Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): a randomised controlled trial

*Carlos Ferrando, Marina Soro, Carmen Unzueta, Fernando Suarez-Sipmann, Jaume Canet, Julián Librero, Natividad Pozo, Salvador Peiró, Alicia Llombart, Irene León, Inmaculada India, Cesar Aldecoa, Oscar Díaz-Cambronero, David Pestaña, Francisco J Redondo, Ignacio Garutti, Jaume Balust, Jose I García, Maite Ibáñez, Manuel Granell, Aurelio Rodríguez, Lucía Gallego, Manuel de la Matta, Rafael Gonzalez, Andrea Brunelli, Javier García, Lucas Rovira, Francisco Barrios, Vicente Torres, Samuel Hernández, Estefanía Gracia, Marta Giné, María García, Nuria García, Lisset Miguel, Sergio Sánchez, Patricia Piñeiro, Roger Pujol, Santiago García-del-Valle, José Valdivia, María J Hernández, Oto Padrón, Ana Colás, Jaume Puig, Gonzalo Azparren, Gerardo Tusman, Jesús Villar, Javier Belda, on behalf of the Individualized PeRioperative Open-lung VEntilation (iPROVE) Network**

Summary

Background The effects of individualised perioperative lung-protective ventilation (based on the open-lung approach [OLA]) on postoperative complications is unknown. We aimed to investigate the effects of intraoperative and postoperative ventilatory management in patients scheduled for abdominal surgery, compared with standard protective ventilation.

Methods We did this prospective, multicentre, randomised controlled trial in 21 teaching hospitals in Spain. We enrolled patients who were aged 18 years or older, were scheduled to have abdominal surgery with an expected time of longer than 2 h, had intermediate-to-high-risk of developing postoperative pulmonary complications, and who had a body-mass index less than 35 kg/m^2. Patients were randomly assigned (1:1:1:1) online to receive one of four lung-protective ventilation strategies using low tidal volume plus positive end-expiratory pressure (PEEP): open-lung approach (OLA)–iCPAP (individualised intraoperative ventilation [individualised PEEP after a lung recruitment manoeuvre] plus individualised postoperative continuous positive airway pressure [CPAP]), OLA–CPAP (intraoperative individualised ventilation plus postoperative CPAP), STD–CPAP (standard intraoperative ventilation plus postoperative CPAP), or STD–O_2 (standard intraoperative ventilation plus standard postoperative oxygen therapy). Patients were masked to treatment allocation. Investigators were not masked in the operating and postoperative rooms; after 24 h, data were given to a second investigator who was masked to allocations. The primary outcome was a composite of pulmonary and systemic complications during the first 7 postoperative days. We did the primary analysis using the modified intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT02158923.

Findings Between Jan 2, 2015, and May 18, 2016, we enrolled 1012 eligible patients. Data were available for 967 patients, whom we included in the final analysis. Risk of pulmonary and systemic complications did not differ for patients in OLA–iCPAP (110 [46%] of 241, relative risk 0·89 [95% CI 0·74–1·07; p=0·25]), OLA–CPAP (111 [47%] of 238, 0·91 [0·76–1·09; p=0·35]), or STD–CPAP groups (118 [48%] of 244, 0·95 [0·80–1·14; p=0·65]) when compared with patients in the STD–O_2 group (125 [51%] of 244). Intraoperatively, PEEP was increased in 69 (14%) of patients in the standard perioperative ventilation groups because of hypoxaemia, and no patients from either of the OLA groups required rescue manoeuvres.

Interpretation In patients who have major abdominal surgery, the different perioperative open lung approaches tested in this study did not reduce the risk of postoperative complications when compared with standard lung-protective mechanical ventilation.

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*Additional investigators are listed in the appendix

Department of Anesthesiology & Critical Care, Hospital Clínico Universitario, Valencia, Spain (C Ferrando PhD, M Soro PhD, I León PhD, E Gracia MD, J Puig PhD, J Belda PhD); **CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain** (C Ferrando, F Suarez-Sipmann PhD, J Villar PhD); **Department of Anesthesiology & Critical Care, Hospital Universitario Sant Pau, Barcelona, Spain** (I India MD, M Giné MD, G Azparren MD, C Unzueta PhD); **Hedenstierna Laboratory, Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden** (F Suarez-Sipmann); **Department of Anesthesiology & Critical Care, Hospital Universitario Germans Tries i Pujol, Badalona, Spain** (J Canet PhD, A Brunelli MD); **Navarrabiomed-Fundación Miguel Servet. Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Pamplona, Spain** (J Librero PhD); **INCLIVA Clinical Research Institute, Hospital Clinico Universitario de Valencia, Valencia, Spain** (N Pozo PhD); **Centro Superior de Investigación en Salud Publica (CSISP-FISABIO), REDISSEC, Valencia, Spain** (S Peiró PhD); **IISLAFE Clinical**

Introduction

Major abdominal surgery is associated with a high incidence of severe postoperative complications that negatively affect patient survival and health-care costs.[1] Non-protective intraoperative mechanical ventilation contributes to postoperative complications in patients with healthy lungs.[2–4] Furthermore, postoperative factors, such as lung derecruitment or diaphragm dysfunction, might contribute to further impairment of lung function in these patients.[5]

Tidal hyperinflation and tidal recruitment are the two main mechanisms associated with lung injury during mechanical ventilation.[6–8] Intraoperative protective mechanical ventilation minimises postoperative

Research Institute (A Llombart Pharm) **and Department of Anesthesiology & Critical Care** (O Díaz-Cambronero MD, N García MD), **Hospital Universitario y Politécnico La Fe, Valencia, Spain; Department of Anesthesiology & Critical Care, Hospital Universitario Río Hortega, Valladolid, Spain** (C Aldecoa PhD, M García MD); **Department of Anesthesiology & Critical Care, Hospital Universitario Ramón y Cajal, Madrid, Spain** (D Pestaña PhD, L Miguel MD); **Department of Anesthesiology & Critical Care, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain** (F J Redondo PhD, S Sánchez MD); **Department of Anesthesiology & Critical Care, Hospital General Universitario Gregorio Marañón, Madrid, Spain** (I Garutti PhD, P Piñeiro MD); **Department of Anesthesiology & Critical Care, Hospital Clínic i Provincial Universitario, Barcelona, Spain** (J Balust MD, R Pujol MD); **Department of Anesthesiology & Critical Care, Hospital Fundación de Alcorcón, Alcorcón, Spain** (J I García MD, S García-del-Valle MD); **Department of Anesthesiology, Hospital de la Marina Baixa de la Vila Joiosa, Alicante, Spain** (M Ibáñez MD, J Valdivia MD); **Department of Anesthesiology & Critical Care, Hospital General Universitario, Valencia, Spain** (M Granell PhD, M J Hernández MD); **Department of Anesthesiology, Hospital Universitario Doctor Negrín, Las Palmas de Gran Canaria, Spain** (A Rodríguez PhD, O Padrón MD); **Department of Anesthesiology & Critical Care, Hospital Universitario Miguel Servet, Zaragoza, Spain** (L Gallego PhD, A Colás MD); **Department of Anesthesiology & Critical Care, Hospital Universitario Virgen del Rocio, Sevilla, Spain** (M de la Matta PhD); **Department of Anesthesiology, Hospital Universitario de León, León, Spain** (R Gonzalez MD); **Department of Anesthesiology & Critical Care, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain** (J García PhD); **Department of Anesthesiology, Hospital de Manises, Valencia, Spain**

