Trial protocol - NIVAS Study

METHODS

Study oversight

The Non-Invasive Ventilation after Abdominal Surgery (NIVAS) was an investigator-initiated, multi-center, stratified, two-arm parallel-group trial with a computer-generated allocation sequence and an electronic system-based randomization. The study protocol and statistical analysis plan were approved for all centers by a central Ethics Committee (Comité de Protection des Personnes Sud Mediterranée III, Nimes, France) according to French law. The NIVAS study was conducted in accordance with the declaration of Helsinki and was registered at http://www.clinicaltrials.gov with trial identification number NCT01971892. Depending on the severity of the illness and competency, informed written or witnessed oral consent from the patient, or witnessed consent from a relative, was obtained upon study inclusion. Whenever possible, written consent for continued participation in the trial was obtained from the patient in the subsequent 7 days.

An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded safety data, with interim analyses performed after the inclusion of 100 and 200 patients. The steering committee vouched for the accuracy and completeness of the data and analysis, and the fidelity of the study to the protocol, and took the decision to submit the manuscript for publication. The writing committee wrote all drafts of the manuscript without editorial assistance; all the authors provided revisions and comments. There was no industry support or involvement in the trial. Patients were screened and underwent randomization between May 2013 and September 2014 at 20 ICUs in 17 French university and 3 non-university hospitals. All sites had a long experience with NIV (more than 10 years of NIV use for ARF, and more than 5 years of NIV use for ARF following abdominal surgery). Randomization was performed centrally, with the use of a computer-generated and blinded assignment sequence. Randomization was stratified according to study site, age (less or more than 60 years), site of surgery (upper or lower abdominal) and according to the use of postoperative epidural analgesia, which may influence outcomes. Treatment assignments were concealed from research staff, the statistician and the data monitoring/safety committee.

Patients

Inclusion criteria

1. Adult patients older than 18 years
2. Laparoscopic or non-laparoscopic elective or non-elective abdominal surgery under general anesthesia
3. Acute respiratory failure occurring within 7 days of the surgical procedure, defined as presence and persistence > 30 minutes of at least one of the two following:

   1) a respiratory rate above 30 breaths/min and

   2) clinical signs suggesting respiratory muscle fatigue, labored breathing, or both, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retractions and

   3) hypoxemia defined by a partial oxygen pressure lower than 60 mmHg when breathing room air, or lower than 80 mmHg with 15 liters per minute of oxygen or a peripheral oxygen saturation of ≤90% breathing room air (PaO_2/FIO_2≤300 mmHg).
4. And informed consent obtained
5. And valid affiliation to the Social Security System

Exclusion criteria

1. Limitation of therapy
2. Contraindications to noninvasive ventilation: required immediate tracheal intubation and invasive mechanical ventilation, hemodynamic instability defined by systolic arterial blood pressure below 90 mm Hg or mean arterial blood pressure below 65 mm Hg, use of vasopressors; a Glasgow Coma Scale score of 12 points or less (on a scale from 3 to 15, with lower scores indicating reduced levels of consciousness)
3. Required an emergent surgical procedure (operation that had to be performed within 12 hours after inclusion in the study)
4. Previous recruitment in another trial.
5. Pregnancy
6. Refusal to participate

Interventions and trial settings for NIVAS trial

Patients were randomly assigned to receive either NIV (NIV-group) or standard-oxygen therapy alone (oxygen-group) from randomization until day 30 or ICU discharge, whichever came first. Patients assigned to standard-oxygen therapy received supplemental oxygen at a rate of up to 15 liters per minute in order to maintain peripheral oxygen saturation ≥94%. In the intervention group (NIV-group), NIV was delivered through a face mask connected to an ICU or NIV-dedicated ventilator, using either heated humidifier or heat and moisture exchanger to warm and humidify inspired gases. NIV was started at an inspiratory positive airway pressure of 5 cm of water and was increased to a maximum inspiratory pressure of 15 cm of water aiming to achieve an expiratory tidal volume between 6 to 8 ml per kilogram of predicted body weight and a respiratory rate of less than 25 breaths per minute. Positive-end expiratory airway pressure (PEEP) was started at 5 cm of water and was increased to a maximum of 10 cm of water. PEEP and inspired oxygen fraction were titrated to maintain an arterial oxygen saturation ≥94%. Ventilator settings were subsequently adjusted as needed for patient comfort. Patients in this group were encouraged to use NIV for at least 6 hours, continuously or fractioned, during the first 24 hours after randomization. Between NIV sessions, patients received standard-oxygen therapy as described above. The use of high-flow oxygen nasal cannulae (>15 liters per minute) was not permitted in either group. The decision regarding when to discontinue NIV was left to the attending physician. Participants who did not receive the assigned treatment or who did not adhere to the protocol were followed up in full, and their data were included in the analysis according to the intention-to-treat principle (see statistical analysis section). All other aspects of patient care in both groups were conducted according to each center's routine clinical practice.

