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Clinical Investigation

CLINICAL INVESTIGATION

High-flow nasal oxygenation or standard oxygenation for gastrointestinal endoscopy with sedation in patients at risk of hypoxaemia: a multicentre randomised controlled trial (ODEPHI trial)

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Abstract

Background: We aimed to determine whether high-flow nasal oxygen could reduce the incidence of decreased peripheral oxygen saturation (SpO_2) compared with standard oxygen in patients at risk of hypoxaemia undergoing gastrointestinal endoscopy under deep sedation.

Methods: This was a multicentre, randomised controlled trial with blinded assessment of the primary outcome evaluating high-flow nasal oxygen (gas flow 70 L min^{-1}, inspired oxygen fraction 0.50) or standard oxygen delivered via nasal cannula or face mask (6 L min^{-1}) or nasopharyngeal tube (5 L min^{-1}) in patients at risk of hypoxaemia (i.e. >60 yr old, or with underlying cardiac or respiratory disease, or with ASA physical status >1, or with obesity or sleep apnoea syndrome) undergoing gastrointestinal endoscopy. The primary endpoint was the incidence of SpO_2 ≤92%. Secondary outcomes included prolonged or severe desaturations, need for manoeuvres to maintain free upper airways, and other adverse events.

Results: In 379 patients, a decrease in SpO_2 ≤92% occurred in 9.4% (18/191) for the high-flow nasal oxygen group, and 33.5% (63/188) for the standard oxygen groups (adjusted absolute risk difference, −23.4% [95% confidence interval (CI), −28.9 to −16.7]; $P<0.001$). Prolonged desaturation (>1 min) and manoeuvres to maintain free upper airways were less frequent in the high-flow nasal oxygen group than in the standard oxygen group (7.3% *vs* 14.9%, $P=.02$, and 11.1% *vs* 32.4%, $P<0.001$).

Conclusions: In patients at risk of hypoxaemia undergoing gastrointestinal endoscopy under deep sedation, use of high-flow nasal oxygen significantly reduced the incidence of peripheral oxygen desaturation.

Clinical trial registration: NCT03829293.

Keywords: colonoscopy; deep sedation; gastrointestinal endoscopy; gastroscopy; hypoxaemia; high-flow nasal oxygenation

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Editor's key points

- High-flow nasal oxygen therapy may be useful to prevent hypoxaemia during gastrointestinal endoscopy under sedation, but it is not clear whether this therapy is more effective than a conventional oxygen therapy when similar oxygen concentrations are used.
- This multicentre study has shown that, in patients (who were at risk of hypoxaemia) undergoing gastrointestinal endoscopy under sedation, high-flow nasal oxygen (gas flow 70 L min^{-1}, inspired oxygen fraction 0.50) significantly reduced the incidence of decreased peripheral oxygen saturation.
- Further studies are required to establish the role of high-flow nasal oxygen therapy in patients undergoing gastrointestinal endoscopy under sedation, and to determine which patients would benefit from receiving this therapy.

Gastrointestinal endoscopy is a common medical procedure often performed under deep sedation in patients breathing spontaneously. The use of sedation improves the quality of examination and patient comfort.[1,2] Hypoxaemia can occur in 26–85% of cases[3–5] and results from the combination of airway obstruction by the endoscope, anaesthesia-induced upper airway collapse, and respiratory depression and lung compression because of intestinal gas insufflation. Patients with obstructive sleep apnoea syndrome,[6,7] obesity,[3,8] hypertension,[9] diabetes,[9] heart disease,[9] age older than 60 yr,[3] or high American Society of Anesthesiologists (ASA) physical status class[8,10] are particularly at risk of hypoxaemia and potentially prone to hypoxaemia-induced complications.[11]

Some methods of oxygenation and airway management have been shown to prevent hypoxaemia during gastrointestinal endoscopy,[12–15] but none of these techniques are commonly used. Currently, standard oxygen therapy is recommended to prevent and treat hypoxaemia during gastrointestinal endoscopy.[11] Standard oxygen therapy can be delivered by a nasal cannula, a nasopharyngeal tube, a simple (low flow system) face mask, or a non-rebreather face mask (high concentration oxygen mask). High-flow nasal oxygen therapy may be an alternative. High gas flow (40–70 L min^{-1}) allows for setting a high inspired oxygen fraction (FiO_2) resulting in high and relatively stable effective FiO_2, and provides a washout effect of dead-space, and maintains a slight PEEP.[16,17] Two recent RCTs have suggested that high-flow nasal oxygen may reduce the rate of hypoxaemia during gastrointestinal endoscopy in patients at low[18] or high risk[19] of hypoxaemia. However, the design of these studies clearly disadvantaged patients of the control group, who received 2 or 5 L min^{-1} oxygen via standard nasal canula, providing an FiO_2 of <0.35 or 0.50 on average,[20] whereas patients in high-flow oxygen groups received an FiO_2 of 1.00. In contrast, a recent, small RCT of morbidly obese patients undergoing colonoscopy under sedation showed no benefit of high-flow nasal over standard oxygen when FiO_2 was set at 0.40 in both groups.[21] Therefore, whether high-flow nasal oxygen should replace standard oxygen therapy to prevent hypoxaemia during gastrointestinal endoscopy remains an open question.

