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META-ANALYSIS

High-flow versus conventional nasal cannula oxygen supplementation therapy and risk of hypoxia in gastrointestinal endoscopies: a systematic review and meta-analysis

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ABSTRACT

Background: Gastrointestinal endoscopy (GIE) represents a mainstay diagnostic and therapeutic procedure in clinical practice. Hypoxemia constitutes a major complication for endoscopists. Emerging evidence supports the utilization of high-flow nasal cannula (HFNC) over conventional nasal cannula (CNC) for avoidance of hypoxemia. Our aim was to compare the hypoxemia risk in patients undergoing GIE with HFNC versus CNC oxygen supplementation recruited by randomized controlled trials (RCTs).
Methods: We searched in medical databases PubMed, EMBASE and Cochrane to identify RCTs investigating the abovementioned association. Enrolled studies were evaluated for risk of bias and inserted into a random effects model for meta-analysis; subgroup analyses and publication bias were also assessed.
Results: Out of 271 articles, five RCTs were eligible (patients n=2656, HFNC 1299 and CNC 1357). A statistically significant reduced relative risk (RR) of hypoxemia among HFNC patients was revealed (RR=0.18, CI95%: 0.05–0.61), whilst with high heterogeneity (I2:79.94%, p<0.01). Patients undergoing upper GIE with HFNC displayed a significantly lower hypoxemia risk (96%, p<0.001, I2:15.59%), even after exclusion of endoscopic retrograde cholangiopancreatography cases (RR:0.03, CI95%:0.01–0.21), albeit with higher heterogeneity (I2:41.82%).
Conclusion: Patients undergoing upper GIE with HFNC experience significantly less hypoxemia burden than CNC counterparts. Further research is warranted to target optimal safety during endoscopy.
Abbreviations: ASA, American Society of Anesthesiologists; ASGE, American Society for Gastrointestinal Endoscopy; BMI, Body Mass Index; CI, confidence interval; CNC, conventional nasal cannula; ERCP, endoscopic retrograde cholangiopancreatography; FiO_2, fraction of inspired O_2; GI, gastrointestinal; GIE, gastrointestinal endoscopies; HFNC, High-Flow nasal cannula; ICU, intensive care unit; PEEP, positive end-expiratory pressure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs, randomized control trials; RR, relative risk (or risk ratio)

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1. Introduction

Gastrointestinal endoscopy (GIE) constitutes a substantial diagnostic and therapeutic modality being implicated in a plethora of management algorithms for various conditions. Intravenous sedation in patients breathing spontaneously, primarily with the usage of short-acting agents, such as propofol or benzodiazepines/opioids, is common practice in both hospitalized and outpatients [1–3]. Moreover, it provides a plethora of advantages including, among others, patients' comfort and analgesia, thus improving the examination quality and the conditions for advanced interventions.

On the other hand, sedation is considered as a core safety parameter in terms of GIE and its significance is underlined by the respective American Society of Gastrointestinal Endoscopy (ASGE) guidelines [4]. In this regard, the adoption of measures ameliorating potential safety burdening factors is expected to improve the overall quality of endoscopic services [5,6]. Hypoxemia and hypercapnia represent two of the most common complications during GIE, with a prevalence of 10–60%, especially during advanced procedures such as endoscopic retrograde cholangiopancreatography (ERCP) [7], and are attributed to a multifactorial etiology; anesthesia-associated upper airway collapse,

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Supplemental data for this article can be accessed here.

apnea after direct respiratory center depression and bronchospasm comprise some of the most recognized hypoventilation mechanisms during sedation, in addition to mechanical lung compression through secondary pressure of the diaphragm due to air insufflation in the intestine as well as airway obstruction by the endoscope [1,3,8,9]. Moreover, advanced age combined with cardiopulmonary comorbidities, metabolic syndrome, or obstructive sleep apnea syndrome – classified by a high (more than III) American Society of Anesthesiologists (ASA) score – have been recognized as independent risk factors for respiratory insufficiency, arrhythmias and cardio-cerebral ischemia [1,2,7,10].

