iPROVE-OLV

INFORMATION BROCHURE

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1 Online randomization and study website

In order to facilitate various procedures for researchers, the iPROVE-OLV trial makes available the website from which it is possible to download patient information sheets, data collection notebooks and other documentation of interest related to the project.

The randomization of patients must be done through an online application which is accessed from the website, in the section "RANDOMIZATION AREA". To enter it, the user must enter with their own password provided. Then, clicking on the link "Access to the randomization application" the website will launch a form where the center code that was provided and the patient code should be written according to the established coding. Pressing the button will execute the randomization that will be stored in the database, and the result of the group to which the patient has been assigned will appear on the screen, with the option of printing it**. IMPORTANT: Only one randomization per patient must be done through the web application.** Launching the application more than once for the same patient code can lead to errors in the subsequent analysis of the results of the data collected in your center. To avoid errors, there is a link which can be used to perform randomization tests without sending or storing results.

- The code of your center is the same user with which the private area is accessed.
- The patient code has the structure "pac", followed by a 3-digit number that represents the number of the patient recruited in your center. For example: pac-002, pac-123 ...

On this website, you can also download paper data collection forms. However, once completed, the researcher must download the digital data collection forms, in Microsoft Word format, prepared to facilitate the entry of paper data into electronic format.

THE WEBSITE WILL BE READY IN FEW WEEKS. THEN, MORE ACCURATE INFORMATION FOR USER WILL BE GIVEN.

2. Scales and calculations

Body mass index (BMI): Kg/m^2

Predicted body weight (PBW):

men: PBW (kg) = 50 + 0.91 (height in cm-152)

women: PBW (kg) = 45.5 + 0.91 (height in cm-152)

8 ml/kg PBW in men				8 ml/kg PBW in women		
162 cm 470 ml	164 cm 485 ml	166 cm 500 ml		153 cm 370 ml	155 cm 385 ml	157 cm 400 ml
168 cm 515 ml	170 cm 530 ml	171 cm 535 ml		159 cm 415 ml	160 cm 420 ml	161 cm 425 ml
172 cm 540 ml	173 cm 550 ml	174 cm 560 ml		162 cm 435 ml	163 cm 440 ml	164 cm 450 ml
175 cm 565 ml	176 cm 570 ml	177 cm 580 ml		165 cm 455 ml	166 cm 465 ml	167 cm 470 ml
178 cm 585 ml	179 cm 595 ml	180 cm 600 ml		168 cm 475 ml	169 cm 485 ml	170 cm 490 ml
182 cm 615 ml	184 cm 630 ml	186 cm 645 ml		171 cm 500 ml	172 cm 505 ml	174 cm 520 ml
188 cm 660ml	190 cm 670 ml	192 cm 685 ml		176 cm 530 ml	178 cm 550 ml	180 cm 565 ml

6 ml/kg PBW in men				6 ml/kg PBW in women		
162 cm 354 ml	164 cm 465 ml	166 cm 376ml		153 cm 278 ml	155 cm 289 ml	157 cm 300 ml
168 cm 387 ml	170 cm 398 ml	171 cm 403 ml		159 cm 311 ml	160 cm 316 ml	161 cm 322 ml
172 cm 409 ml	173 cm 414 ml	174 cm 420 ml		162 cm 327 ml	163 cm 333 ml	164 cm 338 ml
175 cm 426 ml	176 cm 431 ml	177 cm 436 ml		165 cm 344 ml	166 cm 349 ml	167 cm 355 ml
178 cm 442 ml	179 cm 448 ml	180 cm 453 ml		168 cm 360 ml	169 cm 366 ml	170 cm 371 ml
182 cm 458 ml	184 cm 464 ml	186 cm 469 ml		171 cm 377 ml	172 cm 382 ml	174 cm 388 ml
188 cm 475 ml	190 cm 480 ml	192 cm 486 ml		176 cm 393 ml	178 cm 399 ml	180 cm 404 ml

ASA physical status classification system

ASA I	**A normal healthy patient** Healthy, non-smoking, no or minimal alcohol use
ASA II	**A patient with mild systemic disease** Only mild diseases without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	**A patient with severe systemic disease** Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	**A patient with severe systemic disease that is a constant threat to his life** Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis

