PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol
AUTHORS	Bulyez, Stéphanie; Pereira, Bruno; Caumon, Elodie; Imhoff, Etienne; Roszyk, Laurence; Bernard, Lise; Bühler, Leo; Heidegger, Claudia; Jaber, S.; LEFRANT, Jean Yves; Chabanne, Russell; Bertrand, Pierre-Marie; Laterre, Pierre-François; Guerci, Philippe; Danin, Pierre-Eric; Escudier, Etienne; Sossou, Achille; Morand, Dominique; Sapin, Vincent; Constantin, Jean-Michel; Jabaudon, Matthieu

VERSION 1 - REVIEW

REVIEWER	Benhamou Dan Service d'Anesthésie - Réanimation Chirurgicale Hôpitaux Universitaires Paris-Sud (AP-HP) Hôpital de Bicêtre 78, rue du Général Leclerc 94275 Le Kremlin Bicêtre
REVIEW RETURNED	17-Dec-2016

GENERAL COMMENTS	This submission describes a study protocol (already in progress) in which patients with acute and severe pancreatitis are randomised to receive (or not) thoracic epidural analgesia. The information on which the study was planned and organised is well described and represents state of the art knowledge. The study group is well known in its country and has published several high-quality studies, suggesting that the study will be done and published. The reviewer has only one major comment which is related to the study power. The authors have calculated that they are going to enrol 74 patients in each group to identify a between group difference of seven days of ventilator-free days. They state that they define this goal based on previous literature, and they cite 9 references to support their hypothesis. However, among these papers, only four relate directly to patients with pancreatitis. In addition, they are only series of cases with no comparator and it is extremely difficult to anticipate that such a huge reduction in the duration of mechanical ventilation (i.e. 50 % reduction) will occur “only” with the use of epidural analgesia. There is only one randomised study available today and it is a preliminary study as only 35 patients were enrolled, among whom 12 received epidural analgesia. In that study, most outcomes were not different although patients in the epidural group had less pain (Sadowski et al, 2015). The reviewer thus believes that the authors should modify their manuscript and better discuss their hypothesis. Additional comments P7, L41: what do the authors mean by “versatile”?

	P10, L38: will some patients (or all of them) be on mechanical ventilation? P11, L14: when will epidural be done? It is stated in the Discussion section (P24) that enrolment will occur around the clock. Is there a maximum time interval accepted between arrival in the unit and epidural analgesia placement? P11, L27: what are the predefined factors for the nurse to decide to administer a bolus through the PCEA system?

REVIEWER	Catherine Paugam-Burtz Hopital Beaujon APHP, Paris, France
REVIEW RETURNED	19-Dec-2016

GENERAL COMMENTS	Jabaudon et al present the study protocol of a multicentre randomised controlled study on epidural analgesia in critically ill patients with acute pancreatitis. The mainpoint I would like to underline is related to the primary endpoint wich is ventilator free-days. As stated by the authors, the physicians in charge of the patients, particularly when mechanical ventilation may be required, will not be blind of the treatment group. To limit the risk of bias, strict criteria should be precised for mechanical ventilation. The second point is related to safety of EA: complications related to EA (hematoma, infection) should be collected

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1

3. The reviewer has only one major comment which is related to the study power. The authors have calculated that they are going to enrol 74 patients in each group to identify a between group difference of seven days of ventilator-free days. They state that they define this goal based on previous literature, and they cite 9 references to support their hypothesis. However, among these papers, only four relate directly to patients with pancreatitis. In addition, they are only series of cases with no comparator and it is extremely difficult to anticipate that such a huge reduction in the duration of mechanical ventilation (i.e. 50 % reduction) will occur “only” with the use of epidural analgesia. There is only one randomised study available today and it is a preliminary study as only 35 patients were enrolled, among whom 12 received epidural analgesia. In that study, most outcomes were not different although patients in the epidural group had less pain (Sadowski et al, 2015). The reviewer thus believes that the authors should modify their manuscript and better discuss their hypothesis.