This was a multicentre RCT involving patients at risk of hypoxaemia undergoing gastrointestinal endoscopy under deep sedation with a similar FiO_2 applied in both groups. We aimed to determine whether high-flow nasal oxygen and its PEEP and dead-space washout effects could reduce the rate of decreased peripheral oxygen saturation as compared with standard oxygen during the procedure (upper or lower gastrointestinal endoscopy, or both).

Methods

Study design

This trial was a multicentre, open-label, and assessor-blinded RCT with two parallel groups conducted in four French centres (one university hospital, one regional and teaching hospital, one private medico-surgical hospital, and one general district hospital) between March and September 2019. The study protocol (Supplementary file 1) was approved by the central ethics committee (Ethics Committee Paris Sud Est V, Paris, France, registration no. 2018-A03481-54). All enrolled patients gave written informed consent. The protocol and statistical analysis plan were published before the beginning of data analysis.[22]

Participants

Eligible patients were adults aged 18 yr or older who were undergoing gastrointestinal endoscopy (upper, lower, or both) under deep sedation and were at risk of hypoxaemia. Patients considered at moderate or high risk of hypoxaemia when the patients had underlying cardiac or respiratory disease, were older than 60 yr, were ASA physical status 2, 3, or 4,[10] were obese (BMI $\geq$30 kg m^{-2}), or had obstructive sleep apnoea syndrome, documented or highly suspected by using the 'snoring, tiredness, observed apnoea, high blood pressure–body mass index, age, neck circumference and gender' (STOP-Bang) questionnaire (STOP-Bang score $\geq$3).[23] Patients were excluded if the procedure was performed in emergency or required planned tracheal intubation or if they had tracheotomy, were pregnant, or were on oxygen therapy at home.

Randomisation and masking

Patients were randomised by a computer-generated block randomisation (EOL Random, Medsharing, France) in a 1:1 ratio to undergo high-flow nasal oxygen therapy or standard oxygen therapy with stratification according to centre and to the planned use of opioids or not for sedation (in the 'no opioids' stratum, clinicians were free to use opioids during the procedure if absolutely necessary). The investigators were not aware of the size of the randomisation blocks. During the endoscopy procedure, the clinicians noted in real time the time of every event and of every decrease in oxygen saturation measured by pulse oximetry (SpO_2), noted the lowest observed SpO_2, and noted if and when poor SpO_2 signals occurred on a paper case report form. The patients, anaesthesia team, and physicians performing the endoscopy could not be blinded, but SpO_2 was recorded at 1 min intervals during the procedure and printed out to allow for delayed reading by an assessor who had no access to the case report form and was blinded to treatment allocation.

Procedures

For both groups, the period of intervention lasted from the pre-oxygenation phase to the time when the patients were

disconnected from the anaesthesia monitor (generally at the end of the endoscopy procedure or a few minutes after) and transferred to the recovery room.

An oxygen flow rate in standard oxygen group was chosen to have an FiO_2 of approximately 0.50, similar[24] to that applied in the high-flow nasal oxygen group at the beginning of endoscopy to test whether high-flow nasal oxygen may improve oxygenation via PEEP, dead-space washout effects, or both.

In the high-flow nasal oxygen group, pre-oxygenation with a gas flow of 40 L min^{-1} and FiO_2 1.00 was applied at least 3 min before anaesthesia induction by using the Thrive device (Fisher and Paykel Healthcare, Auckland, New Zealand). At the time of abolition of the eyelash reflex, the gas flow was increased to 70 L min^{-1} and the FiO_2 was lowered to 0.50.

In the standard oxygen group, pre-oxygenation with 100% oxygen was performed with an oxygen flow of 8 L min^{-1} with a face mask at least 3 min before anaesthesia induction. At the time of abolition of the eyelash reflex, 100% oxygen was administered with a nasal cannula or a face mask at or with a nasopharyngeal catheter at an oxygen flow rate adjusted (according to the current practice in each centre) to ensure an FiO_2 of approximately 0.50 similar to that applied in the high-flow nasal oxygen group.[24]

Anaesthesia regimen and sedation monitoring

Except for the need to declare in advance (for stratification) whether or not opioids were to be used, the anaesthesia regimen was left to the discretion of the anaesthesia team, but all anaesthesia protocols were started with propofol infusion. The endoscopist introduced an endoscope at the peak effect of propofol. The level of sedation and ventilatory frequency were clinically monitored by the anaesthesia team throughout the procedure. The deep sedation target had the same definition in all centres and for all involved anaesthesia teams: patients should exhibit a relaxed facial expression, no agitation, no response to voice, but slow response to glabellar stimulation or loud voice during the procedure. In case of premature arousal, agitation, oppositional behaviour, or facial expression of pain, the anaesthesiologists could choose to use an additional dose of propofol or increase the propofol infusion rate, administer another anaesthetic drug (benzodiazepine, opioids), or both, as in their usual practice.

Outcomes

The primary outcome was the incidence of decreased SpO_2 $\leq$92% observed during the interval between the start of sedation and the end of the procedure. Although hypoxaemia is often defined as SpO_2 <90%, we chose, as other researchers did,[19,20,25,26] the 92% threshold considering that in patients breathing an FiO_2 of at least 0.50 (as planned per protocol), this would reflect clinically significant oxygenation impairment. SpO_2 and heart rate were recorded every minute during the procedure by the usual anaesthesia multiparameter monitor (Datex Ohmeda or Carescape B450 or Carescape B650; General Electric Healthcare, Chicago, IL, USA). The clinicians were instructed to print out or electronically save the SpO_2 records at the end of the procedure. Assessors blinded to treatment allocation read the SpO_2 records, noted the primary outcome before having access to the case report form, and then checked whether they were in concordance with events reported by clinicians on the case report forms. In case of discrepancy between the lowest SpO_2 reported in the case report form and that recorded, the SpO_2 observed on the records was considered true, unless the clinicians had noted that the SpO_2 signal was of poor quality.