The standard oxygen delivery method for GIE procedures is the administration of oxygen via a conventional nasal cannula (CNC) [1]. The maximal CNC oxygen delivery is limited to 15 L/min and the inspired oxygen reaches the distal airways in an FiO_2 (fraction of inspired O_2) of 30%–40% [2]. According to the latest ASGE clinical practice guidelines for sedation and anesthesia in GIE [11], the routine utilization of pulse oximetry and supplementation of oxygen is acknowledged for GIE with at least moderate sedation. However, beyond airway support maneuvers, no further recommendation is currently given for situations when hypoxemia occursfor instance, the implementation of other devices capable of efficiently administering oxygen, other than CNC or insertion of nasal or oral tubes. High-Flow nasal cannula (HFNC) is a rather new technological approach with promising clinical applications, since it offers better oxygenation than conventional ventilation devices, and can be considered as an option in GIE [7]. The mainstay individual property is the administration of humidified oxygen in flows as high as 60–80 L/min, thus providing an adjustable titration of FiO_2 up to 100%. Furthermore, HFNC enables the application of positive end-expiratory pressure (PEEP) up to 7.5 cm H_2O, prevents the collapse of the upper airways and reduces the dead-space to decrease the work of ventilation by CO_2 washout [7,12,13]. HFNC has been repeatedly used in intensive care units (ICU), but its usage beyond these facilities is rather confined [14,15].

The implementation of HFNC during GIE in order to avoid hypoxemia and/or hypercapnia, particularly, by focusing on patients with high-risk profiles, seems an intriguing, albeit barely established approach. In this regard, we conducted for the first time a systematic review of the literature and a meta-analysis of existing randomized control trials (RCTs) utilizing HFNC versus CNC oxygenation in GIE. Aim of the study was primarily to compare the risk of oxygen desaturation between HFNC and CNC in patients undergoing GIE procedures and secondarily to investigate any required airway support maneuvers per patients' arm for hypoxemia reversal.

2. Methods

2.1. Protocol and eligibility criteria

This study has been carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (Suppl) [16]. The protocol of the current systematic review has been registered at PROSPERO [17], the international prospective register of systematic reviews (CRD42021268632, University of York, UK). Furthermore, the study is in accordance with the latest revision of Declaration of Helsinki principles [18]. An ethical approval or patient consent for a systematic review and meta-analysis is not necessitated.

Eligibility criteria were structured according to the validated PICO (population, intervention, control, and outcomes) principal format for systematic reviews [19]: The population included adult patients undergoing GIE; the intervention was administration of oxygen via HFNC; the control group were adult patients with similar demographic characteristics and CNC; and outcome was clearly defined as hypoxemia (O_2 desaturation <90%). Inclusion criteria of the meta-analysis incorporated 1) prospective RCTs 2) articles written in English language 3) comparison HFNC versus CNC in the setting of GIE 4) adult patients of any age, BMI, gender or race. Exclusion criteria were 1) article type other than an original RCT (for instance reviews, editorials, letters to the editor, case reports/series, preclinical studies) 2) missing substantial data that could not be retrieved after contacting the corresponding or first author 3) inappropriate control group, 4) studies with high risk of bias according to RoB2 tool.

2.2. Outcomes

As primary outcome was set the occurrence of hypoxemia (O_2 desaturation <90%) and as secondary outcome any required maneuvers (including but not limited to them for reversal of hypoxemia jaw thrust, chin lift, nasal airway insertion, discontinuation of sedation) for hypoxemia reversal.

2.3. Information sources and search strategy

Two authors (M.D. and F.S.) performed independently an in-depth electronic search of the PubMed/Medline, EMBASE (Ovid) and Cochrane databases from inception to 23rd of June 2021, by implementing the following Boolean search terms, modified according to the demands of each database; 'high-flow' OR 'high-flow nasal oxygen' OR 'HFNC' OR 'High-Flow nasal cannula' AND 'gastrointestinal endoscopy' OR 'gastroscopy' OR 'colonoscopy' OR 'esophagogastroduodenoscopy' OR 'ERCP' OR 'EUS' or 'endosonography' OR 'PEG' OR 'digestive endoscopy'. No publication date restriction was set, and only English articles were considered. Furthermore, after abstract screening, all remaining eligible articles and their reference lists were thoroughly reviewed for additional information. Moreover, additional relevant articles were detected from bibliography of the retrieved articles. Of note, results of gray literature, such as unpublished works, oral or poster presentations as well as abstracts were also considered in the screening process. If missing data were demanded, E-mail(s) were sent to the first and/or the corresponding authors. A database of the obtained articles was kept and managed with the Reference Manager Endnote 20 for Mac (Clarivate Analytics). The algorithm of article selection is illustrated as a flowchart according to the PRISMA 2020 statement, in Figure 1.

