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ORIGINAL ARTICLE

Impact of High-Flow Nasal Cannula Oxygenation on the Prevention of Hypoxia During Endoscopic Retrograde Cholangiopancreatography in Elderly Patients: A Randomized Clinical Trial

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Abstract

Background Hypoxia is the most frequently occurring adverse effect during endoscopic retrograde cholangiopancreatography (ERCP) under sedation; thus, oxygen must be properly supplied to prevent a reduction of oxygen saturation. In this study, we intend to verify the preventive effect for hypoxia during ERCP, using a high-flow nasal cannula (HFNC), in elderly patients.

Methods As a multicenter prospective randomized trial, patients who underwent ERCP with propofol-based sedation were randomly assigned into two groups: Patients in the HFNC group were supplied with oxygen via an HFNC, and those in the standard nasal cannula group were supplied with oxygen via a low-flow nasal cannula. The co-primary end points were the lowest oxygen saturation rate and hypoxia during the overall procedure.

Results A total of 187 patients (HFNC group: 95; standard nasal cannula group: 92) were included in the analysis. Unexpected hypoxia events were more frequently observed among patients in the standard nasal cannula group than among patients in the HFNC group (13% vs. 4%, odds ratio 3.41, 95% confidence interval 1.06–11.00, $p=0.031$). The mean of the lowest oxygen saturation rate during ERCP was significantly lower in the standard nasal cannula group than in the HFNC group (95% vs. 97%, $p=0.002$).

Conclusion Oxygen supplementation with an HFNC can prevent oxygen desaturation and hypoxia events in patients undergoing ERCP under sedation.

Trial registration Clinical Research Information Service (CRIS; KCT0004960).

Keywords High-flow nasal cannula · Endoscopic retrograde cholangiopancreatography · Propofol sedation · Hypoxia

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced endoscopic procedure used to diagnosis and treatment of biliary tract diseases. Sedation is important in ERCP for reducing patients' anxiety and pain, and for safe procedure completion [1]. In most cases, ERCP is performed under moderate to deep sedation by a non-anesthesiologist rather than under general anesthesia outside the operating room [2, 3]. Propofol is a widely used sedative medicine, and it is revealed to be safe for non-anesthesiologist administration in ERCP procedures [3, 4].

Hypoxia is the most common adverse cardiopulmonary complication in sedated endoscopy, and it is caused by respiratory depression, airway obstruction [5, 6]. The incidence of hypoxia during endoscopy under sedation is reportedly up to 51% in general endoscopic procedures, which tends to

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be increased in ERCP procedures [7–9]. In particular, older patients, those with higher American Society of Anesthesiologists (ASA) grade, and higher body mass index (BMI) values frequently experienced hypoxia during endoscopy were considered as high-risk patients for desaturation during ERCP [7, 10, 11]. Prolonged hypoxia can lead to life-threatening events, such as cardiac arrest and death, especially in patients with high-risk factors and those who underwent ERCP [12]. Thus, it is important to sufficiently prevent hypoxia during ERCP, especially in high-risk and older patients.

Oxygen supplementation is mandatory to prevent hypoxia in patients who undergo ERCP under sedation. Generally, a conventional oxygen delivery system uses a low-flow nasal cannula during ERCP. However, the low-flow nasal cannula can only be used at flow rates of 1–5 L per minute (L/min) and provide a fractional inspired oxygen concentration (FIO_2) of 0.27–0.4 [13]. A high-flow nasal cannula (HFNC) is a recently introduced oxygen delivery device that has advantages in oxygenation and ventilation. HFNC can provide a significantly high-flow rate (up to 60 L/min), heated and humidified gas with physiological temperature, and constant oxygen concentration (21–100%). HFNC with high-flow rates generates positive pressure in the upper airways, which increases end-expiratory lung volume, thereby improving oxygenation [14, 15]. In addition, high-flow rates may decrease physiological dead space by flushing expired carbon monoxide from the airway, which explains the observed decrease in the work of breathing [16]. It has been proven to produce better oxygen supplement compared to the Venturi face mask and low-flow nasal cannula during flexible bronchoscopy and gastroscopy [17, 18]. Therefore, we sought to investigate whether HFNC oxygenation can reduce hypoxia events and desaturation in elderly patients who underwent ERCP under propofol sedation.

