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Original Article

Effect of high-flow vs. low-flow nasal plus mouthguard oxygen therapy on hypoxaemia during sedation: a multicentre randomised controlled trial

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Summary

Whether high-flow vs. low-flow nasal oxygen reduces hypoxaemia for sedation during endoscopic retrograde cholangiopancreatography is currently unknown. In this multicentre trial, 132 patients ASA physical status 3 or higher, BMI > 30 kg.m^{-2} or with known or suspected obstructive sleep apnoea were randomly allocated to high-flow nasal oxygen up to 60 l.min^{-1} at 100% F_IO_2 or low-flow nasal oxygen at 4 l.min^{-1}. The low-flow nasal oxygen group also received oxygen at 4 l.min^{-1} through an oxygenating mouthguard, totalling 8 l.min^{-1}. Primary outcome was hypoxaemia, defined as S_pO_2 < 90% regardless of duration. Hypoxaemia occurred in 7.7% (5/65) of patients with high-flow and 9.1% (6/66) with low-flow nasal oxygen (percentage point difference −1.4%, 95%CI −10.9 to 8.0; p = 0.77). Between the groups, there were no significant differences in frequency of hypoxaemic episodes; lowest S_pO_2; peak transcutaneous carbon dioxide; hypercarbia (transcutaneous carbon dioxide > 2.66 kPa from baseline); requirement of chin lift/jaw thrust; nasopharyngeal airway insertion; bag-mask ventilation; or tracheal intubation. Following adjustment for duration of the procedure, the primary outcome remained non-significant. In high-risk patients undergoing endoscopic retrograde cholangiopancreatography, oxygen therapy with high-flow nasal oxygen did not reduce the rate of hypoxaemia, hypercarbia or the need for airway interventions, compared with combined oral and nasal low-flow oxygen.

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is performed in the supine, prone or lateral position. Moderate to deep sedation is most frequently used, with general anaesthesia and tracheal intubation employed for selected patients [1]. Hypoxaemia may occur during propofol sedation for ERCP, with reported rates ranging from 15 to 21%, [2–5] with one study reporting a 60% incidence [6]. In these five studies, hypoxaemia was inconsistently defined and study populations were heterogeneous. Contributing factors to hypoxaemia may include decreased cardiopulmonary reserve; respiratory depression; duration of procedure; prone positioning; ASA physical status 3 or higher; BMI > 30 $kg.m^{-2}$; and known or suspected obstructive sleep apnoea (OSA) [2, 7-12]. Prolonged hypoxaemia is a known risk factor for periprocedural cardiac arrhythmia and myocardial ischaemia [13, 14]. In a large retrospective analysis of 73,000 gastrointestinal interventions, sedation-related hypoxaemia was associated with three periprocedural cardiac arrests across 5239 ERCP procedures [15]. Inadequate oxygenation/ventilation has been highlighted as a distinct damaging event during procedural sedation for gastro-intestinal procedures in closed claims analysis [16, 17]. Although analyses from closed medicolegal claims lack denominator data, they indicate poor patient outcomes can occur, including hypoxaemia leading to end-organ damage. The 2019 joint position statement by the British Society of Gastroenterology, Joint Advisory Group and Royal College of Anaesthetists on deep sedation and anaesthesia in complex gastro-intestinal endoscopy including ERCP, includes advanced age, obesity and comorbidity as risk-factors for cardiopulmonary complications [18].

Sedation for ERCP usually includes low-flow nasal oxygen cannula and/or a mouthguard with an oxygen delivery port. At nasal flow rates of 2–4 $l.min^{-1}$, assuming nasal breathing only, F_IO_2 may reach 0.3–0.4 [19]. However, F_IO_2 is minute volume dependent and, with the addition of mouth breathing, may be much less. High-flow nasal oxygen (HFNO) is a recent approach employed to improve oxygenation during procedural sedation [20, 21]. It can provide flows up to 70 $l.min^{-1}$, F_IO_2 of 100% and generate a flow-dependent positive airway pressure, and may improve oxygenation [22]. While it has been shown to be effective in reducing hypoxaemia in some procedural sedation settings such as simple [20] and advanced endoscopy [21] and post-lung transplant bronchoscopy with transbronchial lung biopsy, [23] similar benefits were not observed during colonoscopy in morbidly obese patients [24] and endobronchial ultrasound procedures [25]. There are few studies regarding the application of HFNO in high-risk patients undergoing advanced endoscopic procedures, and it is unclear whether it provides superior benefits as compared with low-flow nasal plus mouthguard oxygen.