2.4. Data extraction

Data extraction was performed independently by two authors (M.D. and F.S.), whereas a third author (V.K.) controlled the two independent datasets for any discrepancies. Disagreements were resolved after consulting a senior investigator (A.T.) in order to reach a consensus. The extracted data included the following parameters; surname of first author along with year of publication, digital object identification and journal, country of origin, study design, type of GIE, type of sedation, type and upper limit of oxygen administration for both arms, sample size, mean age, gender, Body Mass Index (BMI), ASA status, exposure/control group and outcome data.

2.5. Assessment of risk of bias

Quality assessment was carried out independently by two authors (F.S. and V.K) using the Risk of Bias tool (RoB 2) for RCT [20]. The authors classified the included studies as low, moderate, or high/serious risk. Risk of bias visualization was performed in R Project for Statistical Computing (The R Foundation, Version 3.2.0, Vienna, Austria) using the Risk-of-bias VISualization (ROBVIS) package (Figure 2).

2.6. Statistical analysis and data synthesis

All meta-analyses were executed using STATA v.14.0 software for macOS (Stata Corp., College Station, TX, USA) using the mainstay commands ‘metan’, ‘metareg’, and ‘metabias’. The binary random effects model was applied, and risk ratio (known also as relative risk, RR) was selected

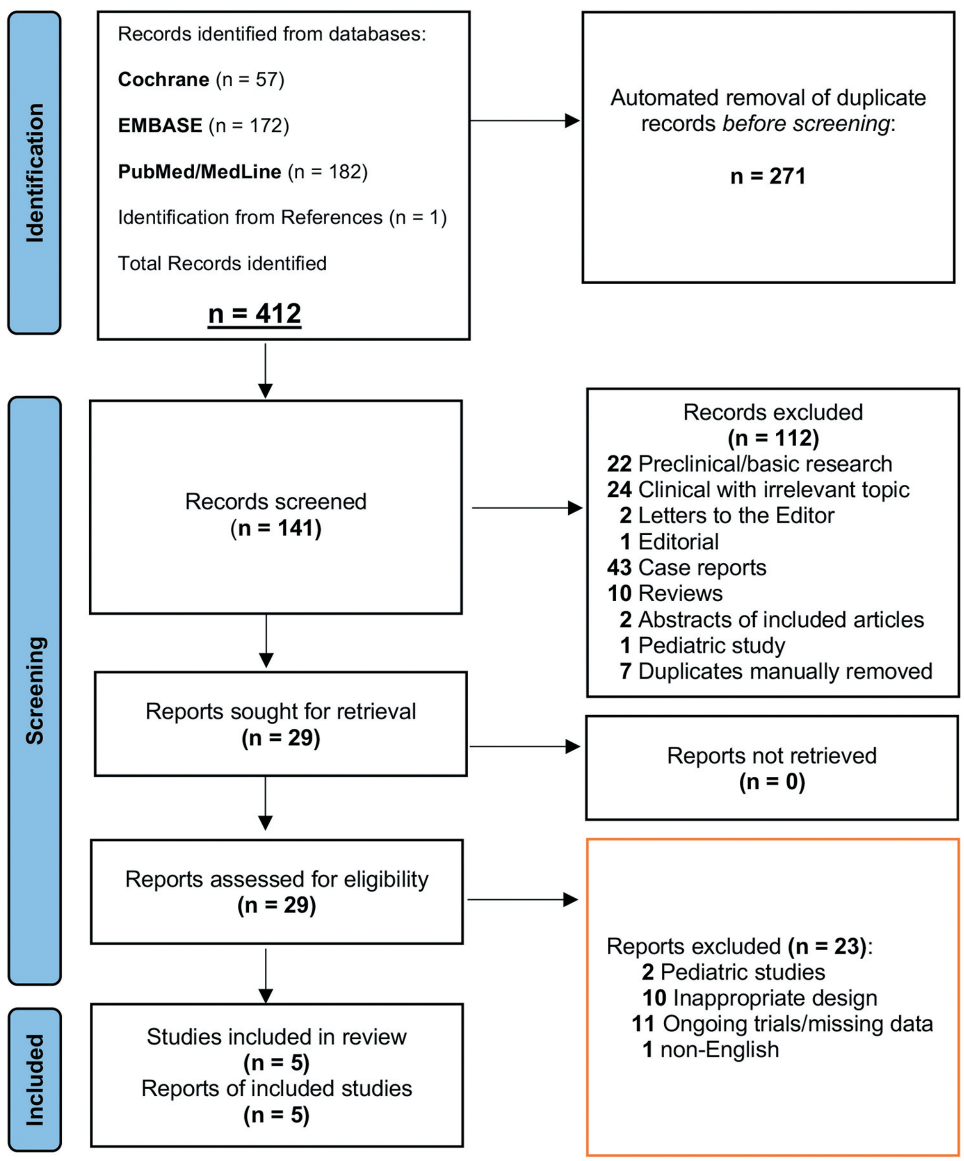

Figure 1. Flowchart based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines interpreting the selection process of the reviewed studies to insert in the meta-analysis.