Methods

Eligibility and Study Design

A prospective, randomized, comparative trial was conducted in two tertiary referral centers in South Korea by expert pancreaticobiliary endoscopists between September 2019 and May 2020. The study protocol was approved by the Institutional Review Board of INHA University Hospital (2019-07-018), and it was registered at Clinical Research Information Service (CRIS, KCT0004960). All patients provided written informed consent. Consecutive patients who were 65 years or older were eligible if they were scheduled to undergo ERCP. Exclusion criteria were allergy to propofol, active nasopharyngeal bleeding or obstruction, endotracheal intubation status, patients who underwent tracheostomy, and the use of home oxygen or ventilators. All authors had access to the study data and reviewed and approved the final manuscript.

The investigators enrolled patients who were randomly assigned in 1:1 ratio using simple randomization, to treatment groups; patients in the HFNC group were supplied with oxygen via HFNC, and those in the standard group were supplied with oxygen via low-flow nasal cannula. In the HFNC group, oxygen was supplied using a nasal high-flow generator (AIRVO2, Fisher & Paykel Healthcare, Auckland, New Zealand) after ensuring proper patient position for ERCP (Fig. 1). The initial setting of the HFNC was 50 L/min for the flow rate and 50% for the intake oxygen fraction (FiO_2). In the standard group, oxygen was supplied at 5 L/min. If a patients developed oxygen desaturation < 90%, the ERCP procedure and sedation were transiently interrupted to secure the airway (e.g., jaw thrust maneuver). Then, ERCP was restarted after restoration of oxygen saturation > 95%. After completing the ERCP procedure, the HFNC oxygenation was discontinued. However, oxygen supply is maintained in patients with reduced oxygen saturation before or during the procedure. Oxygen saturation was measured by pulse oximetry throughout the whole procedure.

Sedation Protocol, Endoscopy, and Monitoring

An initial bolus of propofol (0.5–1 mg/kg) was administered intravenously, followed by a repeated bolus (10–20 mg) according to the patient's condition, or continuous propofol infusion (2–6 mg/kg/h, with an additional bolus administered as needed). Sedation proceeded to the level of deep sedation as described in the American society of anesthesiologist and guideline [19]. The infusion dose was chosen based on the patient risk profile and depth of sedation. Midazolam was given only in the situation where the target conscious level had not been achieved. Maximum doses of

Fig. 1 High-flow nasal cannula device (used with permission from Fisher & Paykel Healthcare.)

propofol (3 mg/kg) and midazolam (10 mg) were limited. No other benzodiazepines or opioids were permitted [20].

ERCP was performed by two expert endoscopists (> 500 ERCP procedures/year) using a standard side-viewing duodenoscope (TJF-260; Olympus Optical Co, Ltd, Tokyo), and a straight standard injection catheter (ERCP catheter, MTW Endoscopie, Dusseldorf, Germany) or sphincterotome (CleverCut3V, Olympus Medical System). All ERCP procedures were conducted using a guidewire cannulation technique. If biliary cannulation was achieved through guidewire insertion, a cholangiogram was obtained through a deep insertion of the catheter or sphincterotome, and when that failed, a needle-knife papillotomy was adopted to access the biliary tree.

Outcomes

The primary end point was the hypoxia, which was defined as an oxygen saturation (SpO2) value less than 90%, during the overall ERCP procedure. The secondary end points were the mean lowest oxygen saturation rate and other complications. Other complications were recorded: patient agitation, arrhythmias, hypotension (defined as systolic blood pressure less than 90 mmHg), seizure or myoclonus, incomplete interruption of procedure, and cardiac arrest.