The secondary outcomes included prolonged desaturation defined as SpO_2 $\leq$92% for at least 1 min (i.e. two consecutive SpO_2 recordings $\leq$92% at a 1 min interval), a decrease in SpO_2 of >5%, occurrence of SpO_2 $\leq$90%, and severe desaturation defined as SpO_2 $\leq$85%.

Adverse events recorded were apnoea or bradypnoea episodes defined as a ventilatory frequency of <6 min^{-1}, bradycardia defined as a heart rate <50 beats min^{-1}, need for tracheal intubation, noninvasive ventilation, use of vasopressor, hospitalisation, and other serious adverse events.

We also recorded the need for modification of oxygen flow settings, mask ventilation, and manoeuvres to maintain free upper airways; duration of endoscopy; duration of sedation; and desaturation during the stay in the recovery room (as declared in the case report forms).

Statistical analysis

In a short preliminary survey of 100 patients undergoing gastrointestinal endoscopy under standard oxygen, we found a 24% incidence of hypoxaemia (SpO_2 $\leq$92%). From published studies that compared different oxygenation devices to standard oxygen therapy,[12,13] we assumed that high-flow nasal oxygen would decrease the incidence of desaturation from 24% to 12%. With a two-sided alpha risk of 5% and a power of 80%, 176 patients in each group were needed. We increased this number to 190 patients in each group to anticipate possible drop-outs and possible defective pulse oximetry.

The analysis of data was conducted according to the randomisation group and following the intention-to-treat principle. Interactions between stratification variables and the randomisation group were tested by logistic regression.

Differences between groups regarding the incidence of decreased SpO_2 $\leq$92% was expressed as the adjusted absolute risk difference (ARD) derived from a mixed-effect logistic regression model,[27,28] with the centre as a variable with a random intercept, the use of opioids and the randomisation group as variables with a fixed effect, and integrating over the estimated distribution of random effects.[29] As boundaries for the 95% confidence interval (95% CI) of the ARD, we chose the 2.5th and 97.5th percentiles of 2000 ARD estimates obtained by replicating the mixed-effects logistic model on 2000 bootstrapped samples of the study population. The number needed to treat (NNT) and 95% CI were derived from the ARD.

All other binary categorical outcome measures were compared using the same approach. When not possible owing to too-small numbers of events in either group, unadjusted ARDs with 95% Wald CIs were calculated. In these cases, groups were compared using Fisher's exact test.

Between-group differences regarding the continuous outcome measures were tested by a Mann–Whitney *U*-test adjusted for the stratification variables[30] and expressed as median differences and 95% CIs obtained by bootstrapping (2000 bootstrapped samples).

