Postoperative pulmonary complications in emergency abdominal surgery. Incidence and risk factors. A prospective multicenter observational study.

Protocol version: PEAL. Version 02.0 data: Diciembre-2022

Sponsor: Department of Anesthesiology and Critical Care, Hospital Clinic de Barcelona.

Protocol registration numbers:

Clinicaltrials.gov identifier: NCT04229810
Ethics Committee number:

1. General Information

1.1 Title: Postoperative pulmonary complications in emergency abdominal surgery. Incidence and risk factors. A prospective multicenter observational study

1.2 Acronym: PEAL

1.3 Protocol version: 02.0 **Version Date:** Diciembre/2022

1.4 Study Sponsor:
Anesthesiology and Critical Care Department.
Hospital Clinic de Barcelona
C/Villarroel, 170. Barcelona. 08036

1.5 Coordinating investigator:
Carlos Ferrando, MD, PhD
Dept. of Anesthesiology and Critical Care
Anesthesiology and Critical Care Department.
Hospital Clinic de Barcelona
C/Villarroel, 170. Barcelona. 08036
Email: cmferrando@clinic.cat
Tel: +34 609 892 732

1.6 Study Methodology:
Julian Librero, MD, PhD
Navarrabiomed, Complejo Hospitalario de Navarra,
UPNA, REDISSEC (Red de Investigación en Servicios de Salud)
Email: julian.librero@gmail.com

1.7 Coordinating and Study monitoring:
Guillermo Laguna
Dept. of Anesthesiology and Critical Care
Anesthesiology and Critical Care Department.
Hospital Clinic de Barcelona
C/Villarroel, 170. Barcelona. 08036
Email: gjlaguna@clinic.cat

1.8 Steering Committee:
Carlos Ferrando. Hospital Clínic de Barcelona, España. **Marina Soro**. Hospital Clínico de Valencia, España. **Javier Ripollés**. Hospital Infanta Leonor de Madrid, España. **Oscar**

Díaz-Cambronero. Hospital La Fe de Valencia, España. **Ignacio Garutti**. Hospital Gregorio Marañón, Madrid, España. **Roger Pujol.** Hospital Clínic de Barcelona, España. **Ricard Mellado.** Hospital Clínic de Barcelona, España. **Miquel Serra**. Zurich University.

1.9 Scientific Committee:

Carlos Ferrando. Hospital Clínic de Barcelona, Barcelona, España. **Jesús Villar.** Hospital Dr. Negrín. Las Palmas de Gran Canaria, Gran Canarias, España. **Gerardo Tusman.** Hospital Privado de Comunidad, Mar de Plata, Argentina. **Fernando Suárez-Sipmann**. Hospital La Princesa, Madrid, España.

1.10 Clinical Research Ethical Committee:

The ethical committee approved the protocol version 02.0 (appendix 1).

1.11 Spanish Agency of Drugs and Medical Devices (AEMPS):

The study was classified by the AEMPS as "Estudio no observacional sin medicamentos" (Appendix 2).

1.12 Participating Centers and Local Principal Investigators:

iPROVE research network: centers that have participated in the iPROVE, iPROVE-O2 and iPROVE-OLV trials will be invited to participate. The study will be open for new centers.

2 Study summary

Background

Postoperative pulmonary complications (PPCs) are the most frequent postoperative complications, with a significant impact on the morbidity, mortality and consumption of health system resources. It has been observed that the incidence of PPCs in this population is between 20% described in observational cohort studies up to 40% in randomized clinical trials. However, the incidence of PPCs in patients undergoing emergency abdominal surgery is not well defined. The lung protective ventilation strategy aims to minimize lung injury favored by mechanical ventilation and therefore to reduce PPCs.

The open lung strategy (OLA), which until now has been defined as a strategy that combines RM to open the alveolar collapse followed by a PEEP level to prevent re-collapse, aims to homogenize the lung decreasing the risk of lung injury and therefore the appearance of PPCs. However, the literature is inconclusive in the benefits that this strategy has over PPCs.

Objectives

We aim to conduct a prospective study that analyzes the incidence of postoperative pulmonary complications in patients undergoing emergency abdominal surgery,

describing the usual ventilatory management and the perioperative factors that are associated with their appearance.

