Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA)

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Abstract

Purpose: High-flow nasal cannula (HFNC) oxygen therapy is attracting increasing interest in acute medicine as an alternative to standard oxygen therapy; however, its use to prevent hypoxaemia after major abdominal surgery has not been evaluated. Our trial was designed to close this evidence gap.

Methods: A multicentre randomised controlled trial was carried out at three university hospitals in France. Adult patients at moderate to high risk of postoperative pulmonary complications who had undergone major abdominal surgery using lung-protective ventilation were randomly assigned using a computer-generated sequence to receive either HFNC oxygen therapy or standard oxygen therapy (low-flow oxygen delivered via nasal prongs or facemask) directly after extubation. The primary endpoint was absolute risk reduction (ARR) for hypoxaemia at 1 h after extubation and after treatment discontinuation. Secondary outcomes included occurrence of postoperative pulmonary complications within 7 days after surgery, the duration of hospital stay, and in-hospital mortality. The analysis was performed on data from the modified intention-to-treat population. This trial was registered with ClinicalTrials.gov (NCT01887015).

Results: Between 6 November 2013 and 1 March 2015, 220 patients were randomly assigned to receive either HFNC ($n = 108$) or standard oxygen therapy ($n = 112$); all of these patients completed follow-up. The median duration of the allocated treatment was 16 h (interquartile range 14–18 h) with standard oxygen therapy and 15 h (interquartile range 12–18) with HFNC therapy. Twenty-three (21 %) of the 108 patients treated with HFNC 1 h after extubation and

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Take-home message: Among patients at moderate to high risk of postoperative pulmonary complications undergoing major abdominal surgery and mechanically ventilated using a lung-protective strategy, preventive application of high-flow nasal oxygen therapy after extubation as compared with standard oxygen therapy did not decrease the incidence of postoperative hypoxaemia.

29 (27 %) of the 108 patients after treatment discontinuation had postextubation hypoxaemia, compared with 27 (24 %) and 34 (30 %) of the 112 patients treated with standard oxygen (ARR 4, 95 % CI –8 to 15 %; $p = 0.57$; adjusted relative risk [RR] 0.87, 95 % CI 0.53–1.43; $p = 0.58$). Over the 7-day postoperative follow-up period, there was no statistically significant difference between the groups in the proportion of patients who remained free of any pulmonary complication (ARR 7, 95 % CI –6 to 20 %; $p = 0.40$). Other secondary outcomes also did not differ significantly between the two groups.

Conclusions: Among patients undergoing major abdominal surgery, early preventive application of high-flow nasal cannula oxygen therapy after extubation did not result in improved pulmonary outcomes compared with standard oxygen therapy.

Keywords: Postoperative hypoxaemia, Oxygen therapy, Postoperative pulmonary complications, Perioperative medicine, High-risk surgery

Introduction

Postoperative respiratory complications are the second most frequent complications after surgery [1], and a major burden in health care [2, 3]. We and others have previously reported that in patients undergoing abdominal surgery, use of lung-protective ventilation is associated with improved clinical outcomes [4, 5]. There remains, however, a significant number of patients who still develop respiratory complications following extubation, especially hypoxaemia [4, 6], thereby suggesting that there is room for improvement in these patients.

Previous studies reported that hypoxaemia, which is one of the most meaningful factors associated with poor patient outcomes, occurs in 10–50 % of patients after surgery [1, 7], depending on patients and surgical conditions. Oxygen therapy is almost invariably applied after elective extubation using low-flow devices to correct residual impairment in oxygenation, but may not always prevent the postoperative deterioration in respiratory function. After disconnection from mechanical ventilation and positive airway pressure, derecruitment of lung areas, with a resulting loss in functional alveolar units, is not uncommon and recently extubated patients are prone to oxygen desaturation.

High-flow oxygen therapy through a nasal cannula (HFNC) is receiving increasing interest as an alternative to standard oxygen therapy and noninvasive ventilation (NIV) in critically ill patients with hypoxaemic respiratory failure [8, 9] and more recently in a mixed population of mechanically ventilated intensive care unit patients at risk for reintubation after extubation [10]. Previous studies have reported several physiological benefits of HFNC [11, 12], among which are a flow-dependent positive airway pressure and increased end-expiratory lung volume, suggesting a possible alveolar recruitment effect. Although it is reasonable to hypothesise a clinical advantage of early and short-term (less than 24 h) application of HFNC after elective extubation to minimize lung derecruitment and prevent hypoxaemia, and subsequent postoperative morbidity, its effects have not been evaluated in randomised trials in surgical patients to whom HFNC might be applied if used in preference to standard oxygen therapy for treatment duration consistent with usual care (i.e. less than 24 h).