Sample Size Calculation and Statistical Analysis

A sample size calculation was performed, assuming an 8.4% more incidence of hypoxia in the conventional nasal cannula oxygen group compared with in the HFNC group based on the large-scale endoscopic study [18]. It was calculated that a total of 89 participants in each group would provide 80% power at a significance level of 0.05. Considering a 10% dropout rate, we determined the required sample size of 98 patients.

Continuous variables compared according to the individual study group are presented as means ± standard deviations, and Student's t test was used for analysis. Categorical variables are presented as the number of patients (proportions), and Pearson's chi-square or Fisher's exact tests were used for analysis. Univariate and multivariable logistic regression analyses were performed to investigate the association between hypoxia and the variables, using clinical and laboratory data within the index admission period. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA).

Results

From September 2019 to May 2020, a total of 187 patients, who underwent ERCP under propofol-based sedation, were finally analyzed in the study; 95 patients were assigned to the HFNC group, and 92 patients were assigned to the standard nasal cannula group. The study flowchart is presented in Fig. 2.

Baseline Characteristics

The baseline characteristics are listed in Table 1; the mean age was 79 years, and 55% of the patients were male. There was a similar distribution in BMI and underlying medical disease between both groups. There was no difference in ASA grades or oxygen profiles.

ERCP Procedure and Sedation Characteristics

Most ERCP procedures have been completed successfully. The mean procedure time was 17 min. The reasons for ERCP were similar in both groups: 107 (58%) for biliary stone, 53 (28%) for malignancy, and 23 (12%) for benign stricture. There were no differences in ERCP procedures: 62 (33%) underwent endoscopic retrograde biliary drainage (ERBD), 46 (25%) endoscopic nasobiliary drainage (ENBD), 6 (3%) endoscopic sphincterotomy (EST), 41 (22%) stone removal, and 27 (14%) stent deployment.

