Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery
A Randomized Clinical Trial

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IMPORTANCE It has not been established whether noninvasive ventilation (NIV) reduces the need for invasive mechanical ventilation in patients who develop hypoxemic acute respiratory failure after abdominal surgery.

OBJECTIVE To evaluate whether noninvasive ventilation improves outcomes among patients developing hypoxemic acute respiratory failure after abdominal surgery.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, parallel-group clinical trial conducted between May 2013 and September 2014 in 20 French intensive care units among 293 patients who had undergone abdominal surgery and developed hypoxemic respiratory failure (partial oxygen pressure <60 mm Hg or oxygen saturation [Spo_2] ≤90% when breathing room air or <80 mm Hg when breathing 15 L/min of oxygen, plus either [1] a respiratory rate above 30/min or [2] clinical signs suggestive of intense respiratory muscle work and/or labored breathing) if it occurred within 7 days after surgical procedure.

INTERVENTIONS Patients were randomly assigned to receive standard oxygen therapy (up to 15 L/min to maintain Spo_2 of 94% or higher) (n = 145) or NIV delivered via facial mask (inspiratory pressure support level, 5-15 cm H_2O; positive end-expiratory pressure, 5-10 cm H_2O; fraction of inspired oxygen titrated to maintain Spo_2 ≥94%) (n = 148).

MAIN OUTCOMES AND MEASURES The primary outcome was tracheal reintubation for any cause within 7 days of randomization. Secondary outcomes were gas exchange, invasive ventilation–free days at day 30, health care–associated infections, and 90-day mortality.

RESULTS Among the 293 patients (mean age, 63.4 [SD, 13.8] years; n=224 men) included in the intention-to-treat analysis, reintubation occurred in 49 of 148 (33.1%) in the NIV group and in 66 of 145 (45.5%) in the standard oxygen therapy group within+ 7 days after randomization (absolute difference, −12.4%; 95% CI, −23.5% to −1.3%; P = .03). Noninvasive ventilation was associated with significantly more invasive ventilation–free days compared with standard oxygen therapy (25.4 vs 23.2 days; absolute difference, −2.2 days; 95% CI, −0.1 to 4.6 days; P = .04), while fewer patients developed health care–associated infections (43/137 [31.4%] vs 63/128 [49.2%]; absolute difference, −17.8%; 95% CI, −30.2% to −5.4%; P = .003). At 90 days, 22 of 148 patients (14.9%) in the NIV group and 31 of 144 (21.5%) in the standard oxygen therapy group had died (absolute difference, −6.5%; 95% CI, −16.0% to 3.0%; P = .15). There were no significant differences in gas exchange.

CONCLUSIONS AND RELEVANCE Among patients with hypoxemic respiratory failure following abdominal surgery, use of NIV compared with standard oxygen therapy reduced the risk of tracheal reintubation within 7 days. These findings support use of NIV in this setting.

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Group Information: The Noninvasive Ventilation for Postextubation Respiratory Failure After Abdominal Surgery (NIVAS) study investigators are listed in eAppendix 1 in Supplement 1.

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Postoperative acute respiratory failure is a major contributor to the overall risk of surgery, leading to an increase in morbidity and mortality.[1-3] The early postoperative period following abdominal surgery is associated with diaphragmatic dysfunction and a decrease in lung vital capacity, which may lead to atelectasis formation and hypoxemia.[4] Treating postoperative acute respiratory failure usually refers to tracheal reintubation and invasive mechanical ventilation.[5] Tracheal reintubation for acute respiratory failure is associated with higher mortality and increased health care utilization, with a longer duration of both intensive care unit (ICU) and hospital stay.[3] Reasons for the increase in mortality include complications during the reintubation period[6,7] and health care-associated infections such as pneumonia.[6-9] This suggests that postoperative outcome may be improved by strategies aimed at avoiding reintubation and invasive mechanical ventilation.[10]

Noninvasive ventilation (NIV) has proven effective in nonsurgical cases of acute exacerbation of chronic obstructive pulmonary disease[11] and cardiogenic pulmonary edema.[12] However, to date, no evidence supports the use of NIV in surgical patients with hypoxemic acute respiratory failure after abdominal surgery. Indeed, NIV is sometimes considered a relative contraindication after recent upper gastrointestinal tract surgery.[13]

To our knowledge, no multicenter randomized clinical trials have evaluated whether NIV could reduce the need for invasive mechanical ventilation and its effect on the incidence of health care-associated infections in patients who develop hypoxemic acute respiratory failure after abdominal surgery.[14,15]

We hypothesized that application of NIV may prevent reintubation and invasive mechanical ventilation and may decrease the rate of health care-associated infections.