We therefore performed a randomised clinical trial to evaluate the clinical effectiveness of preventive application of HFNC directly after elective extubation, compared with standard oxygen therapy after major abdominal surgery, to decrease the incidence of hypoxaemia after major abdominal surgery. We hypothesised that immediate use of HFNC after extubation may reduce the incidence of hypoxaemia after discontinuation of invasive lung-protective mechanical ventilation.

Methods

Study design

The OPERA trial was an investigator-initiated, multicentre, randomised clinical trial conducted in three university hospitals in France. A detailed description of the study protocol has previously been published before enrolment of patients had been completed [13]. The study protocol and statistical analysis plan were approved for all centres by a central ethics committee (Comité de Protection des Personnes Sud-Est VI, Clermont-Ferrand, France). All patients provided written informed consent before surgery.

Patients

All adult patients scheduled for planned or unplanned abdominal, or abdominal and thoracic, surgery with an anticipated duration of 2 h or more and a moderate to high risk of postoperative pulmonary complications, defined by an ARISCAT risk score [14] of 26 points or more, were eligible for recruitment. The ARISCAT risk score is a weighted scoring system comprising seven independent clinical variables, which identifies patients with low (a score of less than 26 points), intermediate, or high (a score of 45 points or more) risk for developing

postoperative pulmonary complications. Exclusion criteria included lack of informed consent prior to randomisation, body mass index greater than 35 kg/m^2, life-threatening condition requiring emergency surgery, obstructive sleep apnoea syndrome, and pregnant patients.

Randomisation and masking

Randomisation was performed (in a 1:1 ratio) with the use of a computer-generated assignment sequence and a centralised telephone system accessible round the clock to receive either HFNC or standard oxygen therapy immediately after tracheal extubation. Randomisation was stratified according to study centre and the planned use or non-use of postoperative epidural analgesia, which is a factor that may influence outcomes [15]. An investigator at each centre was responsible for enrolling patients in the trial and ensuring adherence to the protocol. A trained research coordinator, blinded to the randomised intervention, was responsible for centralisation of data from all sites and recording them onto the electronic database. Although the individual assignments of patients could not be masked to staff members who collected data during surgery and in the post-anaesthesia care unit, treatment allocation was concealed to outcome assessors throughout the study. The coordinating centre remained unaware of the trial group outcomes until the database was locked. The trial statistician analysed the results using an analysis plan that had been finalised before the base was locked and before the blinded data were analysed.

Study intervention

All recruitment centres had expertise in the use of HFNC. Standard oxygen therapy was delivered continuously using nasal prongs or facemask (usual care group). In the HFNC oxygen therapy group (HFNC therapy), oxygen was delivered continuously at a gas flow rate of 50–60 L/min through an MR850 heated humidifier and an RT202 breathing circuit (Optiflow™, Fisher and Paykel Healthcare Ltd, Auckland, New Zealand). In each group, oxygen flow was titrated by the bedside nurse to maintain a peripheral oxygen saturation of 95 % or more. During surgery, a standardised lung-protective ventilation strategy was applied as described in previous reports and in the study protocol [2, 4, 13], and consisted in the combined use of low tidal volume, moderate positive end-expiratory positive pressure and, whenever possible, recruitment manoeuvres [4]. At the end of surgery, tracheal extubation was performed according to predefined criteria [13]. In both groups, the allocated therapy was delivered continuously until 7.00–8.00 a.m., at postoperative day 1, at which time point study treatment was stopped. Patients received additional oxygen if peripheral oxygen saturation was lower than 93 % after treatment discontinuation (Online Appendix p.12). Treatment was interrupted in the case of acute respiratory failure requiring immediate intubation or in the case of severe respiratory discomfort with the assigned therapy. Decisions about all other aspects of patient care during the intra- and postoperative periods were made by the attending physician according to the expertise of the staff at each centre and routine clinical practice.

Outcomes

The primary outcome was the proportion of patients who developed hypoxaemia, defined as an arterial oxygen tension to inspiratory oxygen fraction ratio of 300 or less, 1 h after extubation [16]. In addition, this outcome was analysed at the end of allocated treatment. Arterial blood gases were measured on room air in all patients.

Secondary outcomes were assessed daily during the first 7 days after surgery, since respiratory events after surgery are commonly seen during this period, and at hospital discharge; these were (a) postoperative pulmonary complications due to any cause, graded on a scale from 0 (no pulmonary complications) to 4 (the most severe complications) [17]; (b) need for additional oxygen therapy after 8.00 am on day 1 (end of treatment) defined as peripheral oxygen saturation at most 93 % on room air; (c) the development of postoperative hypoxaemia, pneumonia, reintubation and/or use of curative NIV because of postoperative respiratory failure; (d) postoperative gas exchange after discontinuation of the allocated treatment; (e) respiratory comfort (graded with the use of a numerical rating scale, ranging from 0 to 10); (f) unexpected intensive care unit (ICU) admission or readmission; (g) ICU and hospital lengths of stay; and (h) in-hospital mortality.