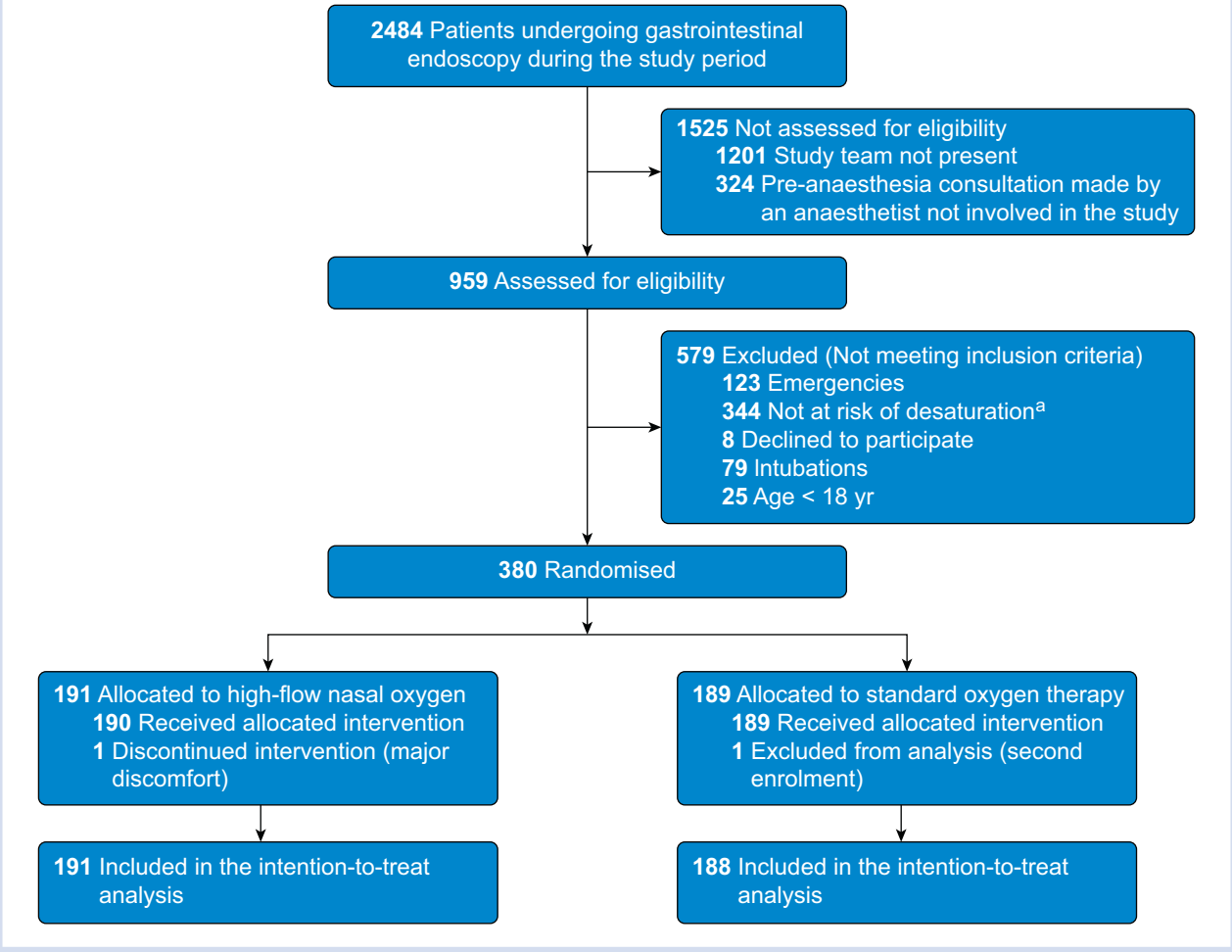

Fig 1. Trial profile. ASA, ASA physical status. [a]ASA 1 and age <60 yr and BMI <30 kg m^{-2} and no underlying respiratory or cardiac disease.

Post hoc exploratory analyses were conducted (1) in patient subgroups formed according to clinical characteristics, which we thought may influence the basal risk of hypoxaemia and the effect size of the intervention (BMI ≥30 kg m^{-2} or not, existence of cardiac comorbidity or not, existence of respiratory comorbidity or not; upper or lower endoscopy; risk of alveolar hypoventilation; see Supplementary file 2 for definition) and (2) to examine the association between different anaesthesia regimens used and the occurrence of SpO_2 ≤92%.

A two-tailed $P<0.05$ was considered statistically significant. *P*-values were not adjusted for multiple testing. R v3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

Results

From March 26, 2019 through September 9, 2019, from a total of 2484 patients who required a gastrointestinal endoscopy in the four centres, 959 were eligible, and 380 patients underwent randomisation. One patient was included twice, in the same group, by error. After excluding the second enrolment, 379 patients were included in the final analysis: 191 in the high-flow nasal oxygen therapy and 188 in the standard oxygen therapy (Fig 1).

Patient characteristics

The median age of patients was 64 yr (inter-quartile range [IQR], 55–71); 54% of patients were male, 54% had hypertension, 20% had diabetes, 20% had respiratory disease(s), and 13% had cardiac disease(s) (excluding hypertension). The characteristics were similar between groups (Table 1). The oxygen saturation in ambient air before the procedure was 96% (IQR, 95–98) and 97% (IQR, 96–98) in the high-flow nasal oxygen and standard oxygen groups. The proportions of upper, lower, and combined (upper and lower) endoscopy were similar between groups (Table 1). Indications and procedures performed during endoscopy were well balanced between groups (Supplementary eTable 1, Supplementary file 2). The groups did not differ in combinations of anaesthetic drugs used for sedation (Supplementary eTables 2 and 3).

Primary outcome

The proportion of patients experiencing an SpO_2 ≤92% during the procedure was 9.4% (18/191) in the high-flow nasal oxygen

Table 1 Baseline characteristics of the intention-to-treat population.