as the measure of effect, to investigate the risk of hypoxemia in the HFNC group compared to the CNC controls. The potential heterogeneity was quantified based on the τ^2 and the χ^2 tests as well as the Higgins' I^2 test [21,22]. In addition, for the primary endpoint of hypoxemia in two groups, we further analyzed individual outcomes, where available, such as the necessity of bag-mas ventilation, increase of FiO_2, nasal airway devices use and intubation or procedure interruption, to declare potential related variables for further research.

Based on a pathophysiological rationale, a subgroup analysis was performed, by dividing endoscopic procedures to upper and lower GI. Moreover, to avoid any bias from ERCP-related results—as it is mainly performed with patients in prone position and is not purely considered as a common upper GI procedure—we performed a subgroup analysis excluding those cases. The statistical significance was set for $p < 0.05$ (two-tailed), and all results were expressed in funnel plots, including the RR estimation, with the respective 95% confidence intervals (CI). Finally, Begg and Egger tests were applied to our data to estimate any potential publication bias generated by small studies effect.

3. Results

3.1. Systematic review

3.1.1. Included studies' research and their main characteristics

As illustrated in Figure 1, our initial research resulted in 271 individual articles relative to the search terms. After excluding non-original and irrelevant articles, we evaluated 29 publications for eligibility. The application of adopted PICO criteria excluded most of them. One study fulfilled the methodological prerequisites but set the hypoxemia cutoff as low as $SpO_2 \leq 92\%$, thus predisposing to a potential selection bias, based on our eligibility criteria [2]. Finally, five RCTs were inserted in our analysis, with totally 2656 patients recruited: 1299 in HFNC and 1357 in CNC group (i.e. low-flow control) [1,13,23–25]. The characteristics of the included studies and patients, as well as the main results are depicted in Tables 1 and 2, respectively.

All included studies were elaborated during the last 3 years, thus reflecting the emerging need for safe and clear conclusions about the role of HFNC application in GIE. The main sedation agent was propofol, occasionally accompanied with adjuvant medications (mostly midazolam, fentanyl or lidocaine). All but one study, evaluated routine endoscopic procedures, gastroscopy or colonoscopy, with patients in left side-recovery position, without time-consuming or advanced manipulations. In this regard, data considering interventional techniques, such as endoscopic mucosal resection or submucosal dissection, peroral endoscopic myotomy, endoscopic ultrasound guided procedures, were not collected by enrolled studies. Nevertheless, Kim et al. evaluated the role of HFNC in ERCP, which is a demanding endoscopic intervention in the pancreato-biliary region, performed with patients in prone position.

3.2. Meta-analysis results

Inserting all patients from the eligible studies into our model, a statistically significant reduction of RR for hypoxemia was evident among HFNC cases compared to CNC controls (*RR* = 0.18, CI95%: 0.05–0.61), albeit with high heterogeneity (I^2:79.94%, $p < 0.01$). Figure 3(a) illustrates the respective results. Endoscopic modality was considered the most probable source of heterogeneity, and thus upper GIE and colonoscopy were submitted to subgroup analyses (Figure 3(b)). Considering upper GIE, patients under HFNC experienced 96% less risk of hypoxemia ($p < 0.001$) compared to CNC, with mild heterogeneity (I^2:15.59%). The statistical significance of an ameliorated *RR* in the HFNC group remained even after exclusion of ERCP cases (*RR*:0.03, CI95%: 0.01–0.21), though heterogeneity increased (I^2:41.82%), as displayed in Figure 4. On the other hand, patients submitted to colonoscopy with HFNC did not exhibit a statistically significant *RR* reduction compared to CNC cases ($p = 0.14$).

Further retrieved data were inserted to our analysis to investigate potential associations between HFNC and intraprocedural breathing control. More specifically, data on airway manipulations – jaw thrust, nasal airway tube insertion, intubation, and ventilation optimization via bag-mask or FiO_2 increase – did not provide a significant RR reduction in the HFNC subgroup, whilst the overall risk of endoscopy interruption was lower, when compared to the low flow group (*RR*:0.12, CI95%: 0.02–0.64, I^2:0%) (Suppl).