Statistical analysis

Assuming an incidence of hypoxaemia of 40 % after extubation in patients with characteristics comparable to our inclusion criteria [1, 7, 16], we calculated that enrolment of 220 patients would provide the trial with 90 % power to detect a relative difference of 50 % in the primary outcome between the two groups at a two-sided alpha level of 0.05. During the trial, a total of eight patients were excluded after randomisation; surgery was stopped prematurely (surgical duration less than 2 h) in three of the eight patients because of extensive illness, and five had violation of exclusion criteria. An additional eight patients were thus randomly assigned to a study group to obtain the full sample (Fig. 1).

All analyses were performed before the breaking of the randomisation code on data from the modified

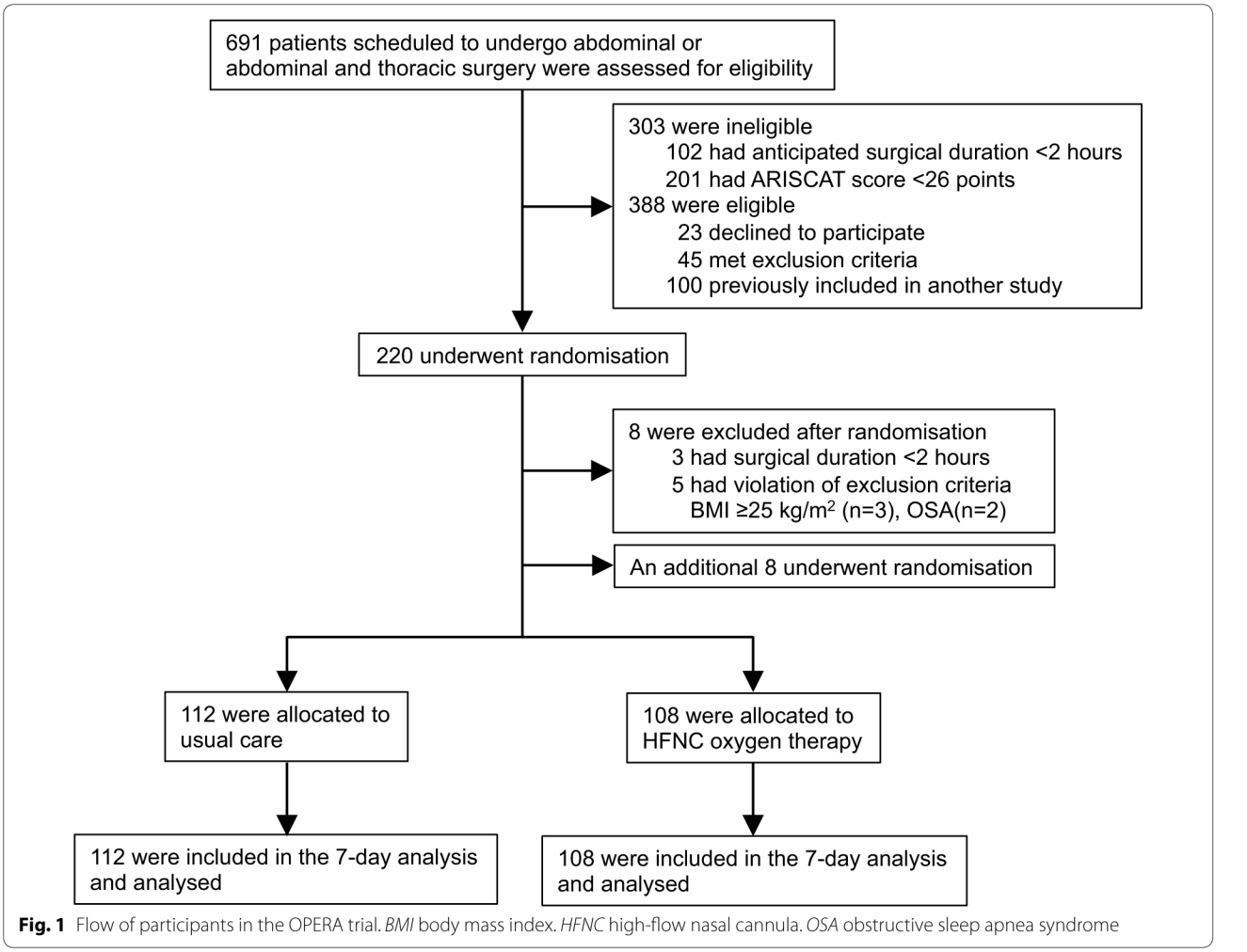

Fig. 1 Flow of participants in the OPERA trial. *BMI* body mass index. *HFNC* high-flow nasal cannula. *OSA* obstructive sleep apnea syndrome