We thus conducted a multicenter randomized clinical trial of NIV in surgical patients who developed hypoxemic acute respiratory failure after abdominal surgery, comparing NIV against standard oxygen therapy.

Methods

Trial Design and Oversight

The trial was an investigator-initiated, multicenter, stratified, parallel-group trial with a computer-generated allocation sequence and an electronic system-based randomization. The study protocol and statistical analysis plan (Supplement 2 and Supplement 3) were approved for all centers by a central ethics committee in accordance with French law. The trial was conducted in accordance with the Declaration of Helsinki. Written informed consent from the patient or consent from a relative was obtained on study inclusion. 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. Patients were screened and underwent randomization between May 2013 and September 2014 at 20 French ICUs. Randomization was performed centrally by the minimization method with the use of a computer-generated and blinded assignment sequence. Randomization was stratified according to study site, age (<60 vs ≥60 years), site of surgery (upper vs lower abdominal), and use of postoperative epidural analgesia, as this may influence outcomes.[16]

Patients

Patients were eligible for participation in the study if they were older than 18 years and had undergone laparoscopic or nonlaparoscopic elective or nonelective abdominal surgery under general anesthesia. Patients were included if they met the following criteria: a diagnosis of acute respiratory failure occurring within 7 days of the surgical procedure,[17,18] defined as the presence and persistence for more than 30 minutes of hypoxemia (defined by a partial oxygen pressure <60 mm Hg when breathing room air or <80 mm Hg when breathing 15 L/min of oxygen or a peripheral oxygen saturation [SpO_2] ≤90% when breathing room air plus either [1] a respiratory rate higher than 30/min or [2] clinical signs suggestive of intense respiratory muscle work and/or labored breathing, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retraction). Exclusion criteria were withholding of life-sustaining treatment,[19] contraindications to noninvasive ventilation, sleep apnea syndrome, immediate tracheal intubation, requirement for an emergent surgical procedure, and previous recruitment in another trial.

Causes of Acute Respiratory Failure

We assigned causes of acute respiratory failure following extubation using adapted published definitions[11,20-23] as follows: upper airway obstruction, aspiration or excess respiratory secretions, encephalopathy, congestive heart failure, pneumonia, and atelectasis.

Study Interventions

Patients were randomly assigned to receive either NIV or standard oxygen therapy alone 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 L/min to maintain an SpO_2 of at least 94%. In the intervention group, NIV was delivered through a face mask connected to an ICU- or NIV-dedicated ventilator, using either a heated humidifier or heat and moisture exchanger to warm and humidify inspired gases.[24] Noninvasive ventilation was started at an inspiratory positive airway pressure of 5 cm H_2O, increasing to a maximum inspiratory pressure of 15 cm H_2O, aiming to achieve an expiratory tidal volume between 6 and 8 mL/kg of predicted body weight and a respiratory rate lower than 25/min. Positive end-expiratory airway pressure (PEEP) was started at 5 cm H_2O and increased as needed to a maximum of 10 cm H_2O.[4,10] PEEP and inspired oxygen fraction were titrated to maintain an SpO_2 of at least 94%. Ventilator settings were subsequently adjusted as needed for patient comfort.[4] Patients in this group were encouraged to use NIV for at least 6 hours, continuously or intermittently, during the first 24 hours after randomization. Between NIV sessions, patients received standard oxygen therapy as described above.