3 List of abbreviations

AEMPS: Spanish agency of drugs and medical devices
ARDS: acute respiratory distress syndrome
ASA: American Society of Anesthesiology physical Status
Cdyn: Dynamic respiratory system compliance
CGS: Coma Glasgow scale
CPAP: Continuous positive airway pressure
CRF: case report form
CT: Computed tomography
DMSC: Data monitoring and safety committee
DP: Driving pressure
EC: Ethical Committee
ECG: electrocardiogram
EtCO2: end-tidal carbon dioxide
FiO2: Inspiratory oxygen fraction
GCP: Good clinical practice
IC: cardiac index
ICU: Intensive Care Unit
iHFNC: Individualized High flow nasal cannula
iOLA: Individualized open lung approach
IOT: oro-tracheal intubation
LUS: Lung ultrasound
MAP: mean arterial pressure
NIV: non-invasive ventilation
O2: Oxygen
PaO2/FiO2: Partial pressure of arterial oxygen to inspiratory oxygen ratio
PaCO2: Arterial partial pressure of carbon dioxide
PACU: Post-anesthetic care unit
Paw: Peak airway pressure
PCV: Pressure controlled ventilation
PEEP: Positive end-expiratory pressure
PPCs: Postoperative pulmonary complications
Raw: Respiratory system resistance
RM: Recruitment maneuvers
RR: Respiratory rate
SAE: Severe Adverse Event
SBP: systolic blood pressure
SOFA: Sequential organ failure assessment
SpO2: Peripherical oxyhemoglobin saturation
STROBE: strengthening the reporting of observational studies in epidemiology
STD: Standard
TOF: train of four

VAS: Visual analogue score
VCV: Volume controlled ventilation
VT: Tidal volume

4 Background (Current State of Scientific knowledge)

Postoperative pulmonary complications (PPCs) are the most frequent postoperative complications, with a significant impact on the morbidity, mortality and consumption of health system resources.[1-3] In recent years there have been numerous publications describing perioperative factors related to these, with the objective of defining the risk of onset and trying to establish prevention strategies,[4,5] as well as clinical studies comparing different lung protection strategies to reduce their appearance.[6-9] Within these, our groups in Spain (iPROVE Research Network group and REDGERM) has lead in the last 5 years three multicenter randomized controlled trials (NCT02158923, NCT02776046, NCT03182062) and 7 multicenter observational (NCT03012802, NCT03570944, NCT03864861, NCT03865810, NCT03814681, NCT03803280, NCT04305314) studies that has generated so far 13 publications in high impact international journals.

One of the most studied populations are patients undergoing scheduled abdominal surgery, a population that, according to the different risk scales, is considered a moderate to severe risk patient suffering from PPCs. It has been observed that the incidence of PPCs in this population is between 20% described in observational cohort studies up to 40% in randomized clinical trials.[7-9] However, the incidence of PPCs in patients undergoing emergency abdominal surgery is not well defined. Different studies such as ARISCAT or LAS VEGAS have shown that emergency abdominal surgery is an independent risk factor for PPCs.[4,5] Recently, Watson et al. described an incidence of 48% in 568 patients included in the British national audit of emergency laparotomy (NELA).[10,11] If this number of PPCs is extrapolated to Spain, where approximately 140,000 emergency abdominal surgeries are performed per year[12], it means that 70,000 patients per year will suffer at least one PPC. With an average cost of 2,800 euros per lung complication, the minimum impact on the public health system is close to 200 million euros / year.[13,14]

To date there is no further data on the real prevalence in Spain and the factors related to its occurrence, as well as randomized clinical trials studying ventilatory strategies to reduce PPCs in this population. Watson et al. in the aforementioned prospective observational study showed interesting data, such as the protective ventilation strategy defined by the authors as a combination of low tidal volume (VT), recruitment maneuvers (RM) and positive end-expiratory pressure (PEEP) > 5 cmH_2O is applied to less than 5% of patients. Among the registered variables related to ventilatory management, it was shown that peak pressure and inspiratory oxygen fraction (FIO_2) were associated with an increased risk of suffering PPCs.[10] However, other variables that

have shown an association with PPCs, such as the plateau pressure or the driving pressure (DP) were not recorded.[15] On the other hand, unlike what has been described in various clinical trials and meta-analysis that have demonstrated a protective effect of RM and PEEP (among which are our studies),[1,8-9,16] in the analysis of Watson et al., these were not related to PPCs. Although the recruitment maneuvers were only performed in 54 (9.5%) patients and the study did not specify how PEEP was adjusted.

The lung protective ventilation strategy aims to minimize lung injury favored by mechanical ventilation, trying to avoid its two main mechanisms: tidal overdistension secondary to the use of high volumes or pressures and atelectrauma produced by repetitive alveolar opening and closure. The open lung strategy (OLA), which until now has been defined as a strategy that combines RM to open the alveolar collapse followed by a PEEP level to prevent re-collapse, aims to homogenize the lung decreasing the risk of lung injury and therefore the appearance of PPCs. However, the literature is inconclusive in the benefits that this strategy has over PPCs. There are several reasons that could justify this lack of consensus on the results, such as the different ventilatory management of the control groups favoring more or less harmful ventilation, or the different definitions of the outcome variables used. Another cause that could also justify these results is the effectiveness of the OLA in its goal of re-expanding the lung and preventing re-collapse. In these studies, different RM have been applied as well as different PEEP adjustments, not monitoring in any of them if the patient, prior to the RM, already had an open lung condition and therefore its application was not necessary. As well as if an open lung condition was achieved with the applied maneuver or if it was maintained during surgery with the PEEP level adjusted. Moreover, most of these studies have not ensured an open lung condition after extubation and during the first hours during the postoperative period.