intention-to-treat population, defined as all randomly assigned patients except those who could be excluded without the risk of bias (eight patients who underwent randomisation by mistake and who never received the study treatment) (Fig. 1). An interim analysis was performed after enrolment of the first 110 patients to review data relating to patient safety and quality of trial conduct using the Lan and DeMets method (East software, Cytel Inc., Cambridge, MA, USA). Premature discontinuation of the trial was not recommended on the basis of that analysis, and 220 patients were therefore included.

Continuous variables were compared using the unpaired *t* test or the Mann–Whitney *U* test as appropriate. The Shapiro–Wilk test was used to assess normality, and the Fisher–Snedecor test to assess homoscedasticity. Unadjusted Chi squared was used for primary outcome analysis. Adjusted analysis was performed with the use of a random-effects robust Poisson generalized linear model to take into account adjustment for possible confounding covariates selected according to univariate results in addition to the stratification variables, and to consider within- and between-centre variability (centre as random effect). Results of primary and secondary outcomes are reported as absolute risk reduction with 95 % confidence intervals, and additionally reported as between-group difference. Results of the regression model are reported as relative risk with 95 % confidence intervals.

Longitudinal analysis using mixed models was used to take into account between- and within-subject variability (patient as random effect). Kaplan–Meier curves were plotted to assess the probability of remaining free of postoperative pulmonary complications after discontinuation of the allocated treatment. The time to complications was analysed using a marginal Cox-proportional hazard model with results reported as hazard ratio with 95 % confidence intervals, and proportional-hazard assumption verified using the Schoenfeld test and plotting residuals.

We conducted one post hoc subgroup analysis, which included patients that received recruitment manoeuvres

as part of the lung-protective ventilation strategy, on the basis of the interaction between randomisation group and recruitment manoeuvres (yes/no) in the regression model.

As less than 5 % of data was missing or unavailable, handling of missing data was not applied. All analyses were performed with the use of Stata version 13.0 (StataCorp LP, College Station, TX, USA). A two-sided *P* value of less than 0.05 was considered to indicate statistical significance.

Results

Between 6 November 2013, and 1 March 2015, of the 691 patients assessed for trial eligibility, 220 patients underwent randomisation, with 112 patients assigned to the usual care group and 108 patients assigned to the HFNC group (Fig. 1). All patients were included in the final intention-to-treat analysis.

The two groups of patients had similar baseline characteristics (Table 1). The mean (SD) preoperative ARISCAT risk scores for postoperative pulmonary complications were 40.1 (6.4) in the usual care group and 40.9 (8.7) in the HFNC group ($p = 0.48$). The distribution of the main intraoperative variables is reported in Table 2. Clinical care other than the trial intervention was similar, especially mean levels of tidal volumes and positive end-expiratory pressure applied during surgery. Sixty-seven of the 108 patients (62 %) assigned to HFNC and 69 of the 112 patients (62 %) assigned to usual care received recruitment manoeuvres during lung-protective mechanical, without any statistically significant difference between groups ($p = 0.85$). There were no significant between-group differences regarding use of epidural analgesia, blood loss, blood transfusion and volumes of intravenous fluids. All patients were successfully extubated at the end of surgery, without significant difference ($p = 0.89$) in the duration of intraoperative mechanical ventilation. The median duration of the allocated treatment after extubation was 16 h (interquartile range, 14–18 h) in the usual care group and 15 h (interquartile range 12–18 h) in the HFNC group ($p = 0.03$). Eight patients (7.4 %) allocated to the HFNC group required premature discontinuation for discomfort related to the interface [median (IQR) time to cessation of treatment, 1.8 h (0.8–4.5 h)] compared with no patient in the usual care group ($p = 0.003$).