Figure 1. Enrollment, Randomization, and Follow-up of Participants in the Noninvasive Ventilation for Postextubation Respiratory Failure After Abdominal Surgery Study
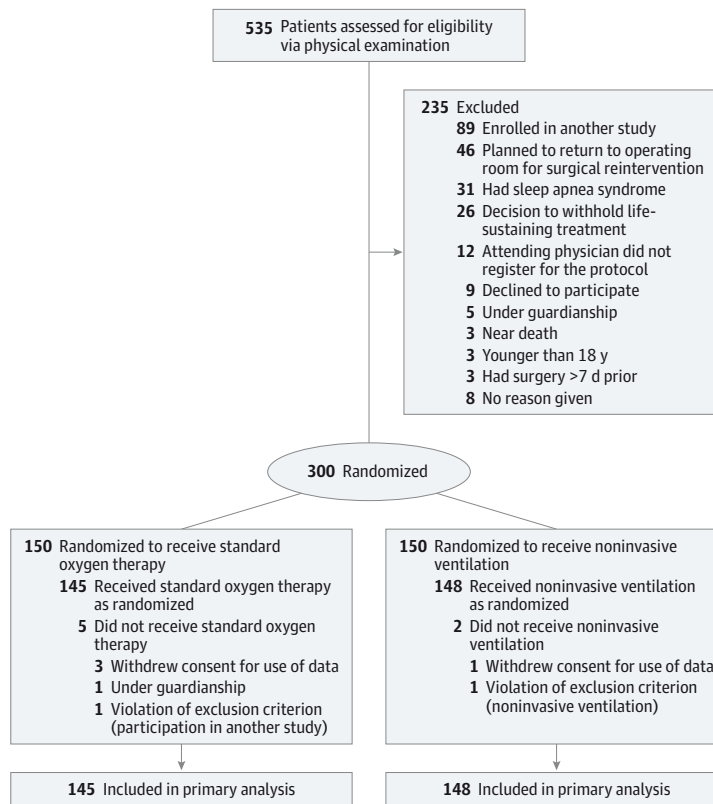
The use of high-flow oxygen nasal cannulas was not permitted in either group. Any decision to discontinue NIV was left to the attending physician. All other aspects of patient care in both groups were conducted according to each center's routine clinical practice.

Criteria for Reintubation

To reduce the risk of delayed reintubation and to ensure consistency of indications for reintubation among all trial sites, predefined criteria were applied. Immediate reintubation was performed if patients had 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 of less than 50/min with loss of alertness, and severe hemodynamic instability without response to fluid and vasoactive drugs. After reintubation, all patients underwent ventilation with the same ventilation protocol, using a low-tidal-volume protective ventilatory strategy.[25]

Study Outcomes

The primary outcome for comparing NIV and standard oxygen therapy was any cause of reintubation within 7 days following randomization. Causes and time to reintubation were recorded. Secondary outcomes included gas exchange, health care–associated infection rate within 30 days, number of ventilator-free days (ie, days alive and without invasive

mechanical ventilation) between days 1 and 30, antibiotic use duration, ICU and in-hospital length of stay, and 30- and 90-day mortality. Five of 7 secondary outcomes are reported in this article. Definitions for each health care–associated infection (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 study entry) are detailed in eAppendix 2 in Supplement 1.

Statistical Analysis

We estimated that with a sample of 150 patients per group evaluated for the primary efficacy outcome, the study had at least 90% power to determine superiority of noninvasive ventilation compared with standard oxygen therapy. For the intention-to-treat analysis, the following assumptions were made: a 65% event rate in the standard oxygen therapy group[10,26,27] and a 40% event rate in the noninvasive ventilation group[14,28,29] (absolute risk reduction with NIV of at least 25% based on expert opinion). Further assumptions (15% of included patients) were made relating to patients randomized despite not being eligible for randomization according to inclusion/exclusion criteria and loss to follow-up for the primary end point. Two interim analyses were conducted after the first 100 and 200 patient randomizations by an independent data and safety monitoring committee for early stopping of the study for safety (mortality within 90 days) using

Table 1. Patient Characteristics and Biomechanical Variables According to Study Group at Randomization