Research in context

Evidence before this study

We searched MEDLINE, PubMed, and Scopus for papers published up to Sept 30, 2017, without language restrictions. We used the terms "abdominal surgery", "mechanical ventilation", "protective ventilation", "positive end-expiratory pressure", "recruitment maneuver", "tidal volume", "pulmonary complication", and "postoperative complications". Abdominal surgical procedures are associated with a high incidence of postoperative complications. Previous trials focused on standard ventilatory strategies in the intraoperative or postoperative period for reducing postoperative complications, but without personalising those strategies to suit the needs of each individual patient, and without considering both periods together for applying a global, perioperative, lung-protective ventilatory approach. Results from several randomised controlled trials have shown that lung-protective mechanical ventilation mitigates lung injury and reduces complications, although the protective effects of positive end-expiratory pressure (PEEP) seems associated with a reduction in driving pressure. In this context, while the effects of an arbitrary level of PEEP on driving pressure are unpredictable, individualised PEEP after an alveolar recruitment manoeuvre seem clearly associated with a reduction in driving pressure. Additionally, some evidence suggests that postoperative continuous positive airway pressure (CPAP) reduces postoperative complications. However, it is not known whether the combination of these two strategies improves outcomes.

Added value of this study

To our knowledge, this study is the first in which the ventilatory strategy is continuously individualised to the patient's lung condition during the intraoperative and postoperative period. We compared three different lung-protective ventilatory strategies, ranging from the most individualised to the most standard, with a standard lung-protective mechanical ventilation approach. Our findings on pulmonary and systemic complications suggest that the open-lung approach, together with a proper selection of patients, could determine the benefits of postoperative CPAP. Our results could not corroborate whether postoperative CPAP reduces postoperative complications. Although the differences between groups had a lower order of magnitude than expected, these findings might be of clinical relevance since all enrolled patients had healthy lungs and were managed with protective mechanical ventilation.

Implications of all the available evidence

Evidence from three of the four largest randomised controlled trials supports the use of recruitment manoeuvre plus PEEP in surgical patients, although the ideal PEEP is still a matter of debate. The reduction in the number of postoperative complications, which seems associated with a decrease in driving pressure, suggests that when PEEP reduces driving pressure, it confers benefits (a reduction in postoperative pulmonary complications). The benefits of postoperative CPAP

complications by reducing both mechanisms, either by using low tidal volume or positive end-expiratory pressure (PEEP). Whereas low tidal volume has been proven to reduce postoperative complications,[2–4] the benefits of an arbitrary level of PEEP with or without a previous recruitment manoeuvre have not been clearly established.[2–4] Such levels appear to be protective only when they are not associated with an increase in driving pressure.[9] Alternatively, the open-lung approach (OLA), in which the PEEP level is individualised to best respiratory system dynamic compliance (Cdyn) after a recruitment manoeuvre, has resulted in favourable physiological effects when used intraoperatively.[10,11] Similarly, in patients with acute respiratory distress syndrome, individualising PEEP on the basis of the OLA approach resulted in more favourable physiological responses, including a decrease in driving pressure when compared with PEEP adjustment according to the ARDSnet ventilation strategy.[12] Additionally, strategies using postoperative continuous positive airway pressure (CPAP) have been shown to reduce postoperative pulmonary complications in patients after major abdominal surgery.[13] Several investigators have suggested that a more holistic, lung-protective mechanical ventilation approach combining these two strategies and aimed at minimising intraoperative lung collapse and postoperative lung derecruitment might result in a greater lung-protective benefit.[14,15]

We hypothesised that an individualised perioperative open-lung ventilation strategy (iPROVE) would confer better lung protection and result in fewer postoperative complications in intermediate-to-high-risk patients when compared with a standard lung-protective mechanical ventilation approach, and we aimed to investigate this theory.

Methods

Study design

The iPROVE study is a prospective, multicentre, four-arm randomised controlled trial done in 21 teaching hospitals in Spain. The trial was done in accordance with the fundamental principles established in the Declaration of Helsinki and the Convention of the European Council for human rights and biomedicine, and following the Spanish legislation for biomedical research. A Steering Committee monitored the study and an independent data and safety monitoring board was constituted. The complete protocol was registered before patient enrolment and is published elsewhere.[16] Some changes were made to the statistical analysis during the study period, which were approved by the steering committee and which are described later. The study was approved by the institutional review board of all participating centres, and written informed consent was obtained from each patient before enrolment.

Participants

People aged 18 years or older, with an intermediate-to-high risk for postoperative pulmonary complications (as defined by the ARISCAT score),[17] who were scheduled for major abdominal surgery (laparotomy or laparoscopy) with an expected surgical time longer than 2 h, and who had a body-mass index (BMI) less than 35 kg/m² were eligible for participation. Patients were excluded if they were younger than 18 years, were pregnant or breastfeeding, had moderate or severe acute respiratory distress syndrome, had cardiac failure, had a diagnosis or suspicion of intracranial hypertension, had mechanical ventilation during the previous 15 days (including CPAP), had pneumothorax or giant bullae, had chronic obstructive pulmonary disease requiring oxygen or CPAP, or were participating in another interventional study.

Randomisation and masking

Participants were enrolled by investigators and randomly assigned with the iPROVE website using the Mersenne–Twister algorithm, with an allocation of 1:1:1:1, into one of four lung-protective mechanical ventilation study groups. People who had access to the randomisation information were not involved with any trial experimental procedure.

In the OLA–iCPAP group, patients received individualised intraoperative ventilation plus individualised postoperative CPAP. After endotracheal intubation, patients had a controlled, step-wise recruitment manoeuvre until airway pressure reached 40 cm H_2O, followed by a PEEP titration trial (stepwise decrease in PEEP until the highest Cdyn was observed). Individualised PEEP was set at 2 cm H_2O above the PEEP level that resulted in the highest Cdyn after a new recruitment manoeuvre was done (appendix). Additional recruitment manoeuvres and PEEP titration trials were done if Cdyn decreased by more than 10% and oxyhaemoglobin saturation (SpO_2) decreased to 96% or lower after 5 min while breathing a fraction of inspired oxygen (FIO_2) of 0·21, assessed every 40 min. For postoperative management, patients received supplemental oxygen through a Venturi face mask (various manufacturers). CPAP was then started in individuals if SpO_2 was 96% or less while breathing room air in a supine position. A CPAP level of 5 cm H_2O (or 10 cm H_2O if the BMI exceeded 30 kg/m²) was applied for 3 h, as specified in the protocol.

In the OLA–CPAP group, patients received individualised intraoperative ventilation plus post-operative CPAP. During intraoperative management, mechanical ventilation was provided as in the OLA-iCPAP group. For postoperative management, patients received 5 or 10 cm H_2O CPAP, depending on BMI, during the first 3 postoperative hours, irrespective of SpO_2 values.

In the STD–CPAP group, patients received standard intraoperative ventilation plus postoperative CPAP. Intraoperatively, lung-protective ventilation was provided with a fixed PEEP of 5 cm H_2O without recruitment manoeuvre. Postoperative management was identical to that in the OLA–CPAP group.