	High-flow nasal oxygen (N=191)	Standard oxygen therapy (N=188)
Median age (IQR), yr	64 (54–71)	64 (55–71)
Male sex, no. (%)	109 (57)	96 (51)
Median BMI (IQR)*	27.0 (23.9–30.5)	26.55 (24.1–30.1)
Mallampati score, no. (%)†	(Missing value: n=1)	(Missing value: n=1)
1	106 (55.5)	100 (53.2)
2	64 (33.5)	61 (32.4)
3	18 (9.4)	25 (13.3)
4	2 (1.0)	1 (0.5)
ASA physical status, no. (%)‡		
1 (all patients were >60 yr old)	24 (12.6)	24 (12.8)
2	114 (59.7)	112 (59.6)
3	53 (27.7)	51 (27.1)
4	0 (0.0)	1 (0.5)
Premedication with anxiolytic, no. (%)	(Missing values: n=2)	(Missing values: n=4)
0	158 (82.7)	154 (81.9)
1	31 (16.2)	30 (16.0)
Regular treatment, no. (%)		
Beta-blockers	43 (22.5)	41 (21.8)
Benzodiazepine	13 (6.8)	19 (10.1)
Neuroleptics	5 (2.6)	4 (2.1)
Underlying illnesses, no. (%)		
Hypertension	88 (46.1)	88 (46.8)
Heart failure with left ventricle ejection fraction ≤45%	2 (1.0)	3 (1.6)
Ischaemic heart disease	16 (8.4)	11 (5.9)
History of acute pulmonary oedema	1 (0.5)	1 (0.5)
Atrial fibrillation	10 (5.2)	11 (5.9)
Chronic obstructive pulmonary disease	8 (4.2)	7 (3.7)
Bronchial dilatation	0 (0.0)	1 (0.5)
Pulmonary emphysema	1 (0.5)	3 (1.6)
Restrictive lung disease	0 (0.0)	3 (1.6)
Asthma	5 (2.6)	9 (4.8)
Sleep apnoea syndrome	21 (11.0)	9 (4.8)
Pulmonary hypertension	0 (0.0)	1 (0.5)
Type 1 diabetes mellitus	1 (0.5)	1 (0.5)
Type 2 diabetes mellitus	37 (19.4)	36 (19.1)
Chronic kidney disease	5 (2.6)	8 (4.3)
Median SpO_2 in ambient air before pre-oxygenation (IQR), %	96 (95–98)	97 (96–98)
Type of gastrointestinal endoscopy, no. (%)		
Upper	35 (18.3)	38 (20.2)
Lower	100 (52.4)	92 (48.9)
Combined	56 (29.3)	58 (30.9)
Invasive procedures performed during endoscopy, no. (%)¶	71 (37.2)	79 (42.0)
Ambulatory patient (%)	154 (80.6)	151 (80.3)
Use of propofol, no. (%)		
Modality of propofol administration, no. (%)	191 (100.0)	188 (100.0)
Target-controlled infusion	134 (70.2)	127 (67.6)
Bolus	57 (29.8)	61 (32.4)
Mean dose of propofol, μg kg^{-1} min^{-1} (SD)	245 (161) (Missing values: n=6)	259 (151) (Missing values: n=5)
Use of ketamine, no. (%)	2 (1.0)	2 (1.1)
Use of midazolam, no. (%)	40 (20.9)	41 (21.8)
Mean total dose of midazolam, mg (SD)	0.25 (0.50)	0.25 (0.51)
Use of opioids, no. (%)	107 (56.0)	106 (56.4)
Use of remifentanil, no. (%)	7 (3.7)	5 (2.7)
Mean total dose of remifentanil, μg (SD)	3.8 (28.3)	2.3 (12.5)
Use of alfentanil, no. (%)	1 (0.5)	4 (2.1)
Mean total dose of alfentanil, μg (SD)	5.2 (72.4)	14.9 (105.9)
Use of sufentanil (%)	96 (50.3)	89 (47.3)
Dose of sufentanil during the procedure (%)		
2.5 μg	1 (0.5)	1 (0.5)
5 μg	52 (27.2)	53 (28.2)
7.5 μg	11 (5.8)	10 (5.3)
10 μg	31 (16.2)	25 (13.3)
15 μg	1 (0.5)	1 (0.5)
In standard oxygen group, modality of oxygenation after pre-oxygenation, no. (%)		
Nasal cannula	–	90 (47.9)
Face mask	–	93 (49.5)
Nasopharyngeal tube	–	4 (2.1)

* BMI is the weight in kilograms divided by the square of the height in meters.

† Mallampati score[31] is a graded four-level pictorial scale created to predict difficult intubation before general anaesthesia; it is routinely used for this purpose in operating rooms worldwide. Class I is a complete visualisation of the soft palate, Class II is a complete visualisation of the uvula, Class III is a visualisation of only the base of the uvula, and Class IV is the absence of visualisation of soft palate.

‡ ASA physical status[10] is a classification to assess and communicate a patient's pre-anaesthesia medical co-morbidities. ASA 1 is a normal healthy patient, ASA 2 is a patient with mild systemic disease, ASA 3 is a patient with severe systemic disease, ASA 4 is a patient with severe systemic disease that is a constant threat to life and ASA 5 is a moribund patient who is not expected to survive without the operation.

¶ See Supplementary file 2 for details. IQR, inter-quartile range; SD, standard deviation.

group and 33.5% (63/188) in the standard oxygen groups (ARD: −23.4% [95% CI, −28.9 to −16.7]; P<0.0001; NNT: 5 [95% CI, 4 to 6]) (Table 2). We found no significant two- or three-way interactions between the intervention, use of opioids, and centres (Supplementary eTable 4), and no significant interactions between the type of endoscopy and the intervention (upper endoscopy alone or combined × intervention: P=0.98; combined endoscopy × intervention: P=0.49).

Secondary outcomes

The median difference in lowest oxygen saturation between the high-flow nasal oxygen and standard oxygen groups was 2% (95% CI, 1–3) (Supplementary eFig 3, Table 3). The high-flow nasal oxygen group showed significantly less frequent SpO_2 ≤90% and ≤85% than the standard oxygen group (Table 2).

As compared with the standard oxygen group, the high-flow nasal oxygen group showed significantly less frequent need for manoeuvres to maintain free upper airways (11.1% *vs*

Table 2 Outcomes in terms of peripheral desaturation events.

	High-flow nasal oxygen (N= 191)	Standard oxygen (N= 188)	Adjusted ARD, % (95% CI)*	P-value†	NNT (95% CI)‡
Primary outcome measure					
Lowest SpO_2 ≤92% (%)	18 (9.4)	63 (33.5)	−23.4 (−28.9 to −16.7)	<0.001	5 (4–6)
Secondary outcome measures					
Lowest SpO_2 ≤90% (%)	11 (5.8)	43 (22.9)	−18.6 (−25.9 to −10.9)	<0.001	6 (4–10)
Lowest SpO_2 ≤85% (%)	6 (3.1)	18 (9.6)	−7.6 (−16.9 to −1.6)	0.013	14 (6–61)
Prolonged hypoxaemia defined by SpO_2 ≤92% at least for 1 min (%)	14 (7.3)	28 (14.9)	−7.9 (−14.8 to −1.5)	0.017	13 (7–65)
Decrease of SpO_2 ≥5% (%)	25 (13.1)	64 (34.0)	−20.3 (−26.81 to −12.6)	<0.001	5 (4–8)

ARD, absolute risk difference; NNT, number needed to treat; SpO_2, oxygen saturation measured by pulse oximetry; 95% CI, 95% confidence interval.
* Adjusted ARDs and their 95% CIs were obtained by mixed-effect logistic regression and bootstrapping.
† P-values are those obtained through mixed-effect logistic regression, unless otherwise stated.
‡ NNT is given only when their 95% CI lower and upper boundaries are both positive or negative (to avoid mixing numbers needed to treat and numbers needed to harm, which would be confusing).