Characteristics	Standard Oxygen Therapy (n = 145)	Noninvasive Ventilation (n = 148)
Age, y		
Mean (SD)	64.4 (13.1)	62.5 (14.5)
≥60, No. (%)	89/145 (61.4)	92/148 (62.2)
Male, No. (%)	108/145 (74.5)	116/148 (78.4)
Body mass index[a]		
Mean (SD)	27.1 (6.2)	27.2 (5.9)
>30, No. (%)	34/143 (23.8)	42/147 (28.6)
Simplified Acute Physiology Score II at study entry, mean (SD)[b]	33.4 (11.7)	33.6 (12.8)
Sequential Organ Failure Assessment score at study entry, mean (SD)[c]	4.5 (2.7)	4.3 (2.6)
Preexisting conditions, No. (%)		
Current smoker	37/138 (26.8)	44/141 (31.2)
Alcohol abuse	26/142 (18.3)	23/141 (16.3)
Psychotropic use	16/144 (11.1)	15/147 (10.2)
Chronic hypertension	72/145 (49.7)	69/148 (46.6)
Ischemic heart disease	16/145 (11.0)	25/147 (17.0)
Chronic heart failure	4/143 (2.8)	7/146 (4.8)
Chronic obstructive pulmonary disease	18/143 (12.6)	29/148 (19.6)
Chronic kidney disease	9/145 (6.2)	5/147 (3.4)
Cirrhosis	26/145 (17.9)	23/147 (15.6)
Cancer	73/144 (50.7)	68/144 (47.2)
Sepsis	32/144 (22.2)	36/144 (25.0)
Clinical variables, mean (SD)		
Body temperature, °C	37.3 (0.8)	37.3 (0.8)
Heart rate, /min	103.2 (19.6)	102.2 (18.6)
Respiratory rate, /min	28.8 (7.3)	28.2 (7.7)
Blood pressure, mm Hg		
Systolic	135.6 (22.3)	132.8 (23.2)
Diastolic	68.7 (13.8)	70.1 (13.7)
Biochemical variables, mean (SD)		
Hemoglobin, g/dL	10.7 (1.9)	11.0 (2.2)
Hematocrit, %	31.7 (5.7)	32.5 (6.4)
White blood cell count, ×10³/μL	13.2 (6.8)	13.8 (9.3)

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] The Simplified Acute Physiology Score II is based on 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease.

[c] The score on the Sequential Organ Failure Assessment includes subscores ranging from 0 to 4 for each of 5 components (circulation, lungs, liver, kidneys, and coagulation). Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure.

a prespecified Haybittle-Peto efficacy boundary[30] (α = .001 for the 2 interim analyses). A secondary modified intention-to-treat analysis was performed for the primary outcome including only patients who did not return to the operating room for reintervention. Unadjusted χ^2 testing was used for primary outcome analysis. Multiple imputation was additionally performed if the frequency of missing data was greater than 5%. A Markov chain Monte Carlo method was used for the multiple imputation procedure; we generated m = 5 complete data sets. Multiple logistic regression analysis was used to identify relevant baseline covariates associated with the primary outcome. Variables tested in the model were selected if $P<.15$ and then presented as absolute difference for binary variables and mean differences for continuous variables with 95% confidence intervals. Kaplan-Meier curves for reintubation and for mortality rates were plotted for the first 30 and 90 days, respectively, after inclusion in the study and were compared by the log-rank test. We compared the primary outcome in prespecified subgroups defined by stratification criteria according to age (<60 vs ≥60 years), site of surgery (upper vs lower abdominal), and use/nonuse of epidural analgesia. A 2-tailed $P<.05$ was considered to indicate statistical significance. SAS software, version 9.3 (SAS Institute Inc), was used for all analyses.

Results

Study Patients

From May 2013 through September 2014, 535 patients with acute respiratory failure within 7 days following abdominal surgery were eligible, of whom 300 underwent randomization, 150 to standard oxygen therapy and 150 to NIV (Figure 1). Seven patients were excluded after randomization because of withdrawn consent (n = 4) or ineligibility (n = 3). Data on the primary outcome were available for all 293 remaining patients (mean age, 63.4 [SD, 13.8] years; n = 224 men). Groups were similar with respect to inclusion, site, duration of surgery,