The primary outcome, postoperative hypoxaemia, was met by 21 % of patients (23/108) treated with HFNC and by 24 % of patients (27/112) treated with standard oxygen 1 h after extubation, and by 29 (27 %) of 108 patients and 34 (30 %) of 112 patients after treatment discontinuation [absolute risk reduction (ARR) 4 %, 95 % CI −8 to 15 %, $p = 0.57$] (Table 3). The results of associated univariate and multivariate analyses are provided in the Online Appendix (p. 3). Following adjustment for baseline covariates, the observed treatment effect remains non-significant [unadjusted relative risk (RR) 0.88, 95 % CI 0.44–1.52]; adjusted RR 0.87, 95 % CI 0.53–1.43; $p = 0.58$) (Table 3 and Online Appendix p. 3). There were no significant between-group differences for any of the secondary outcomes: need for supplemental oxygen therapy for persistent hypoxaemia after treatment discontinuation, grade level of pulmonary complications, number of patients requiring any form of ventilator assistance for acute respiratory failure during the first 7 days after surgery, and service utilization (days in ICU, days in the hospital) (Table 3; Online Appendix p. 13). During the 7-day postoperative follow-up, there was no statistically significant between-group difference in the proportion of patients who remained free of any pulmonary complication (ARR 7, 95 % CI −6 to 20 %, $p = 0.29$; unadjusted RR 1.19, 95 % CI 0.79–1.78; adjusted RR 1.19, 95 % CI 0.80–1.79, $p = 0.40$) (Table 3; Fig. 2).

In a post hoc analysis, there was a significant interaction between use of recruitment manoeuvres during lung-protective ventilation and the treatment group with respect to hypoxaemia after treatment discontinuation ($p = 0.019$). In the subgroup of patients whose lung-protective strategy included recruitment manoeuvres (Online Appendix pp. 6–9), the observed treatment effect was strengthened in the HFNC group as compared with the usual care group (ARR 13, 95 % CI −2 to 27 %, $p = 0.09$; unadjusted RR 0.58, 95 % CI 0.28–1.17; adjusted RR 0.53, 95 % CI 0.26–1.09, $p = 0.08$). There were no significant between-group differences in any of the other outcomes (Online Appendix).

There were no significant between-group differences for patient respiratory comfort, haemodynamics and postoperative gas exchange, 1 h after enrolment and after treatment discontinuation (Online Appendix p. 10).

Discussion

In this multicentre randomised clinical trial, a strategy of preventive application of high-flow nasal oxygen therapy directly after extubation compared with standard oxygen therapy was ineffective at reducing the incidence of hypoxaemia after abdominal surgery. There were also no significant differences in postoperative outcomes, especially pulmonary complications and length of hospital stay.

When planning the study, we assumed an incidence of hypoxaemia of 40 % based on data from previous large cohorts of abdominal surgical patients [1, 7]. Our results showed a lower rate than expected with standard oxygen therapy (30 %), which might have been attributable to overall improvements in perioperative surgical care, to inclusion of patients at lower risk of developing

Table 1 Characteristics of the patients at baseline

Characteristic	No. (%)	
	Usual care ($n = 112$)	HFNC oxygen therapy ($n = 108$)
Age (years)	61 (13)	62 (12)
Male sex	64 (57)	61 (56)
Height (cm)	168 (9)	168 (8)
Weight (kg)	70 (14)	70 (13)
Body mass index (kg/m^2)	25 (4)	25 (4)
Predicted body weight (kg)[a]	61 (11)	61 (10)
ASA grade		
1	20 (18)	20 (18)
2	75 (67)	72 (67)
3 or higher	17 (15)	7 (15)
Preoperative risk score[b]		
Moderate risk	95 (85)	90 (83)
High -risk	17 (15)	18 (17)
Comorbidity		
Hypertension	35 (31)	34 (31)
Current smoker	30 (27)	36 (33)
Recent weight loss >10 %	16 (14)	14 (13)
Alcohol intake	8 (7)	14 (13)
COPD	6 (5)	2 (2)
Asthma	2 (2)	8 (7)
Diabetes	13 (12)	12 (11)
Cancer diagnosis	88 (79)	91 (84)
Type of surgery		
Liver resection	46 (41)	38 (35)
Pancreatico-duodenectomy	35 (31)	34 (32)
Gastrectomy	4 (3)	9 (8)
Oesophagectomy	5 (4)	7 (6)
Colorectal resection	13 (12)	14 (13)
Splenectomy	2 (2)	2 (2)
Other	7 (6)	4 (4)
Planned surgery	112 (100)	106 (98)
Laparoscopic surgery	10 (9)	10 (9)
Surgical incision		
Midline	53 (47)	50 (46)
Transverse	47 (42)	46 (43)
Other	12 (11)	12 (11)
Duration of the surgical procedure (min)[c]	300 (190–380)	270 (195–370)

Data are *n* (%), mean (SD), or median (IQR), unless otherwise stated

ASA American Society of Anaesthesiology physical status classification, *COPD* chronic obstructive pulmonary disease

[a] The predicted body weight was calculated as follows: for men, 50 + 0.91 × (height in centimetres − 152.4); and for women, 45.5 + 0.91 × (height in centimetres − 152.4)

[b] Preoperative risk (ARISCAT) score for postoperative pulmonary complications. The risk index is a scoring system based on seven independent preoperative risk factors indicating three levels of risk: low risk (<26 points), moderate risk (26–44 points) and high risk (≥45 points). Patients having moderate or high risks were eligible for inclusion