The aim of this randomised multicentre trial was to assess the efficacy of oxygen therapy via HFNO compared with low-flow nasal plus mouthguard during ERCP in patients at risk of adverse respiratory events. We hypothesised that the application of HFNO would reduce hypoxaemia during ERCP in high-risk patients defined as ASA physical status 3 or higher, BMI > 30 $kg.m^{-2}$ or with known or suspected OSA.

Methods

The oxygen therapy in high-risk ERCP (OTHER) trial was conducted from 4 February 2019 until 28 September 2020 across three hospitals: the Queen Elizabeth Hospital and Royal Adelaide Hospital, South Australia and John Hunter Hospital, New South Wales. It was approved by the respective Ethics Committees. Inclusion criteria were adults aged > 18 y fulfilling one of the following: ASA physical status 3 or higher; BMI > 30 $kg.m^{-2}$; and known or suspected OSA based on STOP-BANG [26] score 3 or higher. Exclusion criteria were: known or suspected difficult airway; severe cardiorespiratory illness; emergency ERCP; those at risk of pulmonary aspiration; and those requiring general anaesthesia with tracheal intubation.

After obtaining written informed consent, participants were randomly allocated in a 1:1 ratio with the use of sealed envelopes to one of the study groups (HFNO or low-flow nasal plus mouthguard oxygen) in permuted blocks of ten with no stratification. The permuted block size was revealed after completion of the study. Participants and investigators could not be blinded to the allocation due to the obviously different appearance of the oxygen delivery devices.

Patients in the HFNO group received F_IO_2 1.0 using the Optiflow device (Fisher and Paykel, Auckland, New Zealand). Flow rate was commenced at 30 $l.min^{-1}$, then gradually increased, and was maintained at 50 $l.min^{-1}$. It could be increased up to 60 $l.min^{-1}$ if necessary or decreased to 30 $l.min^{-1}$ if high flows were poorly tolerated. Patients in the low-flow nasal plus mouthguard oxygen group received oxygen 4 $l.min^{-1}$ through standard nasal cannula plus 4 $l.min^{-1}$ via a mouthguard. In addition to routine monitoring, transcutaneous blood carbon dioxide was also used (Radiometer Inc, Brea, CA, USA). The sedation technique was standardised using target-

controlled infusion (TCI) of propofol and titrated doses of fentanyl (up to, but not limited to) 1.0 $\mu g.kg^{-1}$. A Marsh model propofol TCI was used, commencing at an initial target plasma concentration of 1.5–2.0 $\mu g.ml^{-1}$ and titrated between 1 and 4 $\mu g.ml^{-1}$ based on satisfactory plane of sedation and ventilation. The anaesthesia providers, by protocol, responded in a standard fashion to subclinical hypoxaemia and hypercarbia with interventions in both study groups. The positioning of the patients was at the discretion of the gastroenterologists.

Primary outcome was the proportion of patients who developed hypoxaemia, defined as $SpO_2 < 90\%$ regardless of duration. A hypoxaemic event was defined as a clearly recognisable desaturation that followed a logical decline (continuous pulsatile upward and downward deflection) from high SpO_2 readings with a precise plethysmographic waveform and rate synchronised with the ECG trace. Data were collected by the attending anaesthetists on a paper-based data extraction sheet during the procedure. Hypoxaemia was defined as a dichotomous event without quantifying the duration or number of episodes. This count (vs. duration) approach has been used by other researchers studying adverse events during procedural sedation [3, 4, 24, 25]. Secondary outcomes included: number of hypoxaemia events per patient; lowest recorded S_pO_2; peak transcutaneous carbon dioxide; proportion of patients who developed hypercarbia, defined as transcutaneous carbon dioxide > 2.66 kPa from baseline; requirement of minor airway manoeuvres such as chin lift/jaw thrust and nasopharyngeal airway insertion and major airway manoeuvres such as bag-mask ventilation and tracheal intubation; adverse effects of oxygen therapy such as dry mouth/nose/throat and abdominal bloating; and any cardiac arrhythmias. A five-point Likert scale of patient satisfaction with the oxygen supplementation approach (5 = very satisfied to 1 = very dissatisfied) was obtained on discharge.