Table 2. Surgery and Acute Respiratory Failure Characteristics at Randomization

Characteristics	Standard Oxygen Therapy (n = 145)	Noninvasive Ventilation (n = 148)
Surgery		
Recent surgical history, No. (%)		
Elective	75/145 (51.7)	77/148 (52.0)
Emergency	70/145 (48.3)	71/148 (48.0)
Upper abdominal surgery, No. (%)	91/145 (62.8)	93/148 (62.8)
Type of surgery, No. (%)		
Liver resection	39/143 (27.3)	40/140 (28.6)
Colorectal resection	38/143 (26.6)	30/140 (21.4)
Gastrectomy	18/143 (12.6)	16/140 (11.4)
Esophagectomy	9/143 (6.3)	14/140 (10.0)
Pancreaticoduodenectomy	13/143 (9.1)	11/140 (7.9)
Other procedures	26/143 (18.2)	29/140 (20.7)
Laparotomy surgery, No. (%)	131/144 (91.0)	134/146 (91.8)
Vertical midline incision	87/137 (63.5)	82/139 (59.0)
Transverse incision	43/137 (31.4)	48/139 (34.5)
Other	7/137 (5.1)	9/139 (6.5)
Laparoscopic surgery, No. (%)	16/144 (11.1)	16/145 (11.0)
Thoracotomy/laparotomy, No. (%)[a]	3/143 (2.1)	7/143 (4.9)
Epidural analgesia, No. (%)	21/145 (14.5)	23/148 (15.5)
Duration of surgical procedure, mean (SD), h	4.3 (2.7)	4.1 (2.6)
Extubated <6 h after end of surgery, No. (%)	90/145 (62.1)	94/148 (63.5)
Acute respiratory failure		
Respiratory rate, mean (SD), /min	29 (7)	28 (8)
Time from end of surgery to acute respiratory failure, mean (SD), d	2.6 (1.7)	2.4 (1.6)
Time from extubation to acute respiratory failure, mean (SD), d	1.9 (1.6)	2.0 (1.6)
Time from acute respiratory failure to inclusion in study, median (IQR), h	3.1 (1.0-8.7)	2.8 (1.0-7.3)
Causes of acute respiratory failure, No. (%)[b]		
Atelectasis[c]	94/143 (65.7)	93/148 (62.8)
Tracheal secretions	54/143 (37.8)	58/148 (39.1)
Pneumonia	36/143 (25.2)	27/148 (18.2)
Pulmonary edema	23/143 (16.1)	21/148 (14.2)
Pleural effusion	19/143 (13.3)	18/148 (12.2)
Pulmonary embolism	11/143 (7.7)	6/148 (4.1)
Arterial blood gas at randomization, mean (SD)		
pH	7.41 (0.07)	7.42 (0.07)
Pao_2:Fio_2 ratio, mm Hg	188 (71)	201 (69)
$Paco_2$, mm Hg	37 (7)	39 (7)
HCO_3, mmol/L	24 (4)	25 (4)

Abbreviations: Fio_2, fraction of inspired oxygen; IQR, interquartile range.

[a] In these patients, 2 incisions were made to perform the surgery, one through the abdomen and one through the thorax.

[b] Causes of acute respiratory failure may be multiple.

[c] Atelectasis was defined as lung opacification with shift of the mediastinum, hilum, or hemidiaphragm toward the affected area and compensatory overinflation in the adjacent nonatelectatic lung.

causes of acute respiratory failure, time from surgery, time from extubation to acute respiratory failure (**Table 1** and **Table 2**), and gas exchange (Table 2 and eTable 1 in Supplement 1). The initial settings were as follows: for the standard oxygen therapy group, mean oxygen flow was 10.4 L/min (SD, 5.1 L/min); for the NIV group, mean inspiratory pressure was 6.7 cm H_2O (SD, 2.9 cm H_2O), mean PEEP was 5.4 cm H_2O (SD, 1.3 cm H_2O), and mean fraction of inspired oxygen was 50% (SD, 16%), resulting in a mean tidal volume of 8.3 mL/kg (SD, 3.1 mL/kg) of predicted body weight (eTable 2 in Supplement 1).

Outcomes

Primary Outcome

Noninvasive ventilation improved the primary outcome of the 293 patients included in the intention-to-treat analysis; reintubation occurred in 49 of 148 patients (33.1%) in the NIV group and 66 of 145 (45.5%) in the standard oxygen therapy group at 7 days after randomization (absolute difference, −12.4%; 95% CI, −23.5% to −1.3%; P = .03) (**Table 3**, **Figure 2**, and the eFigure in Supplement 1). The multivariable analysis is shown in eTable 3 in Supplement 1, and NIV was signifi-