Patients in the STD–O_2 received the standard perioperative protocol. Ventilation was provided intraoperatively, as in the STD–CPAP group. In the postoperative period, patients received supplemental oxygen via a Venturi face mask.

Intraoperative data and data collected in the postanaesthetic care units (PACU) were collected by an unmasked investigator; postoperative data (ie, in the ward) were collected by an investigator who was masked to randomisation. Patients were masked to treatment allocation. All participating patients, regardless of study group, were monitored and managed following general high standard-of-care practices (appendix).

Procedures

Pre-oxygenation was done for 5 min at FIO_2 0·8 with a tightly sealed face mask before anaesthesia induction. In all groups, intraoperative lung-protective mechanical ventilation settings included a volume controlled mode using a tidal volume of 8 mL per kg predicted bodyweight and an airway plateau pressure (Pplat) of 25 cm H_2O or less (appendix). During the awakening period from general anaesthesia, FIO_2 0·8 was applied at the same end-expiratory pressure used, by either PEEP or CPAP. Once extubated, patients were oxygenated with FIO_2 0·5 through a Venturi face mask (appendix).

A recruitment manoeuvre was done after intubation, followed by a PEEP titration trial (appendix). Before starting the recruitment manoeuvre, the attending anaesthesiologist ensured the patient's haemodynamic stability (mean arterial pressure >70 mm Hg, cardiac index of more than 2·5 mL/min per m², or both) for at least 5 min, stroke volume variation less than 10%, and adequate neuromuscular blockade (0 of 4 by train of four).

General postoperative management in the PACU was decided by the attending physician, following the established protocols at each centre. A set of rules and recommendations were applied (appendix).[18]

Rescue therapies were initiated if oxyhaemoglobin saturation (SpO_2) decreased to 92% or less, including during the Air Test (appendix), or if SpO_2 decreased to 95% or less while on FIO_2 0·5, with or without CPAP according to the patient's randomisation group. Assessment of a positive or negative response to the rescue manoeuvre was done in a maximum period of 30 min.

For patients in the OLA–iCPAP group who had FIO_2 of 0·5 while under the Venturi face mask, the rescue manoeuvre was started with 5 cm H_2O CPAP (or 10 cm H_2O when BMI >30 kg/m²). For patients already on 5 cm H_2O CPAP, it was increased to 10 cm H_2O. Inspiratory support with non-invasive ventilation was started for

(L Rovira PhD); **Department of Anesthesiology & Critical Care, Hospital Principe de Asturias, Madrid, Spain** (F Barrios MD); **Department of Anesthesiology & Critical Care, Hospital Son Espases, Palma de Mallorca, Spain** (V Torres MD); **Department of Anesthesiology, Hospital NS de Candelaria, Santa Cruz de Tenerife, Spain** (S Hernández MD); **Department of Anesthesiology, Hospital Privado de Comunidad Mar de Plata, Mar de Plata, Argentina** (G Tusman MD); **Multidisciplinary Organ Dysfunction Evaluation Research Network, Hospital Universitario Doctor Negrin, Las Palmas, Spain** (J Villar); **and Department of Surgery, Universidad de Valencia, Valencia, Spain** (J Belda)

Correspondence to:
Dr Carlos Ferrando, Department of Anesthesiology & Critical Care, Hospital Clínico Universitario de Valencia, 46010 Valencia, Spain
cafeoranestesia@gmail.com

See **Online** for appendix

For more on the **iPROVE website** see http://iprove.incliva.es patients with a BMI greater than 30 kg/m² who had persistent hypoxaemia, hypercapnia (blood partial pressure of carbon dioxide [PaCO$_2$] >50 mm Hg with a pH <7·3), or both, an respiratory rate greater than 25 breaths per min, or increased activity of accessory respiratory muscles.

For patients in OLA–CPAP and STD–CPAP groups, rescue manoeuvres were identical to those described for patients starting on 5 cm H$_2$O CPAP. In the STD–O$_2$ group, FiO$_2$ was increased to 0·8 through a controlled FiO$_2$ mask with a non-rebreathing reservoir bag, and the following steps were identical to those in the OLA–iCPAP group.

The non-invasive and invasive mechanical ventilation indication and management were protocolised and are described in the appendix.

Outcomes

The primary outcome was a composite of postoperative complications during the first 7 postoperative days, including respiratory complications (aspiration pneumonitis, atelectasis, bronchospasm, dyspnoea, pleural effusion, hypoxaemia, pneumothorax, pneumonia, acute respiratory distress syndrome, non-invasive and invasive mechanical ventilation) and systemic complications (surgical site infection, anastomotic dehiscence, sepsis, septic shock, cardiac failure, renal failure, requirement for surgical reintervention). Composite components were similar to previous trials.[7,8] Postoperative complications of perioperative outcome measurements were defined according to the joint taskforce of the European Society of Anaesthesiology and the European Society of Intensive Care Medicine (appendix).[19]

Secondary outcomes included composites of pulmonary or systemic complications during the first 7 postoperative days and total complications between the seventh and 30th day after surgery, non-planned intensive care unit (ICU) admission, hospital readmission, length of stay in the ICU and in hospital, death, and inflammatory markers, the latter of which are not reported. We also assessed infectious complications as a post-hoc composite outcome of surgical site infection, sepsis, septic shock, and pneumonia. Primary and secondary data outcomes were taken 3 h after PACU admission and at 1, 2, 7, and 30 days after surgery, with a 180-day follow-up for all-cause mortality. We also recorded demographic preoperative baseline and intraoperative and postoperative variables.

Statistical analysis

For sample size calculations, we assumed a risk of 25% for developing postoperative complications and an absolute risk reduction of 12·5% in individualised treatment groups; eight people needed to be treated with an individualised approach to prevent one additional person with at least one of the complications included in the composite main endpoint. Taking into account the statistical power for making matched comparisons between the four groups in the study, with a significance level of 5% and a power of 80%, we estimated a sample of 920 patients (230 in each group) to be necessary, which we increased to 1012 to account for dropouts. The recruitment among centres was competitive. In all four groups, the interim analysis revealed a much higher complication rate than that assumed from the literature, which could lead to a loss of statistical power.[20] Therefore, the steering committee decided to reduce the comparisons from the original six-pairwise to only three (each intervention group *vs* the standard control group, excluding comparisons among intervention groups) after the first interim analysis (150 patients). At the same time, the steering committee also modified the pre-planned analysis to include a post-hoc exploratory analysis: patient stratified by number of complications, categorised in an ordinal scale (0, 1–2, >2 complications).[17] An additional post-hoc analysis was hospital length of stay, for which total complications during the first 7 postoperative days were aggregated and analysed for their effect on length of stay using Spearman's correlation coefficient.