A 21.4% incidence of hypoxaemia ($S_pO_2 < 90\%$ for 15 s) was noted in an Australian study on ERCP with propofol sedation with low-flow nasal oxygen [5]. We calculated that, with a power of 80% and an α error of 0.05, a sample size of 132 patients would be required (66 in each group) to detect a 16% absolute difference and 75% relative reduction in hypoxaemia rates between the groups. Data were analysed using STATA 16.1 software (StataCorp LP, College Station, TX, USA) using an intention-to-treat approach. Shapiro–Wilk test and Jarque–Bera tests were conducted to check on normality of data. All categorical data were analysed using Pearson's test and continuous variables were analysed using Student's t-test. As patients who were sedated for different time periods would have had different risk intervals/probabilities for hypoxaemia, the primary outcome was further analysed using a linear regression model adjusting for duration of the procedure. A Bonferroni correction was applied to adjust for multiple comparisons for each of the 15 outcome variables (0.05/15); and hence a p value < 0.003 was considered significant.

Results

A total of 138 patients were assessed for eligibility, 132 participants were recruited and 66 were allocated to each group. Trial screening and recruitment details are shown in Fig 1. One participant required urgent tracheal intubation and ERCP was aborted, hence was not included in the analysis. One participant crossed over from the low-flow nasal plus mouthguard oxygen group to HFNO at the request of the participating investigator to improve airway management. As per our intention-to-treat approach, this participant was retained in the original allocated group for data analysis. Overall, minor protocol variation occurred in six participants where alfentanil was used instead of fentanyl, and it was converted to fentanyl equivalents (alfentanil:fentanyl; 5:1). The two groups of participants had similar baseline characteristics (Table 1).

Hypoxaemic events were observed in 7.7% (5/65) of participants in the HFNO group and 9.1% (6/66) in the low-flow nasal plus mouthguard oxygen group (difference −1.4%, 95%CI −10.9–8.0; p = 0.77) (Table 2). Following adjustment for duration of ERCP, the primary outcome remained non-significant between the groups (p = 0.77).

Among those who experienced hypoxaemic events across both groups, none had more than one episode. There were no significant differences in mean (SD) lowest S_pO_2 (HFNO vs. low-flow nasal plus mouthguard oxygen, 97.1 (4.2)% vs. 95.5 (6.1)%, difference 1.6% 95%CI −0.2–3.4%, p = 0.08); mean peak transcutaneous carbon dioxide (HFNO vs. low-flow nasal plus mouthguard oxygen, 7.4 ± 2.3 vs. 7.8 ± 2.9 kPa difference −0.39, 95%CI −1.4–0.6; p = 0.44); and proportion of hypercarbic episodes (HFNO vs. low-flow nasal plus mouthguard oxygen, 41.8% vs. 33.9%, difference 7.9%, 95%CI −10.1–26.2, p = 0.40) between the two groups (Table 2). Transcutaneous carbon dioxide data were missing in 21 participants, 11 in the HFNO group and 10 in the low-flow nasal plus mouthguard oxygen group due to equipment malfunction. Oxygen saturation < 80% was noted in three patients in the low-flow nasal plus mouthguard oxygen group and none in the HFNO group.

There were no significant between-group differences for the requirement of minor or major airway interventions,