We agree with Reviewer #1 that determining sample size and calculating statistical power for the Epipan study was a difficult step in the design of the study. In the “Statistical methods - Sample size Estimation” section, two references are cited (Jung et al. Ann Fr Anesth Reanim 2011;30:105–12, and Sadowski et al. World J Gastroenterol 2015;21:12448–56).
First, we need to apologize, as we should not have referred to the study from Sadowski et al. because these data were not available yet at the time the Epipan study was designed; therefore, this reference has been deleted from this paragraph.
Second, we acknowledge that is has been very difficult to calculate sample size and statistical power for this study. Indeed, we anticipated that epidural analgesia would be associated with a 50% reduction in the number of ventilator-free days at day 30 (i.e. a composite endpoint comprising the need for invasive ventilation, its duration and mortality), and not in the duration of invasive mechanical ventilation alone. This estimation was extrapolated from the study from Jung et al. (Ann Fr Anesth

Reanim 2011). 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 prospective cohort of critically ill patients with acute pancreatitis to date.
However, and as suggested by Reviewer #1, we discussed this point as a limitation in the third paragraph of the Discussion section.

4. P7, L41: what do the authors mean by “versatile”?

We used this term to describe EA as a polyvalent, widely used anesthetic technique. However, as it may be redundant, and to ensure better clarity, we chose to remove this term.

5. P10, L38: will some patients (or all of them) be on mechanical ventilation?

Indeed, some patients may be under mechanical ventilation at study inclusion.

6. P11, L14: when will epidural be done? It is stated in the Discussion section (P24) that enrolment will occur around the clock. Is there a maximum time interval accepted between arrival in the unit and epidural analgesia placement?

Because the Epipan study was designed as a pragmatic randomised controlled trial and to increase feasibility, there is no strict time interval between ICU admission, enrolment in the study and placement of the epidural catheter in the study protocol.
This addition has been made to the 2nd paragraph of the “Interventions” section.

7. P11, L27: what are the predefined factors for the nurse to decide to administer a bolus through the PCEA system?

As described in the 1st paragraph of the “Interventions” section, analgesic targets (that are common in both groups) are a visual analogue score (VAS) for pain below 40/100 in conscious and communicating patients, and a behavioural pain scale (BPS) of 3-4 in non-communicating patients. Therefore, and based on specific protocols for pain assessment and treatment at each participating centre, nurses may themselves deliver a bolus to the patient to reach the target, e.g. prior to nursing the patient or before a possibly painful procedure.
We did our best to better explicit this point in our revised manuscript.

REVIEWER #2

8. The main point I would like to underline is related to the primary endpoint which is ventilator free-days. As stated by the authors, the physicians in charge of the patients, particularly when mechanical ventilation may be required, will not be blind of the treatment group. To limit the risk of bias, strict criteria should be precised for mechanical ventilation.

We agree with Reviewer #2 that a certain degree of bias may be induced by some variety in clinical practices among centres, with regards to criteria for intubation and initiation of mechanical ventilation, but also to the strategy of weaning from mechanical ventilation. To reduce the risk of delayed intubation and to better ensure consistency of indications for intubation among centres, the application of current recommendations on the management of patients with severe acute pancreatitis in particular (and of critically ill patients in general) is strongly encouraged by the protocol. For example, prompt intubation is recommended if patients have 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. In addition, when mechanical ventilation is needed, the use of a low-tidal-volume protective ventilatory strategy and recommendations on weaning from mechanical ventilation are strongly encouraged (Dellinger et al. Surviving Sepsis Campaign 2012, Crit Care Med 2013, and Boles et al. Eur Respir J 2007). A note has been added to the “Interventions” section to better clarify this point. Of note, all participating centres and investigators have strong expertize in the field of critical care medicine, management of acute pancreatitis, acute respiratory failure, and mechanical ventilation.

9. The second point is related to safety of EA: complications related to EA (hematoma, infection) should be collected

We thank Reviewer #2 for this important comment. Data on the safety of epidural analgesia will be collected in enrolled patients and reported.
As described in the “Secondary outcome measures” section, any minor or major complication that could be attributable to epidural analgesia and/or epidural catheter will be rigorously documented. In particular, patients will be closely monitored to allow early diagnosis and treatment of any EA-attributable complication, including major complications such as epidural hematoma and infection, among others.

VERSION 2 – REVIEW

REVIEWER	Benhamou Dan Service d'Anesthésie - Réanimation Chirurgicale Hôpitaux Universitaires Paris-Sud (AP-HP) Hôpital de Bicêtre 78, rue du Général Leclerc 94275 Le Kremlin Bicêtre France
REVIEW RETURNED	08-Feb-2017

GENERAL COMMENTS	I have read the revised version and I feel that the authors have done a good job and have adequately responded to the reviewers’ concerns.