Table 3 Continuous outcomes.

	High-flow nasal oxygen (N=191)	Standard oxygen (N=188)	MD (95% CI)*	P value†
Median SpO_2 at anaesthesia induction time (IQR), %	100 (98–100)	99 (98–100)	1 (−1 to 1.0)	0.81
Median SpO_2 1 min after anaesthesia induction (IQR), %	99 (99–100)	99 (98–100)	1 (−0.5 to 1.0)	0.07
Duration of the endoscopy, min, [IQR]	21 [15 to 30]	19 [13 to 30]‡	2 (−1 to 4)	0.27
Duration of sedation, min, [IQR]	30 [20 to 40]	28 [20 to 39]	3 (−3 to 5)	0.77
Time from anaesthesia induction until hypoxaemia (SpO_2 ≤92%), min, [IQR]	9 [5 to 15] (n=18)	6 [3 to 13] (n=63)	–	0.18
Median time at which SpO_2 reached its lowest value in patients experiencing hypoxaemia (SpO_2 ≤92%), min, [IQR]	12 [6 to 16] (n=18)	7 [4 to 14] (n=63)	–	0.09

* MD and 95% CI were obtained by bootstrapping (2000 bootstrapped samples).
† Comparison performed using a Mann–Whitney U-test adjusted for the stratification variables.
‡ One missing value in the standard oxygen therapy group for the duration of endoscopy. IQR, inter-quartile range; MD, mean difference; SpO_2, oxygen saturation measured by pulse oximetry; 95% CI, 95% confidence interval.

Table 4 Significant and adverse events.

	High-flow nasal oxygen (N=191)	Standard oxygen (N=188)	ARD* % (95% CI)	P-value†	NNT (95% CI)‡
Need for manoeuvres to maintain free upper airways (%)	21 (11.1)	61 (32.4)	−20.9 (−27.1 to −13.7)	<0.001	5 (4–8)
Increase of oxygen during procedure (%)	15 (7.9)	44 (23.4)	−16.3 (−23.9 to −8.5)	<0.001	7 (5–12)
Interruption of the endoscopy (%)	1 (0.5)	5 (2.7)	−2.2 (−4.9 to 0.4)¶	0.12§	–
Adverse events					
Apnoea or bradypnoea (%)	18 (9.5)	22 (11.9)	−2.4 (−8.5 to 3.3)	0.41	–
Bradycardia (%)	8 (4.2)	11(5.9)	−1.8 (−7.4 to 2.8)	0.45	–
Intubation (%)	1(0.5)	2(1.1)	−0.3 (−1.6 to 1.1)¶	0.62§	–
Noninvasive ventilation (%)	1 (0.5)	3 (1.6)	−0.5 (−2.0 to 0.9)¶	0.37§	–
Use of vasopressor (%)	6 (3.1)	11 (5.9)	−2.9 (−10.0 to 1.7)	0.21	–

* ARDs and their 95% CI were adjusted differences obtained by mixed-effect logistic regression and bootstrapping, unless otherwise stated.
† P-values are those obtained by mixed-effect logistic regression, unless otherwise stated.
‡ NNT is given only when their 95% CI lower and upper boundaries are both positive or negative (to avoid mixing numbers needed to treat and numbers needed to harm, which would be confusing).
¶ Because of the small numbers of events in each group, bootstrapping the mixed-effect regression model to obtain adjusted ARDs and their CIs was not feasible. Simple 95% Wald CIs are given.
§ Comparison by Fisher's exact test. ARD, absolute risk difference; NNT, number needed to treat; SpO_2, oxygen saturation measured by pulse oximetry; 95% CI, 95% confidence interval.