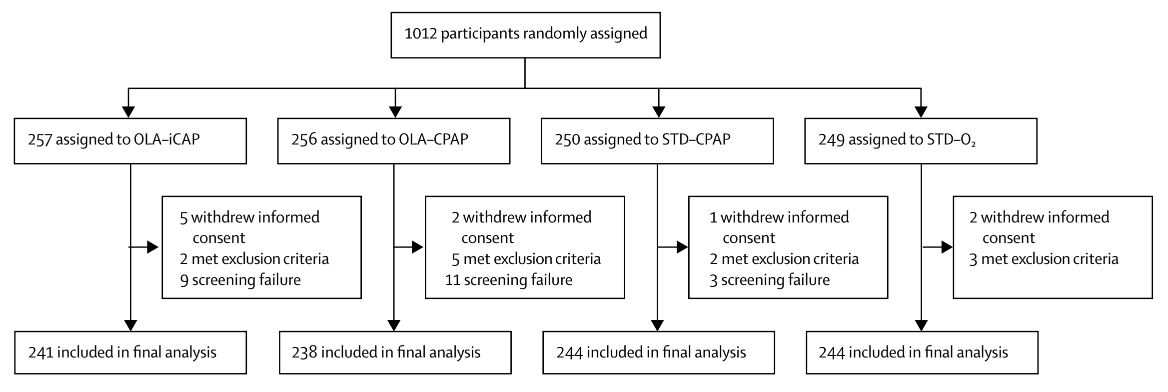

Figure 1: **Trial profile**

OLA=open-lung approach (ie, individualised intraoperative ventilation). CPAP=continuous positive airway pressure. iCPAP=individualised CPAP. STD–CPAP=standard intraoperative ventilation plus CPAP. STD–O$_2$=standard intraoperative ventilation plus standard postoperative oxygen therapy. All CPAP was provided postoperatively.

We did all analyses on a modified intention-to-treat basis, using all available data (967 participants). We compared postoperative variables using either Student's *t* test or the Mann–Whitney *U* test for continuous variables, depending on the variables (we used the Shapiro–Wilk test to assess normality), and the χ^2 test, Fisher's exact test, or asymptotic linear-by-linear association test, as appropriate, for categorical variables. Data are given as mean (SD) or median (IQR), as appropriate. We report primary and secondary outcomes as relative risk (RR) or absolute risk reduction (ARR). Kaplan–Meier curves were used to assess the probability of remaining free of postoperative complications, and we used the log-rank test to report p values. We assessed differences in length of stay using Poisson regression or alternatively negative-binomial if the model did not fulfil Poisson assumptions (overdispersion), and they are expressed as incidence rate ratios (IRRs). Additionally, in the case of length of stay in ICU, which contains excess zero-count data, we used an appropriated zero inflated regression (Poisson or negative-binomial) model. We estimated the CIs of these outcomes (reported as incidence rate ratios) using 1000 bootstrap samples. Other statistical models were introduced to reanalyse the effects of the interventions on the primary outcome, considering a possible hospital effect; we used generalised linear mixed models with a random intercept of hospital to assess the protocol outcome of any complications.

As we made three comparisons (interventions against standard control), following the Hochberg sequential and taking into account the two previous interim analyses, the multiple-comparison-corrected threshold for the third-ordered p value needed to be less than 0·016 to be significant.[21,22] We applied this value to all preplanned outcomes. On the basis of interpreting our analysis as a case of hierarchical testing, which can be considered as a specific multiplicity procedure according to the European Medicines Agency draft guideline on multiplicity issues in clinical trials, we did not introduce multiple comparisons when reporting subcomponents of the primary outcome (ie, secondary outcomes).[23]

All tests were two-tailed. Since less than 5% of data for postoperative primary complications were missing or unavailable, without differences between groups, handling of missing data was not applied.[24] We did two interim analyses following the monitoring plan based on the modified Haybittle–Peto boundaries for stopping trials.[25] The data and safety monitoring board did not recommend stopping the trial. We did all analyses with R (version 3.3.1).

This trial is registered with ClinicalTrials.gov, number NCT02158923.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Jan 2, 2015, to May 18, 2016, we enrolled and randomly assigned 1012 patients (figure 1). Baseline characteristics did not differ between groups (table 1). More than 80% of patients had oncological procedures and about 40% of all procedures were laparoscopies.

	OLA–iCPAP (n=241)	OLA–CPAP (n=238)	STD–CPAP (n=244)	STD–O_2 (n=244)
Mean age (years)	64·3 (13·0)	64·7 (13·2)	66·5 (11·4)	64·8 (12·9)
Sex				
Male	141 (59%)	157 (66%)	163 (67%)	154 (64%)
Female	100 (41%)	80 (34%)	80 (33%)	90 (37%)
Height (cm)	165·5 (9·7)	165·3 (9·0)	165·7 (8·6)	165·0 (8·6)
BMI (kg/m^2)	26·0 (4·0)	26·2 (4·0)	25·8 (3·7)	26·1 (3·9)
Predicted bodyweight (kg)*	61·2 (9·6)	61·4 (9·5)	61·6 (8·8)	60·6 (9·4)
ASA physical status classification				
I	16 (7%)	15 (6%)	17 (7%)	13 (5%)
II	140 (58%)	116 (49%)	119 (49%)	124 (51%)
III	80 (33%)	100 (43%)	96 (40%)	104 (43%)
IV	3 (1%)	1 (<1%)	6 (2%)	0
ARISCAT score†				
Intermediate	187 (78%)	182 (77%)	181 (74%)	182 (75%)
High	47 (20%)	53 (22·6)	56 (23%)	59 (24%)
Preoperative haemoglobin (g/dL)	13·4 (7·5)	12·9 (1·9)	12·8 (2·1)	13·4 (8·9)
Preoperative SaO_2 (%)	97·1 (2·1)	97·1 (2·0)	97·3 (1·9)	97·1 (2·2)
Previous pulmonary infection	11 (5%)	11 (5%)	5 (2%)	7 (3%)
Comorbidity				
Chronic obstructive pulmonary disease	10 (4%)	14 (6%)	12 (5%)	12 (5%)
Obstructive sleep apnoea syndrome	3 (1%)	4 (2%)	0	6 (2%)
Arterial hypertension	102 (42%)	102 (43%)	98 (40%)	96 (39%)
Diabetes	26 (11%)	42 (17%)	45 (19%)	45 (18%)
Obesity (BMI≥30 kg/m^2)	34 (14%)	42 (18%)	30 (12%)	40 (16%)
Type of surgery‡				
Laparoscopy	92 (38%)	85 (36%)	87 (36%)	100 (41%)
Oncological	207 (86%)	200 (84%)	207 (85%)	205 (84%)
Surgical procedure				
Pancreaticduodenectomy	22 (9%)	20 (8%)	25 (10%)	20 (8%)
Liver resection	33 (14%)	50 (21%)	39 (16%)	38 (16%)
Colorectal	113 (47%)	92 (39%)	97 (40%)	111 (46%)
Gastrectomy	24 (10%)	17 (7%)	25 (10%)	22 (9%)
Carcinomatosis	10 (4%)	16 (7%)	10 (4%)	11 (5%)
Bricker	4 (2%)	7 (3%)	8 (3%)	2 (1%)
Vascular	4 (2%)	8 (3%)	6 (2%)	2 (1%)
Other	30 (12%)	27 (11%)	33 (14%)	38 (16%)

Data are mean (SD) for continuous variables and n (%) for categorical variables. There are missing data for some categories. OLA=open-lung approach. iCPAP=individualised CPAP. CPAP=continuous positive airway pressure. STD=standard. BMI=body-mass index. ASA=American Society of Anesthesiologists. SaO_2=oxyhaemoglobin saturation. *Calculated as follows: for men, (50 + 0·91) × (height in cm–152·4); for women, (45·5 + 0·91) × (height in cm–152·4). †Patients with intermediate-to-high risk were eligible for participation in the study, but not those with mild risk. ‡Patients could have both types of surgery.