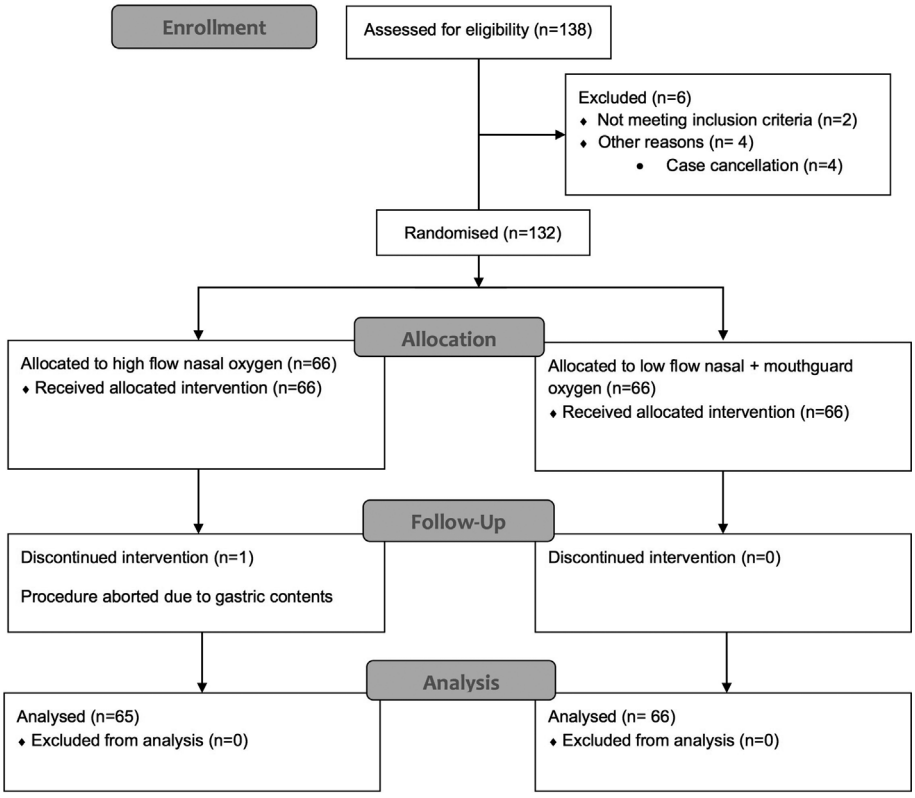

Figure 1 Study flow diagram showing patient recruitment.

Table 1 Baseline characteristics and periprocedural data. Values are mean (SD) or number.

	HFNO group n = 65	**LFN+MG group n = 66**
Age; y	69.1 (17.7)	65.5 (18.9)
Sex; male	28	27
BMI; $kg.m^{-2}$	30.0 (7.1)	28.2 (7.1)
Inclusion criteria		
BMI > 30 $kg.m^{-2}$ alone	29	23
Mean BMI among BMI > 30 $kg.m^{-2}$	36.8 (4.4)	36.3 (4.3)
Known or suspected OSA alone	16	16
OSA and BMI > 30 $kg.m^{-2}$ combined	7	7
ASA 3 and above	52	55
ERCP position		
Prone	34	36
Lateral	32	30
Supine	0	0
Duration of anaesthesia; min	34.5 (19.9)	35.9 (15.9)
Total propofol dose; mg[a]	402 (216)	440 (232)
Total fentanyl dose; μg	75.4 (34.3)	69.2 (36.1)

HFNO, high-flow nasal oxygen; LFN+MG, low-flow nasal + mouthguard oxygen; OSA, obstructive sleep apnoea; ERCP, endoscopic retrograde cholangiopancreatography.
[a]Data unavailable for four patients.

Table 2 Study outcome parameters: comparison between high-flow nasal oxygen (HFNO) and low-flow nasal + mouthguard oxygen (LFN+MG) groups. Values are number (proportion), mean (SD) or median (IQR [range]).

	HFNO n = 65	LFN+MG n = 66	Percentage point difference (95%CI)	p value
Primary outcome				
Hypoxaemic episode (S_pO_2 < 90%)	5 (7.7%)	6 (9.1%)	-1.4% (−10.9–8%)	0.77
Secondary outcomes				
Lowest recorded SpO_2	97.1 (4.2)	95.5 (6.1)	1.6 (−0.2–3.4)	0.08
Minor airway interventions				
Chin lift/jaw thrust	15 (21.5%)	18 (27.3%)	-5.7% (−20.3–10.2%)	0.45
Nasopharyngeal airway	0	0	-	-
Major airway interventions				
Bag-mask ventilation	0 (0%)	1 (1.5%)	-1.5% (−1.4–4.5%)	0.32
Transcutaneous CO_2[a]				
Baseline; kPa	4.7 (0.8)	5.0 (0.9)	-0.27 (−0.6–0.1)	0.10
Peak; kPa	7.4 (2.3)	7.8 (2.9)	-0.39 (−1.4–0.6)	0.44
Hypercarbic episode[b]	23 (42%)	19 (34%)	7.9% (−10.1–26.2%)	0.40
Adverse effects of O_2 therapy				
Dry mouth	32 (49%)	33 (50%)	-0.8% (−17.9–16.4%)	0.93
Dry nose	21 (32%)	23 (35%)	-2.5% (−18.7–13.6%)	0.76
Dry throat	21 (32%)	24 (36%)	4.1% (−20.3–12.2%)	0.63
Abdominal bloating	6 (9%)	9 (14%)	-4.4% (−15.3–6.5%)	0.43
Arrhythmias	10 (15%)	7 (11%)	4.8% (−6.8–16.3%)	0.42
Patient satisfaction[c]	5 (5–5 [3–5])	5 (5–5 [3–5])	-	-