Table 3. Primary and Secondary Outcomes According to Study Group

Variables	Standard Oxygen Therapy (n = 145)	Noninvasive Ventilation (n = 148)	Absolute Difference (Noninvasive Ventilation − Standard Oxygen Therapy), % (95% CI)	P Value
Outcomes, No./Total (%)				
Primary outcome: reintubation to day 7	66/145 (45.5)	49/148 (33.1)	−12.41 (−23.51 to −1.31)	.03
Secondary outcomes[a]				
Reintubation to day 30	72/145 (49.7)	57/148 (38.5)	−11.14 (−22.44 to 0.16)	.06
Overall health care-associated infections to day 7	44/145 (30.3)	27/148 (18.2)	−12.1 (−22.52 to −1.69)	.02
Pneumonia to day 7	32/145 (22.1)	15/148 (10.1)	−11.93 (−20.94 to −2.93)	.005
Overall health care-associated infections to day 30	63/128 (49.2)	43/137 (31.4)	−17.83 (−30.22 to −5.44)	.003
Pneumonia to day 30	38/128 (29.7)	20/137 (14.6)	−15.09 (−25.72 to −4.45)	.003
30-Day mortality	22/144 (15.3)	15/148 (10.1)	−5.04 (−13.32 to 3.24)	.20
90-Day mortality	31/144 (21.5)	22/148 (14.9)	−6.51 (−15.99 to 2.96)	.15
90-Day mortality in intubated patients	29/72 (40.3)	18/57 (31.6)	−8.8 (−17.29 to 4.12)	.31
Service Utilization, Median (IQR)				
Days of invasive mechanical ventilation over 30 d	0 (0-5) [n=145]	0 (0-3) [n=148]	−0.93 (−2.51 to 0.64)[b]	.05
Invasive ventilation-free days to day 30[c]	30 (21.4-30) [n=145]	30 (25.9-30) [n=148]	2.22 (−0.11 to 4.55)[d]	.04
Invasive ventilation-free days to day 30 with deceased accounting for 0 d[c]	30 (20.8-30) [n=145]	30 (25.9-30) [n=148]	2.30 (−0.33 to 4.93)[d]	.04
Days in ICU to day 30	8 (5-15) [n=144]	7 (5-14) [n=146]	−0.06 (−1.99 to 1.87)	.80
Days in ICU to day 90	8 (5-15) [n=143]	7 (5-14) [n=146]	0.18 (−3.08 to 3.44)	.45
Overall days in hospital to day 90	25 (15-39) [n=130]	22 (14-35.5) [n=140]	−2.39 (−7.68 to 2.91)	.19
Days in hospital to day 90 (survivors only)	27 (16-43.5) [n=108]	20.5 (14-32) [n=114]	−5.21 (−11.03 to 0.62)[d]	.02
Time from inclusion to reintubation, h	24 (0-72) [n=72]	48 (24-120) [n=57]	11.67 (−15.64 to 51.27)	.31
Time from extubation to reintubation, d	3 (2-5) [n=72]	4 (2-7.3) [n=60]	0.59 (−0.86 to 2.04)	.14
Time from acute respiratory failure to reintubation, d	1 (1-3) [n=72]	2 (1-6) [n=57]	0.66 (−0.76 to 2.09)	.08

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] For additional data on secondary outcomes, see eTables 2, 3, 5, and 6 in Supplement 1.

[b] Log: −0.13% (95% CI, −0.49% to 0.22%).

[c] The number of invasive ventilation-free days was defined as the number of days without invasive mechanical ventilation at day 30.

[d] Because of nonnormal distribution of some continuous variables, a nonparametric analysis was used to compare groups, but the 95% CI of the mean difference may cross 0.

cantly associated with reduced reintubation. Time from inclusion to reintubation (Table 3) and reasons for reintubation (eTable 4 in Supplement 1) did not significantly differ between the groups.

No significant difference was observed in the number of patients requiring reintubation for reoperation (16/148 [10.8%] in the NIV group and 16/145 [11%] in the standard oxygen therapy group; *P* = .95).

In the modified intention-to-treat analysis including all patients except those reintubated for reoperation (n = 261), NIV also improved the primary outcome. Reintubation occurred in 33 of 132 patients (25.0%) in the NIV group and 50 of 129 patients (38.8%) in the standard oxygen therapy group (*P* = .02).

Secondary Outcomes

Among patients subsequently reintubated, patients who received NIV spent less time under invasive mechanical ventilation than patients treated with standard oxygen therapy alone (Table 3). There were no significant differences in gas exchange between groups (eTable 1 in Supplement 1).