***Table 1:* Patients' characteristics**

	OLA–iCPAP (n=241)	OLA–CPAP (n=238)	STD–CPAP (n=244)	STD–O_2 (n=244)	p value
PEEP (cm H_2O)					
1 h after ventilation start	10·3 (2·7)	10·3 (3·0)	5·6 (1·5)	5·4 (1·3)	<0·0001
End of surgery	10·6 (2·9)	10·4 (3·1)	5·6 (1·5)	5·4 (1·3)	<0·0001
Tidal volume (mL)					
Baseline	483 (72)	487 (71)	487 (67)	481 (64)	0·68
1 h after ventilation start	480 (73)	484 (72)	484 (66)	479 (65)	0·74
End of surgery	481 (72)	485 (71)	489 (69)	479 (65)	0·43
Plateau pressure (cm H_2O)					
Baseline	15·9 (4·0)	15·7 (4·0)	15·3 (3·8)	15·5 (3·8)	0·33
1 h after ventilation start	20·8 (5·1)	20·9 (5·8)	17·8 (5·0)	18·6 (5·5)	<0·0001
End of surgery	19·3 (6·2)	19·2 (5·2)	15·8 (4·0)	16·3 (4·1)	<0·0001
Driving pressure (cm H_2O)*					
Baseline	10·9 (4·0)	10·7 (4·0)	10·3 (3·9)	10·5 (3·8)	0·38
1 h after ventilation start	10·4 (4·3)	10·4 (4·9)	12·2 (4·9)	13·2 (5·5)	<0·0001
End of surgery	8·7 (5·6)	8·7 (4·4)	10·3 (4·1)	10·8 (3·9)	<0·0001
PaO_2/FO_2 (mm Hg)					
Baseline	394·9 (119·2)	404·9 (117·3)	403·1 (117·8)	383·1 (126·1)	0·20
1 h after ventilation start	436·1 (118·0)	445·0 (115·6)	397·9 (124·9)	369·7 (122·9)	<0·0001
End of surgery	441·1 (113·6)	447·4 (111·1)	385·8 (116·5)	367·9 (121·5)	<0·0001
$PaCO_2$ (mm Hg)					
Baseline	37·9 (5·1)	38·3 (5·2)	38·4 (5·4)	38·4 (5·5)	0·69
1 h after ventilation start	39·7 (7·4)	40·1 (7·2)	40·5 (5·5)	40·8 (6·2)	0·34
End of surgery	40·2 (6·0)	40·2 (5·5)	41·9 (22·8)	40·5 (6·0)	0·42
Mean arterial pressure (mm Hg)					
Baseline	78·1 (14·9)	80·3 (15·6)	79·5 (15·5)	78·7 (14·6)	0·42
1 h after ventilation start	80·0 (14·1)	82·5 (14·3)	80·3 (14·5)	81·8 (14·1)	0·17
End of surgery	77·8 (12·9)	77·9 (12·4)	78·4 (12·6)	80·3 (13·7)	0·12
Cardiac index (mL/min per m²)					
Baseline	2·61 (0·61)	2·65 (1·15)	2·54 (0·71)	2·56 (0·60)	0·74
1 h after ventilation start	2·80 (0·65)	2·90 (1·42)	2·74 (0·69)	2·76 (0·61)	0·55
End of surgery	3·08 (2·16)	2·96 (1·45)	2·88 (0·70)	2·85 (0·62)	0·59
Volume of fluids					
Crystalloids (L)	1·92 (1·09)	2·03 (1·22)	1·94 (1·11)	1·80 (1·06)	0·17
Colloids (L)	0·24 (0·38)	0·28 (0·36)	0·26 (0·41)	0·21 (0·33)	0·20
Blood products (mL)	63·1 (176·4)	48·7 (164·9)	95·3 (423·7)	45·1 (159·9)	0·13
Blood loss (mL)	389 (438)	399 (353)	407 (469)	324 (320)	0·11
Urine output (mL)	370 (334)	386 (325)	416 (352)	394 (386)	0·56
Vasoactive drugs†	120 (51·3%)	138 (58·7%)	131 (54·8%)	116 (48·3%)	0·12
Epidural analgesia	140 (58·1%)	144 (60·5%)	134 (55·4%)	122 (50·2%)	0·13
Neuromuscular blockade optimisation‡	79 (33·2%)	66 (28·2%)	76 (31·8%)	66 (27·7%)	0·49
Temperature (°C)§	36·0 (0·7)	35·8 (1·2)	36·0 (0·8)	35·9 (0·8)	0· 21
Prophylaxis of postoperative nausea and vomiting	215 (92·3%)	212 (92·6%)	221 (91·3%)	219 (91·6%)	0·96
Duration of ventilation (min)	240 (190–310)	240 (185–310)	240 (190–320)	225 (180–300)	0·28
Duration of surgery (min)¶	207·5 (160–260)	200 (149–260)	200 (150–271)	190 (145–240)	0·08

Data are presented as mean (SD) or median (IQR) for continuous variables, and n (%) for categorical variables. OLA=open-lung approach. iCPAP=individualised CPAP. CPAP=continuous positive airway pressure. STD=standard. PEEP=positive end-expiratory pressure. PaO_2/FIO_2=ratio of partial pressure of arterial oxygen to inspiratory oxygen fraction. $PaCO_2$=partial pressure of arterial carbon dioxide. *Calculated as plateau pressure minus PEEP. †Vasopressors, ionotropes, or both. ‡Patients in whom neuromuscular blockade was monitored or reversed when considered by the attending physician before extubation. §Recorded at the end of surgery. ¶Time between skin incision and closure of the incision.

***Table 2:* Intraoperative characteristics**

Intraoperatively, 466 (98%) of 479 patients from the OLA–iCPAP and OLA–CPAP groups completed the recruitment manoeuvre-protocol. In 20 (4%) of 479 patients, recruitment manoeuvre was stopped because of transient haemodynamic compromise, but it was successfully completed after stabilisation in all cases.

Median individualised PEEP was 10 cm H_2O (IQR 8–12; appendix). PEEP was increased in 69 (14%) of 488 patients of standard groups, whereas no patients from the OLA groups required rescue manoeuvres because of hypoxaemia (appendix). Postoperatively, 69 (30%) of 241 patients in the OLA–iCPAP group required protocolised CPAP (appendix). There were no differences between groups in the percentage of patients that had early withdrawal of postoperative CPAP (appendix). Intraoperative and postoperative variables are shown in table 2 and the appendix.

Haemodynamics, overall fluid administration, use of vasoactive drugs, urine output, blood losses, type of anaesthesia, duration of surgery, and mechanical ventilation did not differ significantly between groups (table 2).