Charlson comorbidity index

Clinical condition	**Weight**
- Myocardial infarct, Congestive cardiac insufficiency, peripheral vascular disease, cerebrovascular disease. - Dementia - COPD - Ulcers - Conjunctive tissue disease - Cirrhosis or chronic disease of the liver - Diabetes	**1**
- Hemiplegia - Moderate or severe kidney disease - Diabetes with organ complication - Tumor/Leukemia/Lymphoma	**2**
- Moderate or severe liver disease	**3**

- Malignant tumor, metastasis, AIDS	**6**

SOFA (Sequential Organ Failure Assessment) SCORE

System					
	0	**1**	**2**	**3**	**4**
Cardiovascular	MAP > 70 mmHg	MAP < 70 mmHg	Dopamine≤5 µg/kg/min or dobutamine (any dose)	Dopamine>5 or epinephrine≤0.1 or norepinephrine ≤0.1	Dopamine>5 or epinephrine >0.1 or norepinephrine >0.1
Respiratory (PaO_2/FiO_2)	>400	301-400	201-300	101-200	≤ 100
Hepatic (bilirrubin,µmol/l mg/dl	≤ 20 <1.2	20-32 1.1-1.9	33-101 2.0-5.9	102-204 6.0-11.9	>204 >12.0
Kidney (creatinine**,** µmol/l) mg/dl	≤ 110 <1.2	110-170 1.2-1.9	171-299 2.0-3.4	300-440; 3.5-4.9; ó urine output ≤500 ml/d	>440; >5.0; ó urine output <200 ml/d
Coagulation (platelets, x $10^{3/}$microL)	>150	≤150	≤100	≤50	≤20
SNC (Glasgow Coma Scale)	15	13-14	10-12	6-9	<6

Visual Analog Scale (VAS)

The VAS scale allows to measure the pain intensity that the patient describes with the maximum reproducibility among the observers. It consists of a horizontal line of 10 centimeters, at the ends of which are the extreme expressions of a symptom. On the left is the absence of pain or less intensity. The patient is asked to mark the point indicating the intensity on the line and it is measured with a millimeter ruler. The intensity is expressed in centimeters or millimeters.

ARISCAT Score

Age	≤ 50	0
	51-80	3
	≥ 80	16
Preoperative SpO_2	≥ 96	0
	91- 95	8
	≥ 90	24
Respiratory infection (last month)		17
Preoperative hemoglobin (≥ 10 g/dl)		11
Surgical incision	Peripherical	0
	Abdominal	15
	Intrathoracic	24
Duration of surgery (h)	≤ 2	0
	> 2 a 3	16
	> 3	23
Emergency surgery		8

Apfel score for PONV

Risk factors	Points
Female gender	1
Non-smoker	1
History PONV	1
Postoperative Opioids	1
Sum=	0.....4

Richmond agitation sedation scale

Score	Term	Description
+4	**Combative**	Overtly combative or violent; immediate danger for the staff
+3	**Very agitated**	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior towards staff
+2	**Agited**	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	**Restless**	Anxious or apprehensive movements but not aggressive or vigorous
0	**Alert and calm**	Spontaneously pays attention to caregiver
-1	**Drowsy**	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	**Light sedation**	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	**Moderate sedation**	Any movement (but no eye contact) to voice
-4	**Deep sedation**	No response to voice, but any movement to physical stimulation
-5	**Unarousable**	No response to voice or physical stimulation

Coma Glasgow Scale (CGS)

Eyes		**Verbal**	
Open eyes spontaneously	**4**	Opens eyes spontaneously	**5**
Open eyes in response to voice	**3**	Confused, disoriented	**4**
Open eyes in response to painful stimuli	**2**	Utters incoherent words	**3**
Do not open eyes	**1**	Incomprehensible sounds	**2**
Motor		Makes no sounds	**1**
Obeys commands	**6**	**TOTAL**	
Localizes to painful stimuli	**5**		
Flexion/Withdrawal to painful stimuli	**4**		
Abnormal flexion to painful stimuli	**3**		
Extension to painful stimuli	**2**		
Makes no movements	**1**		

Claven-Dindo Score

Grado	**Definition**
Grade I	Any deviation from the expected postoperative course that does not require specific treatment.
Grade II	Complications requiring drug therapy, blood transfusions or nutritional support.
Grade III	Postoperative changes that require invasive treatment (puncture, drainage and re-operations) **Grade IIa:** without general anesthesia **Grade IIb:** with general anesthesia
Grade IV	Complications with imminent risk of death and need for intensive care

	Grade IVa: 1 organ dysfunction Grade IVb: 2 or more organs dysfunction
Grade V	Postoperative death

III. Outcome definition criteria

Standard definition criteria follow definitions of the ESA-ESCIM joint taskforce on perioperative outcome measures.