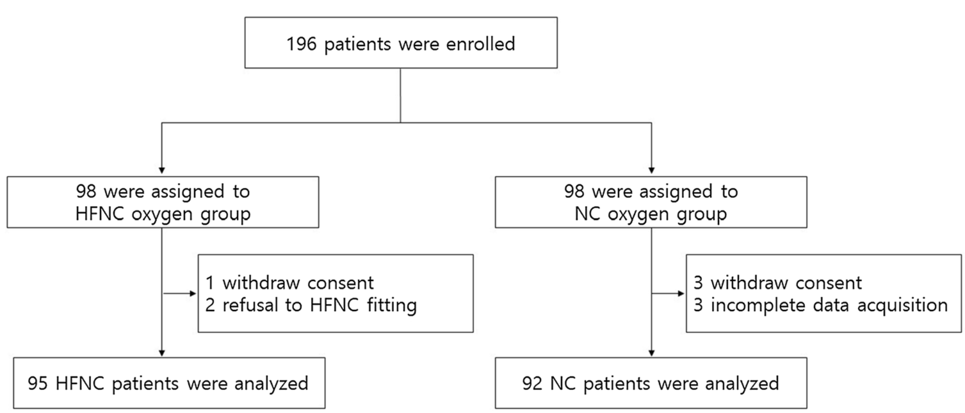

Fig. 2 Study flowchart. *HFNC* high-flow nasal cannula, *NC* nasal cannula

Table 1 Baseline characteristics

	HFNC oxygenation ($n=95$)	Nasal cannula oxygenation ($n=92$)	p value
Age, year	78 ± 7	79 ± 7	0.346
Male gender (%)	51 (54)	51 (55)	0.810
BMI, kg/m^2	22.86 ± 5.62	23.58 ± 3.82	0.314
BSA, m^2	1.55 ± 0.34	1.61 ± 0.20	0.131
Diabetes mellitus	27 (28)	26 (26)	0.981
Hypertension	55 (58)	63 (69)	0.134
Current Smoke	11 (12)	10 (11)	0.878
Coronary artery disease	13 (14)	8 (9)	0.280
Heart failure	3 (3)	2 (2)	0.515
Ischemic stroke	7 (10)	12 (13)	0.199
Intracranial hemorrhage	1 (1)	2 (2)	0.617
COPD or asthma	4 (4)	1 (1)	0.369
ASA grade			0.687
I	17 (18)	10 (11)	
II	55 (58)	67 (73)	
III	18 (19)	13 (14)	
Oxygen saturation at baseline, %	98 ± 2	98 ± 2	0.583
Use of oxygen at baseline	18 (19)	16 (17)	0.756

HFNC high-flow nasal cannula, *BMI* body mass index, *BSA* body surface area, *COPD* chronic obstructive pulmonary disease, *ASA* the American Society of Anesthesiologists

Table 2 Data on ERCP procedure and propofol sedation

	HFNC oxygenation ($n=95$)	Nasal cannula oxygenation ($n=92$)	p value
Reasons for ERCP			0.947
Biliary stone	52 (55)	57 (62)	
Malignancy	33 (35)	20 (22)	
Benign stricture	10 (10)	13 (14)	
Others	0	2 (2)	
Type of ERCP intervention			0.385
ERBD	34 (37)	28 (32)	
ENBD	20 (22)	26 (29)	
EST	3 (3)	3 (3)	
Stone removal	20 (22)	21 (24)	
Biliary stent deployment	16 (17)	11 (12)	
Procedure success	93 (98)	89 (97)	0.679
Total procedure time	17 ± 9	16 ± 8	0.260
Propofol sedation			
Use of midazolam	10 (11)	5 (5)	0.200
Dose of propofol, mg	66 ± 43	60 ± 35	0.322
Dose of propofol, mg per kg	1.16 ± 0.76	1.04 ± 0.61	0.243
Dose of midazolam, mg	3 ± 1	4 ± 1	0.353
Dose of midazolam, mg per kg	0.05 ± 0.24	0.07 ± 0.02	0.212

HFNC high-flow nasal cannula, *ERCP* endoscopic retrograde cholangiopancreatography, *ERBD* endoscopic retrograde biliary drainage, *ENBD* endoscopic nasobiliary drainage, *EST* endoscopic sphincterotomy

Dosages of sedative medicines were not significantly different between the two groups. Additional midazolam was administered in only 8% of the patients. The ERCP and sedation characteristics are listed in Table 2.

Clinical Outcomes

The clinical and safety outcomes are listed in Table 3. The primary end point of hypoxia events occurred less frequently in the group of receiving HFNC oxygenation than in the group of receiving low-flow nasal cannula oxygenation (4% vs. 13%, $p=0.031$). Regarding the secondary end point, the mean lowest oxygen saturation rate was 97% in those receiving HFNC oxygenation and 95% in those receiving standard nasal cannula oxygenation ($p=0.002$). The distribution of the lowest oxygen saturation between groups is shown in Fig. 3. Other complications were similar between the groups. Major adverse events such as cardiac arrest or incomplete termination of ERCP were not identified in the study. HFNC-related side effects were not demonstrated in this study.

Discussion

The main finding of the study is that HFNC oxygenation can reduce occurrence of desaturation in patients with biliary disease who underwent ERCP under propofol-based sedation. There was no significant adverse reaction such as cardiac arrest or incomplete interruption of procedure in both study groups. We demonstrated that HFNC application is more effective and safe as compared with conventional low-flow nasal cannula oxygenation, in the prevention of unexpected hypoxia during sedated ERCP.