In the modified intention-to-treat analysis, there were no significant differences in the primary outcome of the proportion of patients with postoperative complications (110 [46%] of 241 patients in the OLA–iCPAP group, 111 [47%] of 238 patients in the OLA–CPAP group, 118 [48%] of 244 patients in the STD–CPAP group, and 125 [51%] of 244 patients in the STD–O_2 group; figure 2). Risk of pulmonary and systemic complications in the first 7 days after surgery did not differ significantly for patients in OLA–iCPAP (RR 0·89 [95% CI 0·74–1·07; p=0·25]), OLA–CPAP (0·91 [0·76–1·09; p=0·35]), or STD–CPAP groups (0·95 [0·80–1·14; p=0·65]) when compared with standard intraoperative and postoperative ventilation (table 3).

For the secondary outcomes, the OLA–iCPAP group had a lower incidence of pulmonary complications than the standard group (RR 0·80, 95% CI 0·65–0·99; p=0·047), but the difference in systemic complications was not significant (p=0·066) compared with the other groups (table 3; appendix). Although the overall composite outcome for systemic differences did not differ significantly between the OLA–iCPAP and STD–O_2 groups, specific components of the composite outcomes were significantly improved in the OLA–iCPAP group (appendix), including a post-hoc analysis of the proportion of patients with infectious complications (table 3).

In the post-hoc exploratory analysis, fewer patients from the OLA–iCPAP group developed at least three complications (RR 0·46, 95% CI 0·27–0·76; ARR 21%, 95% CI 8–35, p=0·013) than did those in the STD–O_2 group. No significant differences were found between the OLA–CPAP and STD–CPAP groups and the STD–O_2 group. In the OLA–iCPAP group, fewer patients developed at least three postoperative pulmonary complications than in the STD–O_2 group (RR 0·49, 95% CI 0·26–0·92; ARR 19%, 95% CI 2–35, p=0·010). The proportion of patients with at least three systemic complications was also lower in the OLA–iCPAP group (RR 0·23, 95% CI 0·07–0·81; ARR 32%, 95% CI 9–55, p=0·013; table 3).

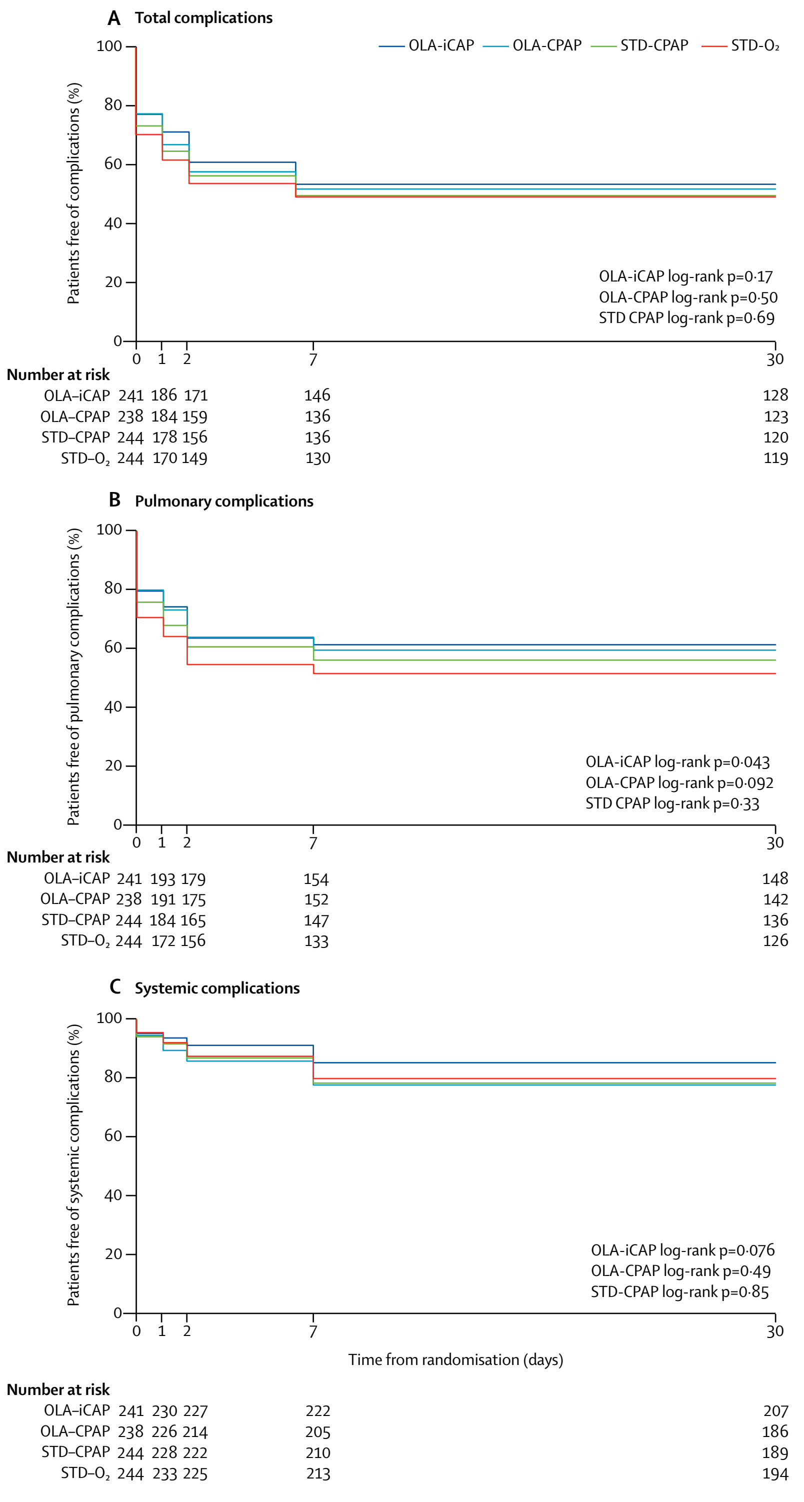

Figure 2: **Number of patients at risk of complications, from day 0 to day 30**
All comparisons are with the STD–O_2 group. Post-surgery data were recorded at the end of the postoperative ventilatory strategy, as indicated in the protocol. OLA=open-lung approach. iCPAP=individualised CPAP. CPAP=continuous positive airway pressure. STD=standard.