[c] The duration of surgery was calculated as the time between skin incision and closure of the incision

hypoxaemia and, in contrast to previous studies, to the use of lung-protective mechanical ventilation. Our findings for postoperative pulmonary complications are also consistent with recent data of a large multicentre study in which patients had entry criteria similar to those in our trial [6]. Furthermore, although the overall

Table 2 Clinical management of patients during the surgical period

Variable	Usual care ($n = 112$)	HFNC oxygen therapy ($n = 108$)
Duration of mechanical ventilation (min)	390 (290–500)	377 (290–490)
Tidal volume (mL/kg of PBW)[a]		
Start of surgery	7.6 (1.3)	7.4 (1.2)
End of surgery	7.5 (1.3)	7.3 (0.9)
PEEP (cm H_2O)		
Start of surgery	6.1 (1.3)	6.3 (1.8)
End of surgery	6.2 (1.3)	6.3 (1.3)
Use of recruitment manoeuvres	69 (62)	67 (62)
Number of recruitment manoeuvres[b]	6 (3)	6 (4)
Plateau pressure (cm H_2O)		
Start of surgery	16.4 (3.6)	15.9 (3.0)
End of surgery	16.2 (2.8)	15.6 (3.6)
FiO_2 (%)	49 (14)	52 (16)
Volume of fluid administered (mL)		
Crystalloids	3000 (2000–4000)	2500 (2000–3500)
Colloids	1000 (500–1500)	750 (500–1000)
Use of epidural analgesia	37 (33 %)	37 (34 %)
Blood loss (mL)	350 (200–700)	350 (150–600)
Blood transfusion	13 (12 %)	12 (11 %)
Use of nasogastric tube	76 (68 %)	63 (58 %)

Data are *n* (%), mean (SD), or median (IQR) unless otherwise stated

FiO_2 inspired oxygen fraction, *PBW* predicted body weight, *PEEP* positive end-expiratory positive pressure

[a] The predicted body weight was calculated as follows: for men, $50 + 0.91 \times$ (height in centimetres $- 152.4$); and for women, $45.5 + 0.91 \times$ (height in centimetres $- 152.4$)

[b] Recruitment manoeuvres consisted of applying a continuous positive airway pressure of 30 cm H_2O for 30 s

rate of hypoxaemia in the usual care group was lower than anticipated, it is unlikely that patients in the HFNC group would have a relative reduction of 50 % in risk, which limits the value of the present work. Nevertheless, although we are aware that a definitive conclusion cannot be drawn from our findings, an absolute risk reduction of 4 % between the two treatments makes the likelihood of a statistically significant difference difficult to achieve and of limited clinical relevance. These concerns need careful consideration.

To the best of our knowledge, this trial is the first to evaluate the usefulness of preventive application of HFNC directly after extubation in abdominal surgical patients. Despite extensive physiological data [12], there are few data on the use of HFNC in preventing the worsening of respiratory function following surgery. Our findings are consistent with those of two previous randomised trials in cardiac surgical patients in which direct extubation onto HFNC after surgery did not confer clinical advantage in terms of oxygenation and respiratory function over standard oxygen therapy [18, 19].

One notable feature of our trial compared with the existing data was the use of intraoperative lung-protective ventilation. However, lung derecruitment is not uncommon after extubation and recently extubated patients are prone to oxygen desaturation [20]. Considering the suspected induced effects of HFNC on lung volumes [12], we hypothesised that early initiation of HFNC could minimize in part lung derecruitment after extubation. Unlike recent findings in mechanically ventilated patients at risk for reintubation [9, 10, 21], we failed to detect any major differences in unadjusted or adjusted outcomes between treatment groups. Several hypotheses could explain these results.

First, previous studies have shown a significant variability of the airway pressures during the respiratory cycle with HFNC [22], and that high flow-rate translates into clinically significant airway pressures only with the mouth closed [23], In keeping with the pragmatic nature of our trial, no attempt was made to ensure that patients had a closed mouth. Although flow rates used in this study are consistent with clinical practice, higher gas flow rates might be required in this setting to minimize lung derecruitment after extubation [24].