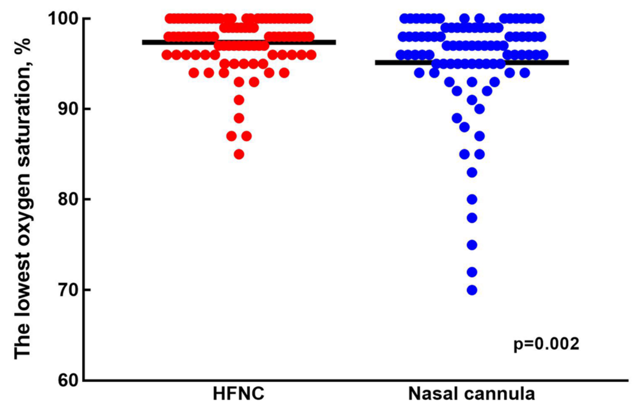

Fig. 3 Distributions of the lowest oxygen saturation rates during ERCP procedure. In patients with conventional nasal cannula, oxygen saturation decreases more steeply, and hypoxia occurs more frequently than in HFNC. *HFNC* high-flow nasal cannula

The preventive effect of an HFNC on hypoxia can be explained by two mechanisms. The first is the physiological effect, which has been described in previous literature works [14, 21]. The HFNC can induce positive oropharyngeal pressure during expiration due to its constant high-flow, which was mainly determined by the flow rate provided by HFNC and the expiratory flow exhaled by the patient [22, 23]. In addition, HFNC can increase the end-expiratory lung volume and tidal volume through changes in lung impedance, especially in patients with high BMI values [24]. Therefore, a certain level of positive end-expiratory pressure (PEEP) and increased end-expiratory lung volume can be obtained with a high-flow rate, which provides a reduction in work of breathing and in respiratory rate. Consequently, HFNC is able to maintain the correct FiO_2 similar to the FiO_2 setup [25]. The second mechanism is maintaining adequate temperature and humidification through a nasal high-flow

Table 3 Clinical and safety outcomes

	HFNC oxygenation ($n=95$)	Nasal cannula oxygenation ($n=92$)	p value
Primary end point			
Hypoxia (SpO2 < 90%)	4 (4)	12 (13)	0.031
Secondary end point			
The mean lowest oxygen saturation (%)	97 ± 3	95 ± 6	0.002
Composite of complications	13 (14)	17 (19)	0.372
Agitation	2 (2)	4 (4)	0.384
Tachycardia	11 (12)	12 (13)	0.760
Bradycardia	1 (1)	0	0.324
Hypotension	1 (1)	1 (1)	0.982
Seizure or myoclonus	0	0	N/A
Incomplete interruption of procedure	0	0	N/A
Cardiac arrest	0	0	N/A

HFNC high-flow nasal cannula, *SpO2* oxygen saturation generator. Cold and dry air inhalation causes upper airway dryness and impairment of mucociliary functions leading to intolerance, and this situation frequently occurs during endoscopic procedure, especially if the procedure time is prolonged [5, 10]. However, HFNC can provide heated and humidified oxygen to patients, which provokes the reduction in airway dryness, mucous secretion, and patient discomfort [14].

Regarding the setting of HFNC, it was initially set to 50 L/min for flow rate and 50% for FiO_2 and adjusted according to clinical requirements in our study protocol. Since there is no specific recommendation on an HFNC setting during ERCP, this setting was determined through the clinical experience, using our instrument before starting this study. Even though our study is the first study to apply HFNC in ERCP, our protocol might be prevented the reduction of oxygen saturation and hypoxia events in the patients, and they did not experience any adverse events. Therefore, we assumed that this HFNC setting could be applied generally in ERCP, and a safe procedure can be expected.