At 30 days, compared with standard oxygen therapy, NIV was associated with significantly more ventilator-free days (25.4 vs 23.2 days; absolute difference, −2.2 days; 95% CI, −0.1 to 4.6 days; *P* = .04). Patients treated with NIV also experienced significantly fewer health care-associated infections (43/137 patients [31.4%] vs 63/128 [49.2%]; absolute difference, −17.8%; 95% CI, −30.2% to −5.4%; *P* = .003), especially less ICU-acquired pneumonia (20/137 patients [14.6%] vs 38/128 [29.7%]; *P* = .003) (Table 3 and eTable 5 in Supplement 1). Microorganisms causing pneumonia are detailed in eTable 6 in Supplement 1. At 90 days, 22 of 148 patients (14.9%) in the NIV group and 31 of 144 (21.5%) in the standard oxygen therapy group had died (absolute difference, −6.5%; 95% CI, −16.0% to 3.0%; *P* = .15) (Table 3 and **Figure 3**).

Clinical Tolerance

No significant difference was seen between the 2 groups in the overall incidence of serious adverse events (eTable 2 in Supplement 1). Seven patients received NIV as rescue therapy

in the standard oxygen therapy group, of whom 3 (42.9%) were subsequently intubated. There were 3 episodes of cardiac arrest, 2 occurring before intubation (1 in the standard oxygen therapy group and 1 in the NIV group). Tolerance and adverse effects of NIV after the first trial in the NIV group are reported in eTable 2 in Supplement 1.

Discussion

In this multicenter randomized clinical trial conducted among patients with hypoxemic acute respiratory failure after abdominal surgery, noninvasive ventilation delivered via face mask reduced the need for reintubation and for invasive mechanical ventilation and was associated with fewer episodes of health care-associated infection compared with standard oxygen therapy.

Hypoxemia develops in 30% to 50% of patients after abdominal surgery and can in some patients be well tolerated without symptoms.[4,22,28] In others, however, hypoxemia can progress to severe acute respiratory failure. The genesis of hypoxemic acute respiratory failure postoperatively is multifactorial and partly related to atelectasis due to hypoventilation and collapsed alveoli, retained secretions, and diaphragmatic dysfunction.[29,31] Atelectasis promotes bacterial growth and increases lung permeability, leading to pneumonia.[32] In our study, NIV significantly decreased overall health care-associated infections and halved the rate of pneumonia. Noninvasive ventilation can reverse loss of pulmonary volume through the combined positive effects of PEEP and inspiratory pressure support, which increase lung ventilation, reopen atelectatic alveoli, and improve gas exchange.[4] Reducing atelectasis by NIV could also decrease bacterial growth, thus mitigating bacterial translocation from the lung into the bloodstream.[32] Avoidance of endotracheal intubation, bypassing the upper airways, is probably the major reason for the pneumonia reduction observed in patients treated by NIV.[33] Moreover, NIV has been shown to reduce overall nosocomial infection rates through reduction in both the number and duration of invasive devices such as intravenous and bladder catheters.[33] Finally, reducing health care-associated infections, especially pneumonia, could contribute to the trend toward lower mortality observed in the NIV group (Table 3 and Figure 3).

Complications have been reported with NIV, such as gastric distention and pulmonary aspiration. Noninvasive ventilation may also potentially impede patients' ability to cough and expectorate postoperatively. In the present study, no adverse events were reported in either group. We did not observe higher morbidity and mortality in the NIV group, contrary to that reported in another postextubation study because of delayed reintubation in the NIV group.[20] The selection of appropriate postoperative patients who may benefit from postextubation NIV is a key factor.[4,34] One randomized clinical study by Squadrone et al[22] evaluated the use of noninvasive continuous positive airway pressure delivered via helmet after abdominal surgery. They studied 209 patients who