	OLA–iCPAP (n=241)	OLA–CPAP (n=238)	STD–CPAP (n=244)	STD–O$_2$ (n=244)	RR (95% CI; p value) or IRR (95% CI)*		
					OLA–iCPAP vs STD–O$_2$	OLA–CPAP vs STD–O$_2$	STD–CPAP vs STD–O$_2$
Primary composite outcome†							
Patients with complications	110 (46%)	111 (47%)	118 (48%)	125 (51%)	0·89 (0·74–1·07; p=0·25)	0·91 (0·76–1·09; p=0·35)	0·95 (0·80–1·14; p=0·65)
Patients stratified by number of complications					0·46 (0·27–0·76; p=0·013)	0·73 (0·47–1·13; p=0·18)	0·72 (0·47–1·11; p=0·29)
0	131 (54%)	127 (54%)	124 (51%)	120 (49%)	..	..	..
1–2	91 (38%)	81 (34%)	88 (36%)	82 (34%)	..	..	..
≥3	19 (8%)	30 (13%)	30 (12%)	42 (17%)	..	..	..
Secondary composite outcomes							
Number of patients with postoperative pulmonary complications	93 (39%)	96 (41%)	105 (43%)	117 (48%)	0·80 (0·65–0·99; p=0·047)	0·84 (0·69–1·03; p=0·11)	0·90 (0·74–1·10; p=0·35)
Patients stratified by number of postoperative pulmonary complications	..	..	..	..	0·49 (0·26–0·92; p=0·010)	0·72 (0·41–1·26; p=0·07)	0·82 (0·48–1·40; p=0·28)
0	148 (61%)	142 (60%)	137 (57%)	127 (52%)	..	..	..
1–2	80 (33%)	77 (32%)	83 (34%)	90 (37%)	..	..	..
≥3	13 (5%)	19 (8%)	22 (9%)	27 (11%)	..	..	..
Patients with systemic complications	29 (12%)	43 (18%)	45 (19%)	45 (18%)	0·65 (0·42–1·00; p=0·066)	0·98 (0·67–1·43; p=1·00)	1·01 (0·69–1·46; p=1·00)
Patients stratified by number of systemic complications	..	..	..	..	0·23 (0·07–0·81; p=0·013)	0·47 (0·18–1·22; p=0·35)	0·70 (0·3–1·60; p=0·75)
0	212 (88%)	195 (82%)	197 (81%)	199 (82%)	..	..	..
1–2	26 (11%)	34 (14%)	36 (15%)	32 (13%)	..	..	..
≥3	3 (1%)	6 (3%)	9 (4%)	13 (5%)	..	..	..
Patients with infectious complications‡	20 (8%)	26 (11%)	27 (11%)	39 (16%)	0·52 (0·31–0·86; p=0·014)	0·68 (0·43–1·09; p=0·13)	0·70 (0·44–1·10; p=0·15)
Other secondary outcomes							
Median ICU length of stay, in days (IQR)*	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–3·0)	1·0 (1·0–3·0)	0·46 (0·18–0·82)	0·56 (0·20–0·98)	0·97 (0·51–1·80)
Median hospital length of stay, in days (IQR)*	7 (5–11)	8 (6–13)	8 (6–13)	8 (6–13)	1·12 (0·95–1·36)	1·22 (1·03–1·50)	1·18 (0·99 –1·47)
Death within 30 days§	2 (1%)	4 (2%)	6 (2%)	2 (1%)	1·00	0·65	0·26
Death within 180 days§	10 (4%)	12 (5%)	13 (5%)	10 (4%)	1·00	0·69	0·50
Death within 365 days§	21 (9%)	25 (11%)	21 (9%)	24 (10%)	0·41	0·45	0·40

Data are n (%) for categorical variables and mean (SD) for continuous variables, unless otherwise indicated. All composite outcomes are within the first 7 postoperative days. Data for non-planned ICU admission and hospital readmission are shown in the appendix. OLA=open-lung approach. iCPAP=individualised CPAP. CPAP=continuous positive airway pressure. STD=standard intraoperative ventilation. RR=relative risk. IRR=incidence rate ratio. ICU=intensive care unit. *All comparisons are with standard intraoperative and postoperative ventilation (STD–O$_2$). †Composite of both pulmonary (aspiration pneumonitis, bronchospasm, dyspnoea, pleural effusion, atelectasis, hypoxaemia, pneumothorax, pneumonia, CPAP, non-invasive and invasive ventilation, and acute respiratory distress syndrome) and systemic complications (surgical site infection, anastomosis dehiscence, sepsis, septic shock, cardiac and renal failure, abdominal abscess, and requirement for surgical reintervention) experienced by the study population. ‡Infectious complication was a post-hoc composite of surgical site infection, sepsis, septic shock, and pneumonia, as defined by standard criteria; for additional data, see the appendix. §Data are IRR only.

Table 3: Results

Patients in the OLA–iCPAP and OLA–CPAP groups had an approximately 50% lower risk of prolonged length of stay in the ICU than did patients in the STD–O$_2$ group (table 3). We noted a significant correlation between the number of postoperative complications per patient and length of stay in hospital (appendix). We found no differences among groups in length of stay in hospital, or the proportion of patients with non-planned admission to ICU (appendix), and overall mortality at days 30, 180, and 365 did not differ significantly between groups (table 3; appendix).

Discussion

To the best of our knowledge, iPROVE is the first randomised controlled trial in patients having major abdominal surgery in whom a ventilation strategy is continuously individualised to their lung condition during the whole perioperative period. There was no significant difference in the primary endpoint (a composite of patients with postoperative complications within the first 7 postoperative days) between the three interventional groups and standard lung-protective mechanical ventilation. Hypoxaemic events decreased during the intraoperative and immediate postoperative period with the open-lung approach. The secondary outcomes of pulmonary complications, infectious complications (a post-hoc analysis), and ICU length of stay were reduced with the most individualised strategy, but these results must be interpreted with caution and need to be corroborated in additional well powered studies.

Although the differences between groups had a lower order of magnitude than expected, these findings might be of clinical relevance, since all enrolled patients had healthy lungs and were managed with protective mechanical ventilation. To our knowledge, this is the first randomised controlled trial in which an intraoperative lung-protective mechanical ventilation of low tidal volume and adequate PEEP has been used as a control group. The selected tidal volume of 8 mL per kg predicted bodyweight for all study groups was based on current recommendations.[2–4] Although the protective effects of PEEP are not clearly established, recent evidence recommends the use of intraoperative 5 cm H_2O of PEEP in patients with healthy lungs.[26] Some of the strengths of this trial were that we compared several combinations of intraoperative and postoperative lung-protective ventilatory mechanical ventilation strategies, from the most individualised to the most standardised. One of the additional strengths of this trial was the inclusion of rescue manoeuvres for all groups and the anaesthetic management based on the Enhanced Recovery after Surgery programme.

By contrast with the IMPROVE trial,[7] in which repetitive recruitment manoeuvres combined with moderate levels of PEEP (6–8 cm H_2O) resulted in a reduction of total postoperative complications, we did not find such a reduction. The results of that study strongly supported the benefits of an open-lung approach, although a non-protective ventilation of tidal volume of 10–12 mL/kg predicted bodyweight and zero PEEP was used as a control, which probably magnified the findings. Our results are in line with the PROVHILO trial,[8] in which there was no significant difference in the primary outcome (a composite only composed of postoperative pulmonary complications) when an open-lung strategy, consisting of a combination of recruitment manoeuvre plus a fixed PEEP of 12 cm H_2O, was compared with a protective strategy (PEEP ≤2 cm H_2O). However, unlike the investigators of the PROVHILO study, we found benefits in some secondary outcomes and post-hoc analyses when an individualised PEEP was used intraoperatively, as in the OLA–iCPAP and OLA–CPAP groups, instead of an arbitrarily high PEEP level. Nevertheless, these secondary outcomes and exploratory results do not justify the use of individualised PEEP and should be corroborated in future, well powered randomised controlled trials. In line with results from the PROVHILO study, a significant number of patients in the standard groups had intraoperative hypoxaemia, which required a rescue with increased PEEP (appendix). The recruitment effect produced by this manoeuvre in the patients rescued might have a potential benefit to these patients that reduced the potential differences in development of postoperative pulmonary complications when compared with the OLA groups.