Recent randomized trials demonstrated preventive effective of HFNC on hypoxia event during propofol-based sedation endoscopy. The large scale of study described 0% incidence of hypoxia in the HFNC group compared to 8% patients using nasal cannula [18]. The study population was relatively low-risk patients with a mean BMI of 22, low ASA grade, younger age, and simple gastroscopy with a mean procedure time of 5 min. Another study presented lower hypoxia episode in the HFNC patients than standard nasal cannula (21.2% vs. 33.1%, $p=0.03$) [26]. The study participants had a mean BMI of 28, a mean of 62 years, and underwent advanced endoscopy with a mean procedure time of 30 min. Our study data showed similar decrease in incidence of hypoxia events in the HFNC patients (4% vs. 13%, $p=0.03$). Although our study population had a mean BMI of 23, low ASA grade, we enrolled only elderly patients with a mean age of 78 years, and all patients underwent ERCP with a mean procedure time of 17 min. Higher BMI and prolonged procedure might be associated with differences in the frequency of hypoxia events. In the study of high-risk patients with ASA grade 3 or more, BMI > 30, or obstructive sleep apnea, the HFNC on prevention for hypoxia episode showed equivocal result compared as nasal and mouthguard oxygenation (7.7% vs. 9.1%, $p=0.77$) [27]. It was difficult to compare with the studies described above because the addition of a mouthguard oxygen support in addition to the nasal cannula could affect oxygen saturation.

Regarding safety issues, there were no adverse events related to HFNC application in the current study. In addition, safety outcomes, except hypoxemia, were similar between the two study groups. Although tachycardia and bradycardia developed occasionally during ERCP, there was no serious arrhythmia, cardiac arrest, or interruption of procedure in all patients. Therefore, we believe that an HFNC is a safe oxygen delivery device, and it is very effective for the prevention of hypoxemia in ERCP. Our findings can be supported by previous studies. In previous studies, HFNC-derived side effects were reported only as anticipated symptoms such as nasal discomfort and epistaxis, and there were no major adverse events [18, 28].

This study has several limitations. First, we did not evaluate arterial blood gas analysis. Partial pressure of oxygen (pO_2) and partial pressure of carbon monoxide (pCO_2) level were not identified. However, peripheral oxygen saturation was measured by pulse oximetry that is generally correlated with pO2. In future studies, it is necessary to investigate blood gas analysis for accurate patient oxygen status. Second, the FiO2 among the two groups was not identical. While the maximum possible FiO2 of a simple nasal cannula is 40%, HFNC can increase the FiO2 by up to 100% [13]. However, our study only compared hypoxia event between nasal cannula and HFNC regardless of FiO2. Third, our data may not be enoughly applicable in patients with other high-risk factors, which were previously presented as high ASA grade or excessive obesity [10, 11]. Of the study participants, only 20% had an ASA grade of 3 or higher, and 5% had a BMI of 30 or more. Patients with lung diseases such as asthma or chronic obstructive pulmonary disease were enrolled, but only a few of them were included. We recruited consecutive patients who underwent ERCP because there were fewer patients with ASA grade > 3 in real-world practice [10, 18]. Thus, our data could reflect the population that will undergo ERCP under sedation. Fourth, our study did not investigate negative effect of mouth breathing on HFNC during ERCP. During sedated endoscopy, more than 58% of patients presented oral breathing [29]. Although oral breathing was frequent in sedated endoscopy, HFNC showed similar preventive effect for hypoxia as compared with mandibular bite block device [30]. Therefore, HFNC might be a useful oxygen delivery system regardless of oral breathing. Fifth, this study was conducted only in a certain area. Caution should be taken when estimating results from outside South Korea.

Conclusion

This study was to investigate the efficacy of oxygen supplementation with an HFNC on ERCP under propofol sedation in elderly patients. HFNC can stably maintain oxygen saturation and prevent hypoxia during ERCP procedure. Thus, routine HFNC support can be considered in patients who underwent ERCP under sedation.

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Author's contributions B.C., M.J.L., and J.S.P. were responsible for the concept and design of the study, as well as the acquisition, analysis, and interpretation of the data and the drafting of the manuscript. J.S., M.H.P., and J.S.K. helped collecting data. J.S., S.Y.C., J.H.H. helped with interpretation of the data, and C.W.Y. assisted revision.

Declarations

Conflict of interest The co-authors have no conflict of interest.

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