Finally, the risk of publication bias was assessed by Egger and Begg's test, thus resulting in a non-significant *p*-value for the null hypothesis considering the small studies effect ($p = 0.33$).

4. Discussion

Within this systematic review and meta-analysis, we demonstrate, that patients undergoing upper GIE with parallel administration of supplementary oxygen via HFNC experienced significantly less hypoxemia events than their CNC counterparts (96% less risk, $p < 0.001$).

To our personal view, besides the low number of included studies, the main weakness of our study is heterogeneity by reasons that we cannot control for. Riccio et al. [24] demonstrates complication rates during sedation of sedation with 45.2% complications with CNC and 39.3% with HFNC. On the other end Lin et al [23]. demonstrated significantly fewer.

In line with our results are additional studies, which were not included in the current meta-analysis due to their retrospective design character; Cha et al. [10] for instance, observed an improvement of oxygen saturation for the HFNC arm in patients undergoing ERCP. Similarly, Schumann et al. [26] concluded that patients undergoing ERCP or endosonography under HFNC required general anesthesia and enhanced oxygenation less frequently compared with CNC controls. Lee et al. [27] deduced positive impressions in a case-series, where the desaturation episodes were lower combined with an optimal patient satisfaction. Comparable results have been reported previously in the literature involving ICU patients on HFNC for medical conditions other than gastrointestinal

Table 1. Basic patient – study characteristics.

Study	Journal	Country	Design	GI Modality	Sedation	Patients (n)	Female (n)	Male (n)	Age (years)	HFNC (n)	CNC (n)	HFNC L/min, FiO2 (%)	doi
Kim et al 2021	J Can Anesth	Korea	RCT	ERCP	propofol, fentanyl	72	25	47	66.5	36	36	50,100	10.1007/s12630-020-01883-2
Lin et al 2019	Gastroint Endosc	China	RCT	Gastroscopy	propofol	1994	1171	823	47.5	994	100	30–60, 21–100	10.1016/j.gie.2019.06.033
Nay et al 2021	BJA	France	RCT	mixed	propofol with(out) opioids/ benzodiazepines or ketamine	379	174	205	64 median	191	188	70, 50	10.1016/j.bja.2021.03.020
Riccio et al 2019	J Clin Anesth	USA	RCT	Colonoscopy	propofol, lidocaine	59	51	8	56.5	28	31	up to 60, 40	10.1016/j.jclinane.2018.10.026
Teng et al 2019	BioMed Research International	Taiwan	RCT	Gastroscopy	propofol, midazolam, alfentanil	152	92	60	49.7	50	102	30,100	10.1155/2019/4,206,795

CNC, conventional nasal cannula; doi, digital object identification; ERCP, endoscopic retrograde cholangiopancreatography; FiO2, fraction of inspired oxygen; GI, gastrointestinal; HFNC, high-flow nasal cannula; n, sample size; RCT, randomized controlled trial.

a

b

Figure 2. (a) Risk of bias evaluated by utilizing Rob2 tool. The included studies are illustrated along with the risk of bias per domain (b) Graphical representation of the percentage of risk of bias per domain of interest.

pathologies, i.e. enhancement of arterial oxygenation in patients post-extubation or with pulmonary edema on grounds of left cardiac failure [25]. On the other hand, Klotz et al. [12] investigated, within an RCT in a pediatric population (n = 25 per arm), whether HFNC offers an advantage over CNC in terms of respiratory instability (apnea, hypercapnia, hypoxia) during GIE and found no statistically significant difference between the two arms. Worth mentioning is also the study of Pelaia et al. [28], where the authors assessed the same questions with us by means of flexible bronchoscopy, after conducting a pool data analysis. It was demonstrated, that HFNC is preferable compared to CNC in patients characterized by moderate acute respiratory failure undergoing bronchoscopy, by avoiding the episodes of desaturation and enhancing oxygen saturation.

On a mechanistic level, the finding of reduced RR in patients on HFNC can reasonably be attributed to multifactorial synergistic effects; avoidance of end-expiratory losses of lung volume as well as preservation of the same tidal volume with a parallel lower diaphragm activation might be two possible explanations [29]. Nevertheless, we must clarify that when patients receive EGD with mouth open, the positive end-expiratory pressure generated by HFNC might be reduced up to 50% [30], an effect that is not outweighed by the rest favorable attributes of HFNC, as our results propose.