Second, previous studies stressed that both the timing after extubation and the duration of treatment are important in determining the clinical effectiveness of noninvasive respiratory support [16]. Although HFNC

Table 3 Results for the primary and secondary outcomes

Outcomes	No./total no. (%)		ARR or between-group difference (95 % CI)	*p* value
	Usual care	HFNC oxygen therapy		
Primary outcomes				
Postoperative hypoxaemia[a,b]				
1 h after extubation	27/112 (24)	23/108 (21)	−3 (−14 to 8)	0.62
After discontinuation of the study treatment	34/112 (30)	29/108 (27)	−4 (−15 to 8)	0.57
Secondary outcomes				
Need for supplemental oxygen therapy after treatment discontinuation	92/112 (82)	79/108 (73)	−9 (−20 to 2)	0.11
Pulmonary complications[c] within 7 days				
Grade 1 or 2	49/112 (44)	37/108 (34)	−10 (−25 to 4)	0.17
Grade ≥3	19/112 (17)	21/108 (20)	2 (−8 to 13)	0.63
Bronchial congestion	14/112 (13)	16/108 (15)	2 (−7 to 11)	0.62
Hypoxaemia[d]	30/112 (27)	30/108 (28)	0 (−11 to 13)	0.87
Pneumonia	10/112 (9)	10/108 (9)	0 (−7 to 8)	0.93
Need for intubation or NIV for respiratory failure[e]	14/112 (13)	20/108 (19)	6 (−4 to 16)	0.22
Surgical reoperation within 7 days[f]	5/112 (4)	2/108 (2)	−3 (−7 to 2)	0.45
Unexpected ICU admission	16/112 (14)	16/108 (15)	0 (−9 to 10)	0.91
ICU length of stay (days)	5 (3–13)	6 (4–16)	3 (−5 to 12)	0.53
Hospital length of stay (days)	11 (7–18)	12 (7–20)	0.5 (−3.5 to 4.5)	0.58
In-hospital mortality	3/112 (3)	2/108 (2)	−1 (−5 to 3)	0.68

Data are *n* (%) or median (IQR) unless otherwise stated

ARR absolute risk reduction, *NIV* noninvasive ventilation, *ICU* intensive care unit, *BMI* body mass index, *HFNC* high-flow nasal cannula, *OSA* obstructive sleep apnoea syndrome, *HFNC* high-flow nasal cannula, *PPC* postoperative pulmonary complications

[a] The primary outcome was the proportion of patients with postoperative hypoxaemia (PaO_2/FiO_2 of 300 or less), as established previously

[b] Relative risk for requiring prophylactic NIV after extubation: unadjusted RR 0.88 (95 % CI 0.54–1.44); adjusted RR 0.87 (95 % CI 0.53–1.43); $p = 0.58$. Adjustment was performed for stratification variables (use or non-use of epidural analgesia and study centre) and preoperative risk of postoperative pulmonary complications (ARISCAT score)

[c] Postoperative pulmonary complications were scored with the use of a graded scale ranging from 0 to 4, with grade 0 representing the absence of any pulmonary complications and grades 1–4 representing successively the worst forms of complications

[d] Criteria for postoperative hypoxaemia was defined as peripheral oxygen saturation <92 % while breathing at least 10 L/min oxygen, PaO_2 <60 mmHg on room air or PaO_2 <80 mmHg while breathing any supplemental oxygen

[e] Acute hypoxaemic respiratory failure was defined by one of the hypoxaemic criteria (peripheral oxygen saturation (SpO_2) <92 % while breathing at least 10 L/min oxygen, PaO_2 <60 mmHg on air or PaO_2 <80 mmHg while breathing any supplemental oxygen) and at least one of the following: severe respiratory distress with dyspnoea, accessory muscle recruitment and paradoxical abdominal or thoracic motion, respiratory rate >25 breaths/min, respiratory acidosis with pH <7.30 and arterial carbon dioxide partial pressure ($PaCO_2$) >50 mmHg

[f] Patients who underwent reoperation were systematically intubated. Only patients who required postoperative mechanical ventilation for at least 6 h were considered a reintubation

was applied directly after extubation, the time needed to produce significant effects may be longer than we anticipated. In keeping with the pragmatic nature of the trial, we aimed to reproduce standard practices in oxygen therapy following elective extubation in surgical patients. Hernandez et al. [10] recently showed that in a low-risk population for reintubation of mechanically ventilated patients for more than 12 h, including 15 % of scheduled surgical patients, 24 h of HFNC therapy after extubation was enough to reduce the reintubation rate. In the present study, HFNC therapy was applied for a median (IQR) duration of 15 (12–18) h, which is consistent with the routine postoperative monitoring time in the perioperative environment.