Criteria of endotracheal intubation

To reduce the risk of delayed re-intubation and to ensure the consistency of indications for re-intubation between all trial sites, predefined criteria were applied in all participating centers. In the two groups, immediate re-intubation was performed if the patients met any of the following predefined major clinical events: respiratory or cardiac arrest; respiratory pauses with loss of consciousness or gasping for air; massive aspiration; persistent inability to clear respiratory secretions; heart rate below 50 beats per min with loss of alertness; and severe hemodynamic instability without response to fluids and vasoactive drugs. After re-intubation,

all patients were ventilated with the same ventilation protocol, according to the low-tidal-volume protective ventilatory strategy.

Data collection and definitions

Causes of acute respiratory failure (ARF)

We assigned causes of ARF following extubation, with adapted published definitions: upper-airway obstruction; aspiration or excess respiratory secretions; severe encephalopathy; congestive heart failure; pneumonia and atelectasis. Severe encephalopathy was defined by Glasgow coma scale of 12 points or less (on a scale from 3 to 15, with lower scores indicating reduced levels of consciousness).

Atelectasis was defined as lung opacification with shift of the mediastinum, hilum or hemi-diaphragm towards the affected area and compensatory overinflation in the adjacent non-atelectatic lung.

Health-Care associated infections

Diagnostic criteria for health-care associated infections were adapted from CDC criteria. The sites and dates of diagnosis of all healthcare associated infections were recorded as well as antibiotic regimens given during the ICU stay within 30 days after inclusion in the study.

Pneumonia, urinary tract infection, central venous catheter-related infection, bacteremia and surgical-site infection, occurring both at least 48 hours after ICU admission and after inclusion in the study were collected according to the following definitions.

Pneumonia was suspected in patients with a combination of new and persistent lung infiltrates on chest X-ray, a temperature greater than 38°C, and macroscopically purulent tracheal secretions while receiving either standard oxygen therapy, noninvasive ventilation or invasive mechanical ventilation. Pneumonia was ascertained by the positivity of a quantitative respiratory culture, defined as at least 1 microorganism recovered at concentration of at least 1000 colony forming units per mL for blinded protected telescoping catheter, of at least 10000 colony forming units per mL for broncho-alveolar lavage and of at least 1000000 colony forming units per mL for tracheal aspirates. In patients clinically suspected of having pneumonia but treated with noninvasive ventilation, the positivity of a blinded protected telescoping catheter culture at the same significant threshold, when available, or the sole administration of new antibiotics in the absence of other sites of infection was used to characterize the presence of pneumonia.

The modified Clinical Pulmonary Infection Score (CPIS) at suspected pneumonia was

calculated from the first five variables (see table CPIS). The CPIS gram/culture was calculated from the CPIS score by adding two more points when gram stains or culture were positive. A score of more than six at baseline or after incorporating the gram stains（CPIS gram）or culture（CPIS culture）results was considered suggestive of pneumonia.

The Modified Clinical Pulmonary Infection Score（modified CPIS）

CPIS Points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant＋purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, ℃	≧36.5 and≦38.4	≧38.5. and≦38.9	≧39 or≦36.4
Leukocytes count, per mm^3	≧4,000 and≦11,000	＜4,000 or＞ 11,000	＜4,000 or＞11,000 ＋ band forms≧500
P_{aO2}/F_{IO2}, mmHg	＞240 or ARDS		≦240 and no evidence of ARDS
Microbiology	Negative		Positive

Urinary tract infection was defined by the association of fever (body temperature greater than 38°C) and a urine culture with no more than two species of organisms, at least one of which is a bacteria of at least 100000 colony forming units per ml, in patients with no other evident source of infection.

Catheter-related infection was defined as a combination of fever (body temperature greater than 38°C), a quantitative catheter-tip culture eluate in broth showing at least one microorganism in a concentration of at least 1000 colony forming units per mL, and resolution of fever within 48 h after catheter removal and without any change in antimicrobial therapy, and no other evident source of infection identified.

Primary bacteremia was defined as a combination of fever (body temperature greater than 38°C), at least 1 positive blood culture (two or more blood cultures drawn on separate occasions when coagulase-negative staphylococci were isolated) not related to an infection at another site.

Surgical-site infection diagnostic was performed according standard CDC definitions (Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999: Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-78.).

An independent infectious disease specialist reviewed all clinical and microbiological informations for each patient.

TABLE 1
CRITERIA FOR DEFINING A SURGICAL SITE INFECTION (SSI)*

Superficial Incisional SSI

Infection occurs within 30 days after the operation
and
infection involves only skin or subcutaneous tissue of the incision
and at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.[433]

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
and
infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision
and at least *one* of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopatholog ic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
and
infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation
and at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

* Horan TC et al.[22]
† National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.
‡ If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.

Definitions for outcomes

The primary outcome for comparing NIV and standard-oxygen therapy was any cause of re-intubation within 7 days following randomization. Causes and time to re-intubation were recorded. Secondary outcomes included gas exchange, healthcare associated infections rate within 30 days, the number of ventilator-free days (i.e. days alive and without invasive mechanical ventilation) between day-1 and day-30, antibiotic use duration and numbers, ICU and in-hospital lengths of stay, 30 and 90-day mortality.