Although our results cannot directly support this pathogenetic interpretation, there is comparable evidence derived from bronchoscopies delivering oxygen via HFNC [29]. Like bronchoscopy, gastroscopy is facilitated by the administration of sedatives in order to suppress laryngospasm, gag and cough reflexes, particularly before intubation of the esophagus [31]. The depth of sedation is directly associated with the risk of hypoxemia through respiratory depression, possible subsequent respiratory failure and gastric content aspiration [11,32]. Of note, gastroscopies are per definition 'shared airway' interventions and thereby resemble a partial foreign body obstruction [31]. Hypoxemia may further be exacerbated in example by teeth dislocation through bite-block, GI bleeding, or dysphagia with(out) accompanying food impaction [31]. Hypoxemia consists, therefore, one of the major concerns for both endoscopists and anesthesiologists during GI interventions of spontaneously breathing patients under moderate to deep anesthesia.

HFNC as a contemporary technological achievement combines a variety of favorable specifications such as the capability of delivering up to 100% FiO_2 at a flow-rate up to 60–80 L/min by maintaining simultaneously a mild PEEP (usually 2 cm

Table 2. Further patient characteristics and main results.

Study	BMI HFNC mean (SD)	BMI CNC mean (SD)	ASA I (n) (HFNC/ CNC)	ASA II (n) (HFNC/ CNC)	ASA III (n) (HFNC/ CNC)	ASA IV (n) (HFNC/ CNC)	Hypoxemia HFNC*	Hypoxemia CNC*	Hypercapnic HFNC mmHg (SD)	Hypercapnic CNC mmHg (SD)	Manouvers HFNC (n)	Manouvers CNC (n)	Primary/secondary Outcome(s)	Main result(s)
Kim et al 2021	23.1 (4.1)	22.1 (3.5)	19/21	19/21	17/15	17/15	0/36	7/36	30.4 (6.6)	33.9 (7.4)	0	40	Primary: lowest oxygen saturation. Secondary: incidence of hypoxemia (SpO2 < 90%)	HFNC provided adequate oxygenation without causing procedural interruptions during ERCP
Lin et al 2019	22.84 (3.06)	22.96 (3.23)	636/ 664	358/ 335	0/0	0/0	0/994	90/1000	NA	NA	8	319	Primary: SpO2 ≤ 75% SpO2 < 90% for <60s Secondary: SpO290% ≤SpO2 < 95%, severe hypoxia(SpO2 < 75% for any duration or 75% ≤ SpO2 < 90%for 60s)	HFNC prevents (severe) hypoxia in ASA I–II patients
Nay et al 2021	27 median	26.5 median	24/24	114/ 112	53/51	0/1	18/191	63/188	NA	NA	37	105	Primary: SpO2 ≤ 92%, Secondary: Prolonged or severe desaturations, need for maneuvers to maintain free upper airways	HFNC significantly reduced the incidence of peripheral oxygen desaturation.
Riccio et al 2019	48 (7)	49 (10)	0/0	3/004	25/25	0/002	11/28	14/31	NA	NA	15	16	Primary: SpO2 < 90%, Secondary outcome measures included an assessment of the need for airway interventions as well as the number of desaturation episodes below 90% per patient in each group.	HFNC was not significantly different from CNC in morbidly obese patients
Teng et al 2019	22.51 (4.19)	23.17 (3.58)	7/42	43/60	0/0	0/0	1/50	15/102	NA	NA	NA	NA	Primary: area under the curve of 90% oxygen desaturation for 10s, secondary: airway obstruction episodes, apnea episodes, rescue interventions, and hypoxic events	The HFNC may reduce degree and duration of hypoxemia

* Patients (n) per arm. Abbreviations: ASA, American Society of Anesthesiologists (Status); BMI, body mass index (kg/m^2); CNC, conventional nasal cannula; HFNC, high-flow nasal cannula; NA, not available; SD, standard deviation; SpO2, oxygen saturation