Requirement for fluids and for vasoactive drugs did not differ significantly between groups, despite the use of higher PEEP levels in the individualised mechanical ventilation strategy. The use of a higher but individualised PEEP in a less heterogeneous lung seemed to be better tolerated haemodynamically than did a fixed higher arbitrary PEEP level, as observed in the PROVHILO study.[8] The overall high adherence to the protocol corroborates the safety of the proposed recruitment manoeuvre using a stepwise increase in PEEP and the individualised PEEP titration after recruitment manoeuvre.

Postoperative CPAP mitigates post-extubation lung derecruitment, which frequently occurs during the immediate postoperative period, and has been shown to reduce postoperative pulmonary complications when initiated at the first sign of acute respiratory failure.[13] However, its benefit as a prophylactic therapy remains uncertain and it has never been applied in combination with an intraoperative lung-protective ventilation strategy.[27] Our results suggest that prophylactic CPAP might reduce the proportion of patients with postoperative pulmonary complications when it is applied in individually selected patients with clinical signs of lung derecruitment (SpO_2 ≤96% on room air)[18] in combination with an intraoperatively individualised ventilation aimed at minimising lung derecruitment (ie, the OLA–iCPAP group). Our results also suggest this protective effect was also evident when prophylactic CPAP was applied to all postoperative patients receiving an intraoperative individualised strategy (OLA–CPAP group). This finding is in line with the post-hoc finding of the OPERA trial,[28] in which routine prophylactic postoperative positive pressure after major abdominal surgery reduced hypoxaemia in the subgroup of patients in whom an open-lung strategy was applied intraoperatively.

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The effects of postoperative CPAP on systemic complications are not well known. We found in post-hoc analysis that individually applied CPAP (OLA–iCPAP) reduced infectious complications when compared with standard therapy (STD–O_2), which is in line with the findings of Squadrone and colleagues.[13] However, this finding was not corroborated when routine CPAP was applied (eg, in the OLA–CPAP and STD–CPAP groups). These results might suggest that CPAP might not be universally beneficial and that potential negative effects could prevail over its benefits when used in patients without lung derecruitment. Therefore, proper and careful patient selection seems to be an important determinant for the benefit of prophylactic postoperative CPAP, although it will need to be substantiated in further studies.

We found that patients in the OLA–iCPAP and OLA–CPAP groups had a reduction in length of stay in ICU when compared with patients who received standard ventilatory management. Paradoxically, and despite decreasing the number of complications per patient or severe complications such as infectious complications, we found no difference in length of stay in hospital. This finding might be justified by the different hospital discharge criteria between the 21 hospitals involved in the study. This finding is complemented by the post-hoc analysis that shows an association between number of complications per patient and hospital length of stay. When weighing all four protective strategies, the potential costs associated with postoperative pulmonary complications,[29] the expenses related to CPAP, and the prolonged length of stay associated with the number of complications per patient make the OLA–iCPAP the group with the lowest health-care costs.

Some methodological issues should be discussed. Our primary composite outcome, which included many complications of different weightings, limits clinical interpretation of the results. We complement our analysis with a post-hoc exploratory outcome of patients stratified by number of complications, which is justified by the reported association between the number of postoperative complications and patient mortality at days 30 and 90.[17] However, because of the absence of independence of the different components, this proxy does not satisfactorily overcome the primary outcome limitations and cannot be used to justify one strategy over others. Additionally, the design of the trial did not allow us to identify whether the intraoperative, postoperative, or both types of ventilation management caused the effects found in this trial. We also found a higher-than-estimated incidence of postoperative complications, in all four groups, which reduced the power of the study. In fact, to get a 12·5% absolute risk reduction (number needed to treat of eight) from the 50% rate of complications, the study would have needed to have been designed with an extra 100 patients per arm. In our final analysis, however, we found only a 6% absolute risk reduction between the OLA–iCPAP group and the standard group, which was not significant (appendix). The initially estimated incidence of postoperative pulmonary complications (17·5%) was calculated from the results of the ARISCAT study,[17] which was done in some of the same participant hospitals in Spain, with an estimated proportion of a fifth of included patients having a high-risk ARISCAT score. Finally, adding systemic complications, we estimated a 7·5% increase in patients with a systemic complication but without postoperative pulmonary complications. The higher incidence obtained was, in part, attributable to a higher than estimated number of mild postoperative pulmonary complications such as atelectasis, pleural effusion, or hypoxaemia. This finding could be justified by the accuracy of our diagnosis compared with previous trials, since SpO_2 was continuously monitored, minimising underestimation of hypoxaemia,[30] and because all the patients had at least two postoperative x-rays, which were analysed by an independent radiologist who was blinded for the purpose of the study.[31] Consequently, there is a problem of comparability between studies that use different instruments or measurements. Above all, from our perspective, we face the well known problem of interpreting an outcome for which the components do not compare in terms of clinical relevance.[24] Finally, the decision to change the analysis from six comparisons to three limits the data provided by our work. Although based on statistical arguments, to reduce the likelihood of a false-positive conclusion, it is a conflicting issue. If statistical adjustments for multiple endpoints might sabotage interpretation,[22] multiple comparison adjustments in the case of a multiarm trial (in this case, we adopted 0·016 instead of 0·05 as the significance threshold) is especially subject to controversy. Regardless, readers can read a summary of the results obtained from the original protocol (appendix).

On the basis of the results from this trial, future randomised controlled trials comparing ventilatory protective strategies should limit the number of comparisons by restricting the number of groups in the study design and including only potentially relevant strategies. The selection of single endpoints, or at least composites that have clinically homogeneous and relevant components, will make the interpretation easier. Finally, multicentre trials analysing postoperative complications should include not only the definition of the complication but also the accuracy of the measurements used in this definition. This approach might improve accuracy in the primary outcome estimation and facilitate comparability of studies.

In conclusion, among patients who had major abdominal surgery, the different open lung approaches tested in this study did not reduce the proportion of those with the composite endpoint of postoperative complications when compared with the standard lung-protective mechanical ventilation.

Contributors

CF and JBe had full access to all data and are responsible for the integrity and the accuracy of the data analysis. CF, MS, JVi, CU, GT, FS-S, JL, NP, SP, AL, JC, and JBe were responsible for study design. MS, CU, JC, IL, II, CA, ODC, DP, FJR, IG, JBa, JIG, MI, MGr, AR, LG, MM, RG, AB, JG, LR, FB, VT, SH, EG, MGi, MGa, NG, LM, SS PP, RP, SG-d-V, JVi, MJH, OP, AC, JP, and GA acquired the data. CF, MS, JVi, CU, GT, FS-S, JL, NP, SP, AL, JC, IL, and JBe analysed the data. CF, MS, CU, GT, FS-S, JC, JL, NP, SP, AL, IL, II, CA, ODC, DP, FJR, IG, JBa, JIG, MI, MGr, AR, LG, MM, RG, AB, JG, LR, FB, VT, SH, GT, JVi, and JBe interpreted the data. CF, MS, CU, FS-S, JC, JL, NP, SP, AL, IL, JBe, II, CA, ODC, DP, FJR, IG, JBa, JIG, MI, MGr, AR, LG, MM, RG, AB, JG, LR, FB, VT, SH, EG, MGi, MGa, NG, LM, SS PP, RP, SG-d-V, JVi, MJH, OP, AC, JP, and GA critically revised the manuscript.

Declaration of interests

We declare no competing interests.

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