Jammer Ib, Wickboldt N, Sander M, et al. Standars for definitions and use of outcome measures for clinical effectivenes research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions. A statement from de ESA-ESCIM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015; 32:88-105.

Pulmonary complications.

1. ***Mild acute respiratory failure***

PaO_2 < 60 mmHg, PaO_2/FiO_2 < 300 mmHg, SpO_2 < 90% and requiring oxygen therapy.

2. ***Severe acute respiratory failure***

PaO_2 < 60 mmHg, PaO_2/FiO_2 < 300 mmHg, SpO_2 < 90% and requiring non-invasive ventilation (including CPAP) or invasive ventilation.

3. ***Acute respiratory distress syndrome***

Berlin definition criteria:

- **Mild**: PaO_2/FiO_2 < 300 mmHg with CPAP ≥ 5 cmH_2O y FiO_2 ≥ 0.5.
- **Moderate:** PaO_2/FiO_2 < 200 mmHg with PEEP ≥ 5 cmH_2O y FiO_2 ≥ 0.5.
- **Severe**: PaO_2/FiO_2 < 100 mmHg with PEEP ≥ 5 cmH_2O y FiO_2 ≥ 0.5.

Acute (within one week) symptoms with bilateral pulmonary opacities

4. ***Pulmonary infection***

Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria:

- New or change of lung opacities
- White blood cells > 12.000 WBC/mm3
- Fever > 38,5ºC
- Positive alveolar lavage.

SECONDARY VARIABLES

Complicaciones Pulmonares Postoperatorias

5. ***Atelectasis***

- Chest X-ray: lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected área, and compensatory over-inflation in the adjacent non-atelectasic lung.
- LUS.

- Surgical or/and non-surgical lung

6. ***Pleural Effusion***

- Chest X-ray: Blunting of the costophrenic angle, loss of Sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or a hazy opacity in one hemithorax with preserved vascular shadows.
- LUS

- Surgical or/and non-surgical lung

7. ***Cardiogenic pulmonary oedema***

Fluid accumulation in the alveoli due to cardiac dysfunction.

8. ***Weaning failure (reintubation)***

Reintubation within the first 48h after postoperative extubation.

9. ***Bronchospasm***

Newly detected expiratory wheezing treated with bronchodilators

10. ***Neumothorax***

Air in the pleural space with no vascular bed surrounding the visceral pleura.

- Surgical or/and non-surgical lung.

11. ***Aspiration pneumonia***

Acute lung injury after the inhalation of regurgitated gastric contents.

12. *Pleural empyema*

Collection of pus in the pleural cavity, confirmed by thoracentesis and positive bacterial culture.

13. Bronchopleural fistula

Presence of continuous air leak through the bronchial stump and diagnosed with fiber-bronchoscopy.

14. Therapeutical fiber-bronchoscopy

***15. Pulmonary* embolism**

A new blood clot or thrombus within the pulmonary arterial system.

Systemic complications

1. ***Severe Sepsis***

Infectious focus identified plus organ dysfunction (defined as an increase in SOFA ≥2).

2. ***Septic Shock***

Severe sepsis with hypotension and hypoperfusion that is unresponsive to fluids.

3. ***Surgical Reintervención***

New surgical intervention within the first 30 days as consequence of a complication of the initial intervention.

4. ***Urinary tract infection***

A simplified version of the CDC recommendations defines a urinary tract infection as follows: a positive urine culture of 105 colony forming units ml1 with no more than two species of microorganisms, and with at least one of the following symptoms or signs: fever (> 38.8ºC), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause.

5. ***Heart failure***

Cardiac index <2.5 ml/min/m^2 or >2.5 when ≥5 µg/kg/min dobutamine is required. Clinical signs (hypotension, oliguria, pulmonary edema) together with NT-proBNP >13 pg/ml or echocardiographic diagnosis.

6. ***Myocardial infarction***

Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:10 symptoms of ischaemia; new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block; development of pathological Q waves on ECG; radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus at angiography or autopsy

7. Arrhythmia

ECG evidence of cardiac rhythm disturbance.

8. Acute kidney injury

AKIN scale:

- **Stage I**: Diuresis < 0,5 mg/Kg (6h) or increase in serum Cr > 0,3 mg/dl.
- **Stage II**: Diuresis < 0,5 mg/Kg (12h) or basal Cr x 2 mg/dL.
- **Stage III**: Diuresis < 0,3 mg/Kg (24h) o anuria (12h) or basal Cr x 3 mg/dL, or Cr > 4 mg/dL or renal replacement therapy.