[a]Values missing in 11 patients in the HFNO and 10 in the LFN+MG group.
[b]Defined as transcutaneous carbon dioxide increase of 2.66 kPa from baseline.
[c]5 = very satisfied to 1 = very dissatisfied.

occurrence of early adverse effects of oxygen therapy (e.g. dry mouth) and cardiac arrhythmias (Table 2). Participants were highly satisfied in both groups, with a median satisfaction score of 5 (5–5 [3–5]). Secondary outcomes were non-significant between groups when adjusted for age, sex, BMI, OSA, ASA physical status and positioning in multivariable analysis. Cardiac arrhythmias were noted in 12% (17/131) of participants, nine due to pre-existing arrhythmias (e.g. atrial fibrillation). Rapid atrial fibrillation responding to esmolol and magnesium occurred in two participants, and others were benign (e.g. transient ventricular ectopy). No serious complications such as regurgitation, aspiration of gastric contents or transfer to a high level of care occurred in either group.

Discussion

In this randomised multicentre trial, HFNO compared with low-flow nasal plus mouthguard oxygen did not reduce the incidence of hypoxaemia in high-risk patients undergoing ERCP under deep propofol sedation. There were no significant differences in hypercarbic episodes, peak transcutaneous carbon dioxide, and requirements for minor or major airway interventions.

Three recent randomised controlled trials found HFNO reduced the number of hypoxaemic episodes during endoscopy. The study by Lin et al. compared HFNO up to 60 $l.min^{-1}$ at 100% F_IO_2 with low-flow nasal oxygen at 2 $l.min^{-1}$ in 1994 patients and reported a significant reduction in hypoxaemia (SpO_2 < 90% for < 60 s) in the HFNO group (0% vs. 8.4%, p < 0.001) [20]. The study participants were of low risk (ASA physical status 1–2, mean BMI 22 $kg.m^{-2}$) with a mean endoscopy procedural time of 5 min [20]. The second study enrolled 260 patients undergoing advanced endoscopic procedure including ERCPs [21]. It compared HFNO at 20 $l.min^{-1}$ with low-flow nasal oxygen at 6 $l.min^{-1}$, and found a significant reduction in hypoxaemia in the HFNO group (21.2% vs. 33.1%, p = 0.03). The sedation protocol was left to the discretion of the practitioners and included propofol, fentanyl and midazolam [21]. Although our study cohort and the nature of the procedure were similar to the above-described study, we could not reproduce similar benefits of HFNO as our

observed rates of hypoxaemia were very low. This may be due to our addition of mouthguard oxygen insufflation in addition to low-flow nasal oxygen. Finally, the study by Kim et al. compared low-flow nasal oxygen at 5 $l.min^{-1}$ with HFNO up to 50 $l.min^{-1}$ at 100% F_IO_2 during ERCP and reported a higher mean SpO_2 and fewer episodes of SpO_2 < 90% in the HFNO group [27]. Compared with our study population, the participants were at low risk, with a mean BMI of 22 $kg.m^{-2}$, with only 2/72 patients diagnosed with OSA. The sedation approach varied from our protocol, with their mean (SD) duration of the procedure being 16.4 (7.8) min vs. 35.2 (17.9) min in our study. These studies, along with our own, would indicate there are a multitude of variables that influence hypoxaemia occurring that may not just be due to flow of nasal oxygen.

The relatively low overall rate of hypoxaemia (8.4%) in our study compared with other studies may be due to several reasons including our TCI propofol regimen, the addition of oxygen via mouthguard in addition to low-flow nasal oxygen and titrated opioid administration. Indeed, there is evidence in favour of using TCI propofol sedation to reduce hypoxaemic episodes during endoscopy [28, 29]. Thus far, many studies describing the rates of hypoxaemia during ERCP have employed an intermittent propofol bolus technique. It has been recognised that patients are much more likely to breathe through their mouth when sedated [30]. Besides maintaining airway patency, mouthguards may help deliver oxygen within the oral cavity [31]. Some researchers argue in favour of supplementing oxygen via both oral and nasal routes for oesophagogastroduodenoscopy procedures [32]. It is worth noting that, unlike our present study, none of the above studies neither encourage or discourage the use of HFNO utilised an extra oxygen delivery strategy in the control group [20, 21, 24, 25].