Patient subgroups	Event rate in HFNO group	Event rate in Standard Oxygen group	ARD (95% CI)	*P*-value
Occurrence of SpO_2 ≤ 92%				
Body mass index < 30 kg m^{-2}	10/136 (7.4%)	38/139 (27.3%)	–20.4 (–28.0 ; –11.6)	<.001
Body mass index ≥ 30 kg m^{-2}	8/55 (14.5%)	25/59 (42.4%)	–30.1 (–37.4 ; –19.3)	<.001
Patients with cardiac illness	13/95 (13.7%)	39/93 (41.9%)	–25.7 (–32.6 ; –16.4)	<.001
Patients with no cardiac illness	5/96 (5.2%)	24/95 (25.3%)	–21.9 (–30.3 ; –11.4)	<.001
Patients with respiratory illness	6/29 (20.7%)	9/21 (42.9%)	–23.8 (–37.6 ; –0.9)	.048
Patients with no respiratory illness	12/162 (7.4%)	54/167 (32.3%)	–24.9 (–30.9 ; –17.8)	<.001
Upper endoscopy (combined or alone)	2/91 (2.2%)	37/96 (38.5%)	–33.1 (–37.3 ; –27.2)	<.001
Lower endoscopy	16/100 (16.0%)	26/92 (28.3%)	–12.4 (–23.2 ; –0.7)	.035
Occurrence of SpO_2 ≤ 90%				
Body mass index < 30 kg m^{-2}	4/136 (2.9%)	24/139 (17.3%)	–18.2 (–27.7 ; –7.8)	<.001
Body mass index ≥ 30 kg m^{-2}	7/55 (12.7%)	19/59 (32.2%)	–25.3 (–34.2 ; –12.5)	.002
Patients with cardiac illness	8/95 (8.4%)	30/93 (32.3%)	–23.4 (–31.0 ; –13.4)	<.001
Patients with no cardiac illness	3/96 (3.1%)	13/95 (13.7%)	–13.4 (–28.1 ; –3.3)	<.001
Patients with respiratory illness	4/29 (13.8%)	7/21 (33.3%)	–20.5 (–35.7 ; 0.5)	.067
Patients with no respiratory illness	7/162 (4.3%)	36/167 (21.6%)	–19.9 (–27.8 ; –12.1)	<.001
Upper endoscopy (combined or alone)	0/91 (0.0%)	24/96 (25.0%)	–29.6 (–33.4 ; –24.2)	<.001
Lower endoscopy	11/100 (11.0%)	19/92 (20.7%)	–10.1 (–20.3 ; 0.1)	.059
Occurrence of SpO_2 ≤ 85%				
Body mass index < 30 kg m^{-2}	2/136 (1.5%)	8/139 (5.8%)	–5.2 (–15.1 ; 0.0)	.084
Body mass index ≥ 30 kg m^{-2}	4/55 (7.3%)	10/59 (16.9%)	–14.2 (–27.6 ; –0.7)	.040
Patients with cardiac illness	5/95 (5.3%)	13/93 (14.0%)	–9.1 (–19.5 ; –0.6)	.049
Patients with no cardiac illness	1/96 (1.0%)	5/95 (5.3%)	–4.1(–9.7 ; 1.4)	.109
Patients with respiratory illness	3/29 (10.3%)	3/21 (14.3%)	–4.5 (–24.0 ; 14.0)	.529
Patients with no respiratory illness	3/162 (1.9%)	15/167 (9.0%)	–9.6 (–19.7 ; –2.9)	.009
Upper endoscopy (combined or alone)	0/91 (0.0%)	10/96 (10.4%)	–11.4 (–18.6 ; –4.2)	.011
Lower endoscopy	6/100 (6.0%)	8/92 (8.7%)	–3.1 (–10.8 ; 4.1)	.397

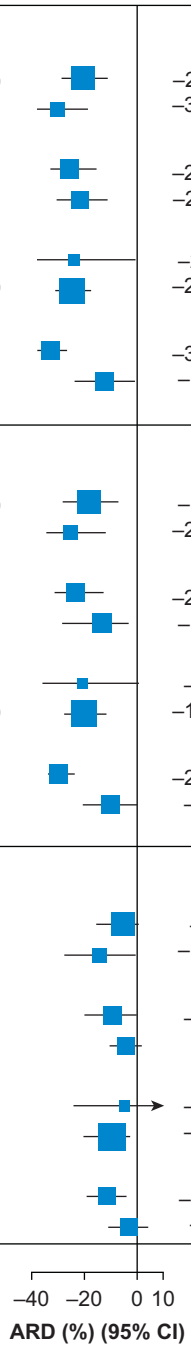

Fig 2. Forest plot showing absolute risk difference in the occurrence of desaturation by patient subgroups. ARD, absolute risk difference; CI, confidence interval; HFNO, high-flow nasal oxygen; SpO_2, arterial oxygen saturation measured by pulse oximetry. [a]Unless otherwise indicated, *P*-values were obtained by mixed effect logistic regression with centres handled as random intercept variables and the intervention and the use of opioids as fixed-effect variables, and 95% CIs obtained by repeating the logistic analysis on 2000 bootstrapped samples of the study population. [b]Because of a too-small number of events in these patient categories, bootstrapping and logistic regression were not feasible. *P*-values in these cases were obtained by Fisher exact test and 95% CIs according to Agresti and Caffo.[32]

32.4%; ARD: −20.9% [95% CI, −27.1 to −13.7], $P<0.0001$) and for increasing oxygen flow (7.9% *vs* 23.4%, ARD: −16.3% [−23.9 to −8.5], $P<0.0001$) (Table 4). The groups did not differ in the use of vasopressor, incidence of apnoea/bradypnoea or bradycardia, interruption of endoscopy, use of noninvasive ventilation or tracheal intubation (Table 4). The duration of endoscopy and sedation did not differ (Table 3). The groups did not differ in outcome measures assessed in the recovery room (Supplementary eTable 5).

Exploratory analyses

The beneficial effect of the intervention on the incidence of hypoxaemia was consistent across all patient subgroups defined by BMI, existence of cardiac comorbidity, existence of respiratory comorbidity, and type of endoscopy (Fig 2). When dividing the study population by use of opioids and risk of alveolar hypoventilation (see Supplementary file 2 for definition), the reduction in incidence of SpO_2 ≤92% was consistent across subgroups (Supplementary eFig 4) and for subgroups according to the type and doses of anaesthetic drugs used (Supplementary eFig 1).