Third, there is evolving evidence that during abdominal surgery, low tidal volume ventilation should include recruitment manoeuvres, in addition to moderate levels of PEEP [4, 25]. Previous studies have emphasized the role of low tidal volume ventilation, even when PEEP is applied, on alveolar derecruitment. Low PEEP levels, in the absence of recruitment manoeuvres, may therefore be insufficient to stabilize alveoli and keep them open. Owing to the perceived effects of HFNC on airway pressure and lung volumes, we had assumed that early

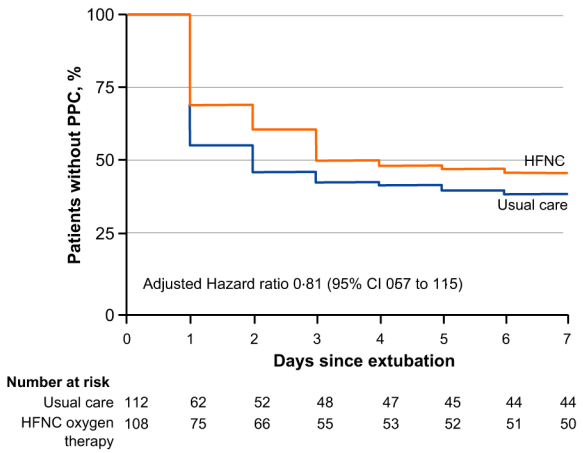

Fig. 2 Kaplan–Meier *plots* of patients without postoperative pulmonary complications from enrollment to day 7 after surgery. *HFNC* high-flow nasal cannula. *PPC* postoperative pulmonary complications

HFNC therapy could, at least in part, minimize alveolar derecruitment following extubation if the treatment is initiated on previously recruited lungs. The observed treatment effect was strengthened in the post hoc analysis in the subgroup of patients that received recruitment manoeuvres (18 % in the HFNC group vs 30 % usual care group), which was justified by a significant interaction with study treatment [26]. Hence, the study may have identified a clinical benefit of HFNC for the primary endpoint that did not demonstrate statistical significance because of a possible lack of power.

The findings of previous trials and meta-analyses have suggested the efficacy of moderate levels of continuous positive airway pressure (CPAP) (7–10 cm H_2O) or noninvasive positive pressure ventilation (NPPV) as preventative treatments, applied either continuously or intermittently for a few hours (6–12 h) in high-risk patients following abdominal surgery, by reducing the incidence postoperative pulmonary complications [27]. There is, however, only limited translation to routine clinical practice in the immediate postoperative period because this usually requires experienced staff and admission to a specialized environment. Although the study patient population and treatment duration were close to those of previous studies using CPAP, the findings of the present study may be seen as somewhat predictable. However, the current evidence base for postoperative CPAP has a number of limitations and the effects on hypoxaemia, invasive mechanical ventilation and mortality are uncertain [28].

This study has several limitations. The definition of our primary endpoint was arbitrary and may not adequately reflect disease severity. We are aware that hypoxaemia might not be considered to be as relevant as patient-centred outcomes, such as reintubation, to guide clinical practice. However, hypoxaemia still remains a matter of concern in daily practice and may be associated with poor patient outcomes. Additionally, our definition is supported in the literature [14, 16] and is not subject to observer bias, and is also highly relevant to clinicians in this surgical population, especially to identify patients who may benefit from an intensification of treatment and initiation of NIV [29]. The current study was intended to explore the effect of HFNC in addition to lung-protective ventilation. Whilst previous studies have shown encouraging results in the abdominal surgery population, its application to routine clinical practice remains uncertain. Whether the use of HFNC may translate into clinical benefits outside this setting deserves further explorations. The study protocol did not include standardisation for different aspects of patient care. It was recommended, however, that the study centres follow routine clinical practice to minimize interference with the trial intervention. Adherence to the use of recruitment manoeuvres during surgery was low (only 61 % of the study population), perhaps resulting in a failure to achieve statistical significance for the primary outcome. Finally, because we studied a homogeneous population of surgical patients, with an overall moderate risk of pulmonary complications, our findings do not preclude the possibility of significant beneficial effects from using HFNC in higher-risk patients.

In conclusion, our study indicates that among patients undergoing major abdominal surgery and receiving intraoperative lung-protective ventilation, preventive application of HFNC after extubation, compared with standard oxygen therapy, did not result in a statistically significant reduction in the incidence of postoperative hypoxaemia. The routine use of postoperative HFNC after extubation does not seem to be justified in similar patients.

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Compliance with ethical standards

Conflicts of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. EF reports receiving consulting fees from Fresenius kabi, and lecture fees from General Electrics Heathcare and Fresenius kabi, nonfinancial support from Drager, and reimbursement of travel expenses from Fisher and Paykel Healthcare. CPB reports receiving consulting fees from Merck Sharp & Dohme, Baxter Gambro and Astellas. TG reports receiving a research grant from LFB Bio-medicaments and meeting support (reimbursement of travel costs) from Baxter Gambro. SJ reports receiving consulting fees from Drager, Maquet, Hamilton and Fisher and Paykel Healthcare, lecture fees from Abbott and Philips, and reimbursement of travel expenses from Pfizer. The other authors declare no competing interests.

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