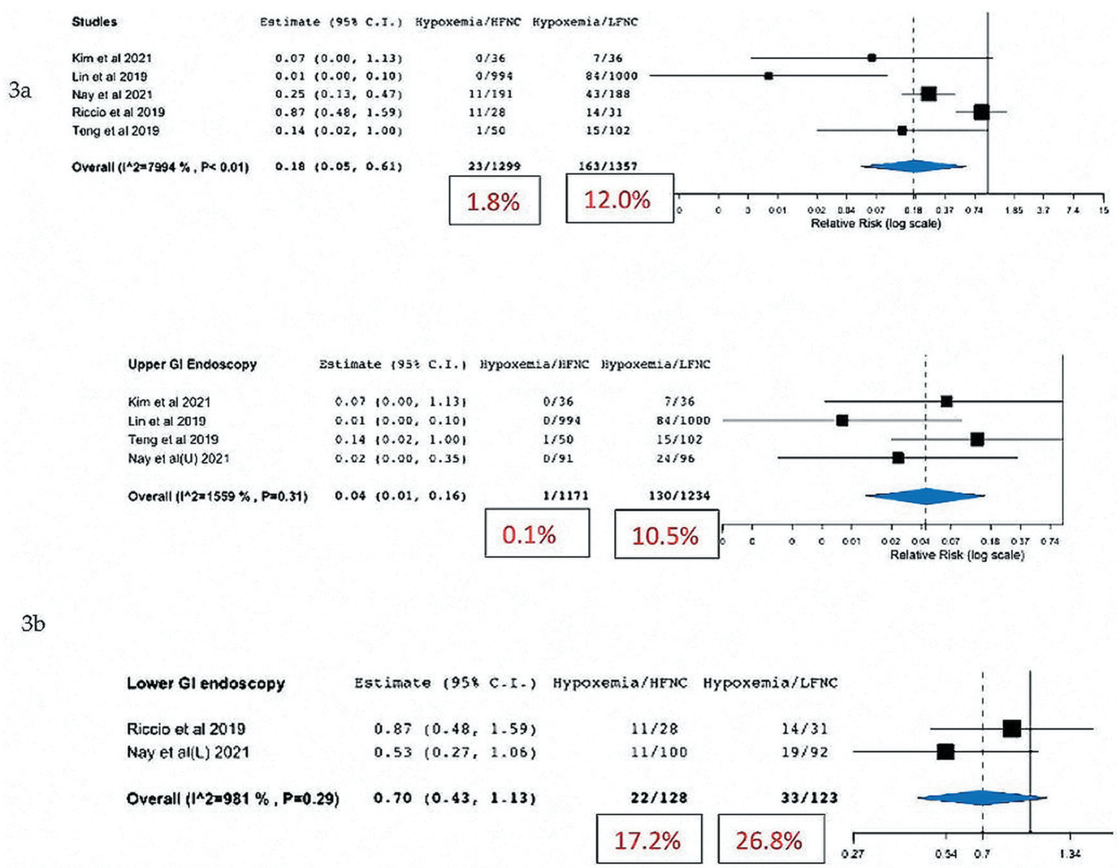

Figure 3. (a) Forrest plot including the meta-analysis results of all included studies. Cases with HFNC administration experienced hypoxemia with a RR of 0.18, compared to controls, albeit with significant heterogeneity I^2: 79.94% (b) Subgroup analysis based on the endoscopic modality. Among patients submitted to colonoscopy HFNC did not provide significant benefit on hypoxemia, whereas it was more beneficial in cases of upper GI endoscopy when compared to the low flow controls (RR:0.04, I^2:15.59%). GI, gastrointestinal; HFNC, high-flow nasal cannula; RR, risk ratio.

4b

	Random Effects Model				Heterogeneity		
Subgroup	Cases with HFNC	RR	CI 95%	p	Q	I^2 (%)	p
Total	1299	0.18	0.05-0.61	<0.1	19.94	79.94	<0.01
Upper GI*	1135	0.03	0.01-0.21	<0.001	3.44	41.82%	0.18
Lower GI	128	0.70	0.43-1.13	0.14	1.11	9.81	0.29

**Excluding patients submitted to ERCP*

Figure 4. (a) Meta-analysis of cases submitted to upper GI endoscopy, excluding ERCP, to eliminate potential artifacts by particular positional and technical characteristics. The RR of hypoxemia remained significantly lower for patients under HFNC. (b) Detailed results of meta-analysis from initial model, including all eligible studies, and subgroup analysis excluding ERCP cases. ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal; HFNC, high-flow nasal cannula; RR, risk ratio.

H_2O) above PEEP) and accomplishing a so-called 'washout' effect. Besides, HFNC compared to CNC provides higher inspired oxygen concentrations to the distal airways with parallel humidification and warmness, an effect that may reduce the risk of epistaxis [33]. Due to these attributes, it could comprise a useful and safe future option, beyond ICU, and might also be the standard modality of oxygen administration in GIE, at least for patients with comorbidities and those requiring advanced GIE. More specifically, ASA class IV–V, BMI more than 20 kg/m^2, age more than 60 years as well as presence of cardiovascular comorbidities and combined endoscopy (upper and lower GI tract) represent potential risk factors of hypoxemia [10]. Similarly, interventional endoscopy requires prolonged procedural sedation time, associated with higher risk of hypoxemia, [2]. General anesthesia and endotracheal intubation as the maximum airway support alternative may be impeded by patient-related risk factors, thus necessitating sufficient alternatives, such as HFNC.