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6 PHASE 1

6.1 Title:

Incidence of **P**ulmonary complications after **E**mergency **A**bdominal **L**aparotomy/scopy. An international prospective multicentre observational cohort study.

6.2 Acronym: PEAL

6.3 Study Objectives

6.3.1 Primary Outcome

- To describe the incidence of postoperative pulmonary complications in patients undergoing emergency abdominal surgery during the first 7 postoperative days.

6.3.2 Secondary Outcomes

- To describe the incidence of postoperative pulmonary complications in patients undergoing emergency abdominal surgery during the first 30 postoperative days.
-To describe the incidence of postoperative non-pulmonary complications in patients undergoing emergency abdominal surgery during the first 7 and 30 postoperative days.
-To define the incidence of intraoperative atelectasis diagnosed by peripheral oxygen saturation (air-test maneuver) and the arterial blood pressure inspiratory oxygen fraction ratio (blood gas analysis).
-To describe the usual ventilatory management of these patients.
-To analyze the perioperative factors associated with the appearance of postoperative pulmonary complications in the study population.

6.4 Study Design/Methodology

6.4.1 Type of study

Observational, prospective cohort study, with 7-day follow-up from recruitment, in patients who meet inclusion criteria and in participating hospitals. Each hospital will

select a single 7-day period for the recruitment of patients during a few predefined months in 2023. (from April to June) It will be reported in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) statement.

6.4.2 Inclusion criteria

All patients older than 18 years undergoing emergency abdominal surgery that firmed the informed consent (If required by each local Ethics Committee).

6.4.3 Exclusion criteria

There are no specific exclusion criteria for the study.

6.5 Study Endpoints

6.5.1 Main study endpoint.

A composite of severe pulmonary postoperative complications during the first 7 days following the surgical intervention. Postoperative pulmonary complication will include any of the following: 1) Acute respiratory failure, 2) Pneumothorax, 3) Weaning failure, 4) Acute respiratory distress syndrome (ARDS), 5) Pulmonary infection.

6.5.2 Secondary study endpoints.

- Postoperative pulmonary complications during the first 7 days following the surgical intervention not included in the primary outcome variable. They include: 1) Atelectasis, 2) Pleural effusion, 3) Bronchospasm, 4) Aspiration pneumonitis, 5) Pulmonary thromboembolism, 6) Pulmonary edema
- The incidence of patients with the presence of intraoperative atelectasis and its relationship with different preoperative and intraoperative factors.
- Postoperative non-pulmonary complications during the first 7 days following the surgical intervention. They include: 1) Cardiac ischemia, 2) de novo arrhythmia, 3) Heart failure, 4) Sepsis, 5) Septic shock, 5) Acute renal failure, 6) Surgical wound infection, 7) Urinary infection, 8) Delirium, 9) Multiorgan failure, 10) Paralytic ileus, 11) Postoperative hemorrhage, 12) Anastomotic dehiscence.

6.5.3 Other follow up variables and definitions.

- Age, sex, height, body weight, body mass index, ASA status, Charlson, SOFA, ARISCAT scale, Clinical Frailty Scale, preoperative peripherical oxygenation saturation (SpO_2), type of intervention, co-morbidities, medication.

-Intraoperative parameters of gas exchange, acid base state and respiratory and hemodynamic variables.

- Anesthetic drugs, anesthetic techniques (epidural, paravertebral), fluid therapy and other parameters such as surgical time, mechanical ventilation time, intraoperative bleeding, urine output, quantitative neuromuscular blockade monitoring, pharmacological neuromuscular reversal, etc.
Outcome definitions and scales are described in appendix 3

6.6 Statistical analysis

6.6.1 Sample size calculation.
Our plan is to recruit 50 centers and ask them to include all eligible patients in the study. We do not have a specific sample size, competitive recruitment will be followed and the statistical models will be adapted to the event rate provided by the sample recruited. The larger the sample, the greater accuracy will be achieved. Therefore, it is intended to recruit as many patients as possible.
We expect to recruit at the Hospital Clínic of Barcelona during the 7 days period 20 patients.