Discussion

In this multicentre RCT, high-flow nasal oxygen decreased the rate of hypoxaemia, defined as SpO_2 ≤92%, as compared with standard oxygen among patients at risk of hypoxaemia and undergoing gastrointestinal endoscopy under spontaneous breathing and deep sedation. These findings suggest that for every five patients, providing high-flow nasal oxygen would prevent hypoxaemia in one patient.

High-flow nasal oxygen can deliver a high and stable FiO_2, which can be increased to 1.00, and a high gas flow (from 30 to 70 L min^{-1}) that maintains a slight PEEP and exerts a dead-space washout effect.[33–35] Because of these characteristics, high-flow nasal oxygen may be a simple and effective tool to secure gastrointestinal endoscopy.

In our study, duration of endoscopy was about 20 min, and almost 40% of patients had invasive procedures, which suggests that procedures were complex. A recent RCT involving patients with class ASA physical status 1–2, whose gastroscopy lasted 5 min on average, also showed that high-flow nasal oxygen could prevent hypoxaemia.[18] However, the rate of hypoxaemia in an ASA physical status 1–2 patient is relatively low, and targeting at-risk patients seems more relevant to optimise the cost/benefit ratio of high-flow nasal oxygen.

In this study, after pre-oxygenation, an approximately similar FiO_2 was then applied to both groups during the procedure by using a conversion table.[24,36] In contrast, previous studies[18,19,21,37] comparing high-flow nasal oxygen to standard oxygen set the FiO_2 at 1.00 and gas flow 20–60 L min^{-1} for high-flow nasal oxygen but oxygen flow 2–5 L min^{-1} for the standard oxygen group. Setting FiO_2 at 1.00 with high gas flow through a large-bore nasal cannula likely maintains a high effective FiO_2.[38] In contrast, administering oxygen at a flow <6 L min^{-1} via a conventional nasal cannula[24] or rebreathing face mask,[38] even in patients with low to moderate inspiratory efforts, may result in effective FiO_2 far below 0.50. Hence, the design of those previous studies,[18,19,21,37] by delivering a greater amount of oxygen to the intervention arm, likely disadvantaged the control arm. By using an approximately similar FiO_2 in both groups at the beginning of the procedure, the present study showed that high-flow nasal oxygen prevented hypoxaemia. This finding suggests that the beneficial effect of high-flow nasal oxygen was predominantly attributable to its PEEP, dead-space washout effects, or both.

This study has several limitations. First, the nature of the intervention did not allow for blinding. However, to minimise information bias, the SpO_2 records were read and scored by an assessor blinded to treatment allocation before having access to the paper case report form. Second, the anaesthesia regimen was not standardised. However, the treatment allocation was stratified on the planned use of opioids known to exert a marked respiratory depression effect, and a *post-hoc* analysis did not suggest that the type and doses of anaesthetic drugs had influenced the primary outcome occurrence (Supplementary eFig 1). Third, pre-oxygenation was applied with different FiO_2 between groups. However, preprocedural oxygenation in spontaneously breathing patients is likely less important than during apnoeic periods owing to neuromuscular blockage before intubation. To be pragmatic, we chose the most effective pre-oxygenation that each method allowed, which resulted in very similar SpO_2 between groups at the time anaesthesia induction or 1 min later (Table 2). Fourth, we intended to apply similar FiO_2 in both groups during the endoscopy by using published tables to convert oxygen flow in the standard oxygen group but did not measure FiO_2. However, we believe this procedure resulted in a rather similar FiO_2, on average, between groups, as also speculated by Riccio and colleagues[21] in their recent RCT. Fifth, as in most studies comparing oxygenation devices or methods, the principal outcomes examined focused on arterial oxygen saturation. This focus obviously lacks directness for assessing patient-centred outcomes. However, studying more direct and stronger outcomes such as myocardial infarction, stroke, or death would have required recruiting tens of thousands of patients. Sixth, we could not assess the adequacy of ventilation by measuring end-tidal carbon dioxide because reliable wave form capnography is not yet available for use during high-flow nasal oxygen administration. A recent RCT[20] did not show more frequent hypercarbia (as assessed by transcutaneous carbon dioxide partial pressure measurements) in the high-flow oxygen than control group but was underpowered to conclude that high-flow oxygen was safe in patients with the highest risk of hypercarbia (e.g. chronic obstructive pulmonary disease or morbid obesity). Therefore, additional studies are necessary to assess the risk of hypercarbia that high-flow nasal oxygen could bring about in at-risk populations.

The cost of high-flow nasal oxygen can be a barrier to its wide use during the millions of gastrointestinal endoscopies performed each year worldwide. The technique could be proposed first and foremost to obese patients and those with cardiac comorbidities or who require upper endoscopy (oesophagogastroscopy) because of their higher basal risk of hypoxaemia than the general population[3,6,8,9] and as observed in our study population (Fig 2). Logically, patients with respiratory comorbidities should also be among the high-priority patients. However, because of too few patients in this category in our study, the between-group comparison of the event

rates was clearly underpowered and did not allow for drawing conclusion.

Conclusions

In patients with moderate to high risk of hypoxaemia undergoing gastrointestinal endoscopy under deep sedation, high-flow nasal oxygen during the procedure decreased the rate of desaturation as compared with standard oxygen therapy.

Authors' contributions

Full access to all of the data in the study: MAN, TB
Responsibility for the integrity of the data and the accuracy of the data analysis: MAN, TB
Contributed equally for the data collection and drafting of the manuscript: AE, LF
Concept and design: MAN, TB, AE, LF
All authors agreed to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.03.020.

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