Although increasing F_IO_2 via HFNO can reduce hypoxaemia compared with low-flow nasal oxygen combined with room air mouth breathing, it is unlikely to improve hypoxaemia developing from pharmacologically induced hypoventilation or shunt [25, 33, 34]. In our study, a 38% incidence of hypercarbia was observed across both interventions. A recent study, using a similar definition of hypercarbia, reported a 43% incidence of hypercarbia during gastrointestinal interventions with propofol sedation [21]. Of the patients who experienced hypoxaemia in our study, only one of the five in the HFNO and two of six in the low-flow nasal plus mouthguard oxygen group also developed hypercarbia. This would indicate that hypoxaemia occurred as a distinct phenomenon from hypercarbia. As the patient's mouth is open during endoscopy procedures, the positive airway pressure generated by HFNO therapy may only reach up to 1.7 cmH_2O with a flow rate of 50 $l.min^{-1}$ as opposed to 5.6 cmH_2O with a closed mouth [35]. This limitation should be acknowledged during any procedural sedation utilising HFNO when a patient's mouth is open.

A clinically meaningful difference of hypoxaemic episodes is yet to be clearly defined in the context of procedural sedation. We presumed a 16% absolute reduction and a 75% relative reduction of hypoxaemia (from 21.4 to 5.4%) as a relevant effect size. Our study may be underpowered to detect a smaller, yet clinically significant, difference that may be important in high-risk patients Nonetheless, absolute reductions at magnitudes of 25% [24], 30% [23] and 33% [25], and relative reductions of 60% [23], 66% [21] and 68.7% [25] were deemed as significant effect size estimates by recent studies assessing HFNO in similar patient populations during advanced endoscopy [21]. While the hypoxaemia estimates in our low-flow nasal plus mouthguard oxygen group were based on existing data, [2–5] similar estimates were not available for the HFNO group, therefore we estimated a hypoxaemia rate of 5.4%. Although the observed hypoxaemia rate in our HFNO group (7.6%) was closer to our prediction, the incidence in the low-flow nasal plus mouthguard oxygen group was much lower than that in the cited literature (9.1% vs. 21.4%). Therefore, the study was under-powered, and the information used in the power analysis over-estimated the incidence of hypoxaemia in the low-flow nasal plus mouthguard oxygen group. Data used by us for power calculation were published 15 years ago [5]. Sedation techniques have changed considerably since that time. With hindsight, a pilot study would have been helpful in deriving a meaningful sample size before our study.

Our study may indicate the combination of low-flow nasal plus mouthguard oxygen may provide equivalent rates of hypoxaemia to that of HFNO alone. From a cost analysis perspective, the base unit of the HFNO device is priced at AU$4200 (£2335, €2648, US$3204). The device set-up cost for a 7-day utility period is AU$65 (£36, €41, US $49), and subsequent disposables for an individual case (cannula and the filter) cost AU$22.40 (£13, €14, US$17). The price of a standard low-flow nasal oxygen is AU$8 (£5, €5, US$6) and the mouthguard with an extension oxygen tubing is AU$2.75 (£1.50, €1.74, US$2.00). The exact cost implications of combined low-flow nasal plus mouthguard oxygen vs. HFNO will therefore vary depending on the indications chosen for use, the case mix in the treated population and the patterns of use. Regardless, the costs of unnecessary use of HFNO are likely to be substantial.

Our study has several strengths. There was adherence to a standardised anaesthetic technique, analysing transcutaneous carbon dioxide, assessing a high-risk cohort, incorporating specific adverse effects as patient-reported outcomes, and being pragmatic and multicentre. Our definition of hypoxaemia is not subject to clinician bias and has been used in similar contexts as a primary outcome [25]. There are also some limitations to our study. Intra-procedural hypoxaemia may not be as relevant compared with other patient-centred outcomes such as procedural interruptions, need for tracheal intubation or prolonged post-anaesthetic care unit stay. Yet, hypoxaemia is often a harbinger of other issues during routine procedural sedation with a shared airway, as well as prolonging procedures due to the need for airway interventions. It has been shown that, during propofol administration for colonoscopy, over 60% of airway interventions were triggered by a fall in SpO_2 < 95% [36]. Baseline oxygen saturation was not accounted for in the analysis, nor did we assess practitioners' satisfaction.

Our study demonstrated that, in high-risk patients undergoing ERCP within the context of target-controlled infusion based propofol administration, oxygen delivery using HFNO did not reduce the rate of hypoxaemia, hypercarbia and the need for major and minor airway interventions, compared with low-flow nasal plus mouthguard oxygen.

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Appendix . Contributors

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