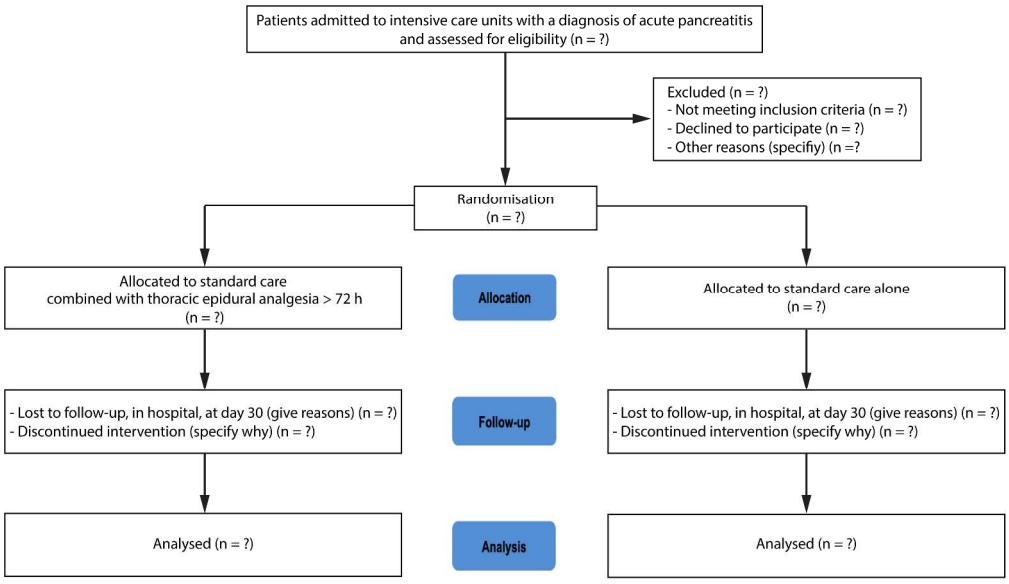

FIGURE 1. CONSORT diagram of the EPIPAN trial illustrating the randomisation and flow of patients in the study.

275x157mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – **PAGE 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – **PAGES 6 and 21**
	2b	All items from the World Health Organization Trial Registration Data Set – **PAGE 21**
Protocol version	3	Date and version identifier – **PAGE 21**
Funding	4	Sources and types of financial, material, and other support – **PAGES 22-23**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – **PAGES 1, 2 and 27**
	5b	Name and contact information for the trial sponsor – **PAGES 2 and 22**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities – **PAGES 22-23**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – **PAGES 20-21**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – **PAGES 7-8-9**
	6b	Explanation for choice of comparators – **PAGES 8-9**
Objectives	7	Specific objectives or hypotheses – **PAGES 9-10**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) – PAGE 10
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained – PAGE 10-11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) – PAGE 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – PAGES 11-12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) – PAGES 21-22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – PAGES 12-25-26
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – PAGES 11-12-13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended – PAGES 13-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) – PAGES 14 and Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations – PAGES 17 and 25

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – **PAGES 14-15**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – **PAGE 15**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – **PAGE 15**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – **PAGE 15-16**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how – **PAGES 16-17**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – **PAGE 16**

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – **PAGES 17-18-19**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – **PAGE 17**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – **PAGE 17**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – **PAGES 17-18-19**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – **PAGES 18-19**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – **PAGES 17-18-19**

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed – **PAGES 21-22**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – **PAGES 18 and 21**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – **PAGES 20-21**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – **PAGE 20**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – **PAGE 21-22**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – **PAGE 23**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – **PAGE 23**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – **PAGE 23**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – **PAGES 22-23**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site – **PAGE 23**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – **PAGE 23**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – **PAGE 23**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – **PAGES 5 and 23**
	31b	Authorship eligibility guidelines and any intended use of professional writers – **PAGE 23**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – **PAGE 23**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – **Appendix**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable – **Table 1**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.