6.6.2 Data analysis

All data will be anonymized before publication.
Only one final analysis is foreseen that will follow the following sequence: 1. Univariate description: normal distribution variables will be presented as mean and standard deviation or, in the absence of normality, medium and interquartile range; Categorical variables as proportions. 2. Bivariate analysis will be used to assess the relationship between each factor and the indicated outcome variables: Comparisons will be made using the $\chi 2$ test or Fisher's exact test for categorical variables and the Kruskall-Wallis t test and will be used to evaluate the differences between depending on distribution. 3. Multivariate analysis, through logistic regression, including all the variables that presented a $p < 0.01$ value in the bivariate analysis, and whose intervention is biologically and statistically plausible (in accordance with the information contained in a Directed Acrylic Graph prepared from the literature and the expert´s opinion).

7. Ethical aspects.

This study will respect the fundamental principles established in the Declaration of Helsinki, in the European Council Convention on human rights and biomedicine in the Unesco Universal Declaration on human genome and human rights, as well as the requirements established by Spanish legislation in the field of biomedical research, personal data protection and bioethics. It will be submitted for authorization to the Ethical Research Committee (EC). Only patients who sign informed consent will be included in the study. At all times, confidentiality and data security will be maintained. The promoter of the study will be responsible for the preservation of records in each center and for the publication policy.

8. Dissemination of research results and sub-studies

The Scientific Committee will appoint a Drafting Committee to draft the scientific report (s) of this research, which will be disseminated in a timely manner. It is expected that a series of secondary analyzes will be carried out. Researchers will have priority to direct this type of analysis and are encouraged to do so. Participation will be based on the contribution to the study in its two phases. The Steering Committee will take into account the scientific validity and the possible effect on the anonymity of the participating centers before the granting of any of these applications. If necessary, a prior written agreement will establish the terms of this type of collaboration. The Scientific Committee must approve the final version of all manuscripts, before submission. In case of disagreement within the Steering Committee, the head of the investigation will make a decision. Any data from the PEAL analysis with the incorporation of two or more study sites will be taken into account for possible secondary analyzes and will be subject to predefined rules.

All participants in the study will be included as co-authors under the iPROVE Network Group.

9. Data management and data ownership

The promoter of the study, the iPROVE Group, will act as custodian of the data. In line with the principles of preservation and exchange of data, the Steering Committee, after the publication of the general database, will take into account all reasonable requests to carry out the secondary analyzes. (sub-studies). The main consideration for these types of decisions will be the quality and validity of any analysis that is proposed. Only summary data will be presented publicly and all data at International, national, institutional and patient level will be strictly anonymous. The data of the individual

patients provided by the participating hospitals are property of the respective institution. Once each local coordinator has confirmed that the data provided from their hospital is both complete and accurate, they will be transferred to an online data database. The complete data set of the participants with respect to the patients, the hospitals and the communities will be codified, however, they will be made freely available to the public for two years following the publication of the main scientific report. Prior to this, the Scientific Committee is under no obligation to publish the data to any collaborator or third party if they believe that this is not in line with the broader objectives of the project.

Data will be collected in each hospital on an individual paper (CRF) for each patient recruited. Paper CRFs will be store in a locked office in each center. The local principal investigator will be responsible of these CRFs. This will include patient identification data in order to allow follow-up of clinical results. Study data will be codified by encryption, generating a unique numerical code prior to entry to an online database via an electronic CRF (eCRF). The Castor EDC platform will be used to collect the data https://www.castoredc.com/. Castor EDC complies with all applicable laws and regulations: good clinical practice (GCP), 21 CFR Part 11, annexed 11 of the European Union and UE and the European Directive on data protection. Each local investigator will have its own username and password to introduce local data. Each patient will only be identified in the eCRF by their numerical code. Therefore, the research coordination team will not be able to associate data to an individual patient without contacting the local team. In each center there will be a list of individual patients and their identification codes in the database in order to track clinical results and provide any data that might be missing. Once the local coordinator has confirmed the data entry is complete for their hospital, they will receive a spreadsheet with unprocessed data. This will allow more data integrity and precision controls. Individual data at each hospital may be used by local investigators, however, they may not be published on an individual basis under any circumstance.

All identifiable data collected, processed and stored for the purposes of the project will be kept confidential at all times and will comply with the guidelines of Good Clinical Practice for Research (GCP) and the General Regulation of Data Protection (GDPR) (Regulation (EU)) 2016/679).

10. Privacy and use of clinical information

The treatment, communication and transfer of the data will be done in accordance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons in terms of data processing. and the free circulation of data, and Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights.

11. Legal and organizational aspects.

11.1 Trial funding

The study is not founded yet

11.2 Compensation

Neither the trial sites, researchers and patients will receive compensations.

11.3 Insurance

Do not apply