Despite the multiple advantages of HFNC, the high purchase expenditure and service cost compared to CNC might be an obstacle to overcome, at least in certain developing countries and/or health-care facilities [1]. Nevertheless, the overall cost, considering expenditures after hypoxemia complications, necessity for further management, or hospitalization should be calculated in respective future reports. In this regard, Turner et al. [34] calculated the cost-effectiveness of HFNC compared with standard oxygen in patients at risk of intubation and suggested HFNC as a cost saving approach, at least for the respective patient group.

Hypercapnia in patients with chronic lung diseases (especially chronic obstructive lung disease) is of exceptional significance but could not be considered as a secondary outcome in our meta-analysis due to the lack of relevant data in most of the included eligible studies. Kim et al. [25], however, investigated hypercapnia as a dependent variable for the HFNC arm, with no reported incidences [25].

A further consideration concerns the wide variety of administered oxygen and FiO_2 among the included studies. These unavoidable discrepancies might have influenced our results. A relevant editorial emphasizes how FiO_2 of HFNC and not only the flow rate may impact hypoxia outcome of respiratory and gastrointestinal endoscopies in pediatric population [30]. Moreover, airway maneuvers were heterogeneously imprinted in enrolled studies, thus providing weak results regarding their incidence in the HFNC group. A potential outcome of interest in future studies could be the risk of procedure interruption, which was significantly lower in our study, endotracheal intubation and potential prolonged hospitalization. Finally, the plethora of different anesthetic agents, their combinations and dosage might also have affected the incidence of respiratory depression and hypoxemia. In this regard, future RCTs should be based on strict and matched evaluated variables, such as endoscopic modality and duration, HFNC device settings, sedatives dosage, underlying diseases (probably quantified by relative tools), and potential outcomes (hypoxemia, hypercapnia, intubation, procedure interruption, etc.).

5. Conclusion

HFNC may constitute a valuable modality to prevent hypoxemic events during upper GIE procedures. Additional results from ongoing RCTs are warranted in order to further support these data and identify patients with optimal expected benefit from HFNC during GIE.

6. Expert opinion

HFNC is indubitably a novel and attractive technological attainment and offers, as it was previously discussed a wide variety of favorable properties.

We can safely assume that since the CNC is inferior to HFNC in populations of better clinical and performance status, CNC in a fragile population with concurrent comorbidities, most likely will be proven inadequate. Although the current piece of evidence, based on this meta-analysis supports its utilization for upper GIE, it cannot be regarded as a realistic 'first line' option outside ICU, due to mainly cost-efficiency reasons, especially in developing countries. A pragmatic approach for the clinical endoscopist is to screen before the procedure the profile of the patients and identify the candidate ones with a high-risk for oxygen desaturation during the procedure. As abovementioned, to those belong primarily patients with an advanced ASA class (IV–V) or relevant BMI as well as with age exceeding 60 years along with the presence of cardiovascular or respiratory comorbidities. A further non-neglectable parameter that has to be regarded is the type of GIE since an advanced upper GIE such as endoscopic submucosal resection, peroral endoscopic myotomy, endoscopic ultrasound with fine needle aspiration or ERCP with sphincterotomy and stent placement are linked to more complications and significantly greater operational time than merely diagnostic gastroscopies, impacting therefore relevantly the risk of hypoxemia. A validated tool identifying such patients with scoring points and a certain cutoff, would be of paramount importance. Currently, there are several RCTs in pipeline, which will further elucidate in the future the role of HFNC on GIE, including also the lower GIE. Relevant outcomes that have to be considered are also the incidence of hypercapnia, lowest peripheral oxygen saturation and maneuvers to reverse hypoxemia. The former, albeit clinically very relevant parameters could not be assessed within this meta-analysis, due to the scarcity of the available data. A further crucial methodological component to be considered for the future RCTs is also the flow rate and FiO_2 of administered HFNC, which probably influence significantly the hypoxemia results.

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Authors contributions

Conceptualization of this study belongs to F. Sampsonas. Data extraction was performed by M, Doulberis and F. Sampsonas and validation of them through V. Karamouzos and A. Tzouvelekis. Statistical analysis was performed by A. Papaefthymiou and V. Karamouzos. Manuscript was drafted – written by M. Doulberis, F. Sampsonas, A. Papaefthymiou and T. Kuntzen. M. Lagadinou, T. Karampitsakos and G. Stratakos substantially revised and critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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