9. Delirium

Positive CAM-ICU

10. Surgical site infection

The CDC defines a superficial incisional surgical site infection as one which meets the following criteria.

(1) Infection occurs within 30 days after surgery and

(2) Involves only skin and subcutaneous tissue of the incision and

(3) The patient has at least one of the following:

(a) purulent drainage from the superficial incision

(b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision

(c) at least one of the following symptoms or signs of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture negative finding does not meet this criterion.

(d) diagnosis of an incisional surgical site infection by a surgeon or attending physician.

IV. Recommendations for intraoperative management.

The objective of these recommendations is to homogenize our sample to the maximum. Although they are not mandatory for the inclusion of patients in the study, the homogenization of the sample will facilitate the subsequent statistical analysis and the interpretation of the results.

1. Hypnotics

The use of halogenated anesthetics is recommended during the intraoperative period, maintaining levels of anesthetic depth by bispectral analysis (BIS) of between 40-60.

Although the literature does not demonstrate differences in the appearance of postoperative complications, recent studies suggest a greater anti-inflammatory effect of sevoflurane with respect to propofol.

- Schilling et al. Anesthesiology 2011; 115:65 – 74.
- De Conno et al. Anesthesiology 2009; 110:1316 – 1326.

2. Analgesia

The perioperative use of thoracic epidural analgesia or thoracic paravertebral block without preference for one or another is recommended.

In the case of VATS, the use of incisional catheters is also recommended as an alternative.

- Rodgers et al. BMJ 2000; 321:1493.
- Seller et al. Rev Esp Anestesiol Reanim 2008; 55:360-6.
- Liu et al. Anesth Analg 2007; 104:689 – 702.
- Popping et al. Arch Surg 2008; 143:990 – 999; discussion 1000.

3. Fluid therapy

It is recommended to minimize the administration of intravenous fluid therapy. Fasting to liquids should be minimized, allowing the intake of water up to two hours before surgery and restarting fluid tolerance from 4-6 hours postoperatively. During the intraoperative and immediate postoperative period, a maximum of 2 ml / kg / h of balanced plasmalyte-type solutions plus blood losses will be administered. Hypotensions related to anesthesia, including analgesic techniques, will be treated with vasopressors.

- **Verheijden Breemharr et al.** *Thorax 1990; 45: 239*
- **Parquin et al.** *Eur J Cardio-thorac Surg 1996; 10:929-33*
- **Licker et al** *Anest Analg 2003; 97: 1558-65*
- **Fernandez-Perez et al** *Anesthesiology 2006; 105: 14-8*

4. Antibiotic prophylaxis

Time of administration of antibiotic prophylaxis

The first dose of antibiotic should be administered strictly within 60 minutes before the incision of the skin. Therefore, as a general rule, it is recommended to start this first dose immediately after the anesthetic induction.

Surgeries lasting longer than 4 hours or with very significant blood losses, it would be admissible to administer a new intraoperative two.

We recommend 1 dose of cefazolin 2g/iv (preoperative dose only)

- Bassetti et al. Minerva Anestesiologica 2014

5. Neuromuscular blocking

Intraoperative monitoring (TOF) of neuromuscular blocking and pharmacological reversal (neostigmine, sugammadex) is recommended prior to extubation if TOF ratio <0.9.

- Murphy et al. Anesth Analg 2010; 111:120 – 128.

- Cammu et al. 2006; 102:426 – 429.

6. Prevention of postoperative nausea and vomiting (PONV)

The administration of intravenous 4-5 mg dexamethasone after induction plus 4 mg intravenous Ondansetron at the end of surgery is recommended as a measure of prevention of PONV in patients with an Apfel score ≥2 points.

- Gan et al. Anesth Analg 2014; 118:85-113.

7. Glycemic control

Control of glycaemia is recommended, maintaining levels < 200 mg/dl during the intraoperative period and 6h postoperatively. In case of hyperglycemia should be corrected with insulin according to usual practice.

- Known et al. Ann Surg 2013; 257:8-14.
- Kotagal et al. Ann Surg 2015; 261:97-103.

8. Temperature

We recommend the control and maintenance of a temperature always above 36ºC.

- Baucom et al. JAMA Surg 2015; 150:570-575