Figure 2. Cumulative Incidence of Reintubation Between Randomization and Day 30 According to Study Group
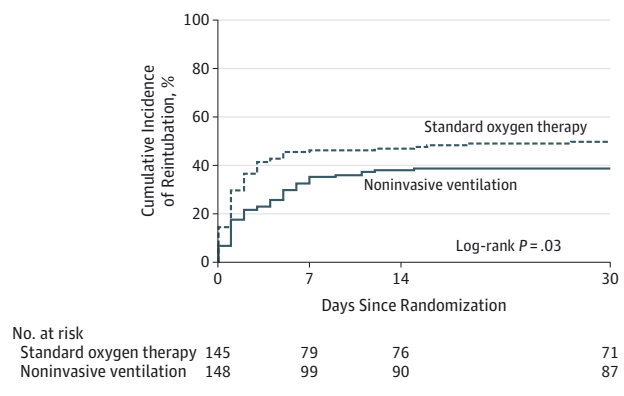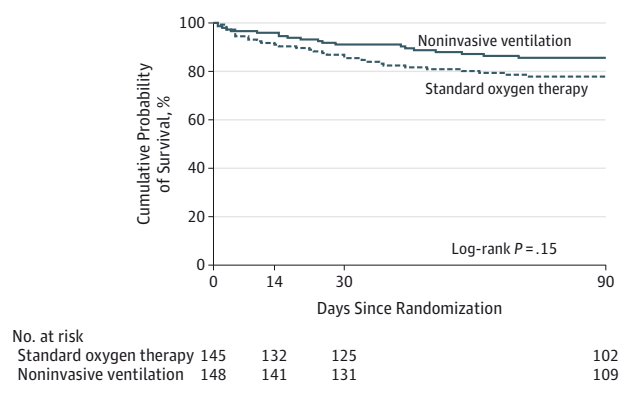

No. at risk

Standard oxygen therapy	145	79	76	71
Noninvasive ventilation	148	99	90	87

Figure 3. Probability of Survival Between Randomization and Day 90 According to Study Group

No. at risk

Standard oxygen therapy	145	132	125	102
Noninvasive ventilation	148	141	131	109

developed hypoxemia immediately after extubation without necessarily having signs of respiratory distress. Nonetheless, their early use of noninvasive continuous positive airway pressure significantly decreased the incidence of reintubation from 10% to 1%. Our study presents several differences: (1) we evaluated the efficacy of NIV delivered with face mask using 2 levels of positive airway pressure and (2) NIV was used as a therapeutic application in a more severe patient cohort with hypoxemic acute respiratory failure and not prophylactically in patients with hypoxemia alone. As a result, the respective incidence of reintubation (standard oxygen therapy control group rate of 10% for the study by Squadrone et al vs 45.5% in the current study) and mortality (3% in the control group of the study by Squadrone et al vs 22% in the current study) differed between the 2 studies (Table 3).

The strengths of the present study are its large sample size, the selected population base, multicenter design, the explicit criteria for reintubation, and a complete postoperative follow-up. Baseline characteristics in the 2 groups were well matched, and the criteria for health care-associated infection diagnosis are both validated and robust. The trial excluded patients who underwent another immediate surgical procedure, and stratification was performed according to study site, age, site of surgery, and use/nonuse of postoperative epidural analgesia.

Our study has several limitations. First, the observed rate of reintubation in our study was lower than predicted in the standard oxygen therapy group.[2,3,17,35] This could be due, in part, to exclusion of patients in whom acute respiratory failure was an early symptom of surgical complications needing immediate reintervention. Although invasive endotracheal mechanical ventilation has remained the cornerstone of ventilatory strategy for severe acute respiratory failure for many years,[2] several studies have shown that mortality associated with pulmonary complications is largely related to the risks of postoperative reintubation and mechanical ventilation.[2,3,36-38] Second, the present study was not designed to show a significant decrease in mortality in the NIV group. The lack of significance for lower mortality observed in the NIV group (from 22% to 15% at day 90) could be due to an underpowered design. The low mortality rate in the NIV group may result from the cumulative effects of a decreased reintubation rate, a shorter duration of invasive mechanical ventilation, and a reduced rate of health care–associated infections, especially pneumonia (Table 3). Third, although we applied predefined criteria for reintubation, bias cannot be completely ruled out because blinding with NIV was not feasible. Fourth, the clinically relevant effect size used in the power analysis was 25%. Because we were not able to identify randomized clinical trials that included similar patients, this was based on expert opinion and was chosen to limit the likelihood of a type 1 error.

Recent high-impact trials have demonstrated the benefits in nonsurgical hypoxemic respiratory failure[21] or equivalence of high-flow nasal cannula compared with NIV in patients after cardiothoracic surgery with moderate to severe hypoxemia.[23] Future studies comparing use of high-flow oxygen cannula vs standard oxygen therapy and NIV for patients after abdominal surgery as preventive (prophylactic)[39] or curative application are needed.[40]

Conclusions

Among patients with hypoxemic respiratory failure following abdominal surgery, use of NIV compared with standard oxygen therapy reduced the risk of tracheal reintubation within 7 days. These findings support use of NIV in this setting.

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