의학박사 학위논문

프로포폴과 레미펜타닐을 이용한 감시 마취에서 산소공급을 위해 사용하는 고유량 비강 캐뉼라와 단순 마스크의 효과 비교

Comparative effects of high-flow nasal cannula and simple face mask during monitored anesthesia care with propofol-remifentanil

울 산 대 학 교 대 학 원

의 학 과

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지 도 교 수　　　함 경 돈

이 논문을 의학박사 학위 논문으로 제출함

2022년 2월

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Abstract

Background: Propofol and remifentanil is the most used combination in radiofrequency ablation (RFA) under monitored anesthesia care (MAC), but these has a serious problem as a respiratory depression. Some studies reported that high-flow nasal cannula (HFNC) can reduce hypoxic events during various procedures under sedation. In this study, we compare to the oxygenation contents and incidence of hypoxic event of simple face mask and HFNC for MAC in the patients undergoing RFA on hepatic neoplasm.

Methods: In this study, fifty-two patients were randomly allocated into two groups for elective RFA. Patients were received oxygen either simple face mask (Mask group) or HFNC (HFNC group). The primary outcomes were intraprocedural partial pressure of arterial oxygen (PaO_2), pre- and intraprocedural differences in PaO_2, and the incidence of hypoxic event. The secondary outcomes were intraprocedural the ratio of PaO_2 to inspiratory oxygen fraction (FiO_2) ratio (PaO_2/FiO_2), the difference of pre- and intraprocedural partial pressure of arterial carbon dioxide ($PaCO_2$), respiration rate (RR) change during procedure, and patient's satisfaction score after RFA

Results: Intraprocedural PaO_2 and the difference of pre- and intraprocedural PaO_2 were significantly different between two groups. Intraprocedural PaO2 of mask groups and HFNC were 199.9 (154.3 – 224.9) and 287.0 (191.3 – 379.9) mmHg, respectively (p = 0.009) and the differences of pre- and intraprocedural PaO_2 of mask groups and HFNC were, 111.6 (67.4 – 141.8) and 188.5 (100.1 – 280.3) mmHg, respectively (p = 0.0091). The incidence of hypoxic event was not significantly different between two groups. (36% of mask group vs. 25.0% of HFNC group, respectively; p = 0.505). However, the incidence of severe hypoxic event was significantly lower in HFNC group than mask group. (32% of mask group vs. 4.2% of HFNC group, p = 0.045). Intraprocedural PaO_2/FiO_2 were significantly different between two groups. PaO_2/FiO_2 of mask group was significantly higher than HFNC group [399.9 (308.6 – 449.7) and 287.0 (191.3 – 379.9) mmHg, respectively (p = 0.005)]. RR was significantly different between two groups (F = 7.944; p = 0.08). There were significant differences in patient's satisfaction score between two groups. Patients in mask group were more satisfied than HFNC group [60.6 (56.8 – 66) vs. 54.0 (44.0 – 62.0), respectively; p =0.031].

Conclusion: The use of HFNC improve oxygen profile and reduce the incidence of severe hypoxic event in patients undergoing percutaneous RFA under MAC with propofol-remifentanil.

Keywords: High flow nasal cannula, Face mask, Hypoxia, Monitored anesthesia care

Table of contents

Table and figure

Introduction

The American Society of Anesthesiologists (ASA) defined as monitored anesthesia care (MAC) is a planned procedure during which the patient undergoes local anesthesia together with sedation and analgesia [1]. During MAC, procedure related anesthesia such as local infiltration and field block is performed by surgeon and systemic sedation, analgesia and monitoring vital signs are provided by an anesthesiologist [2].

In the past days, MAC is a second choice for patients too compromised to undergo general anesthesia. But now, it is the first choice in 10–30% of all the surgical procedures [3]. As medical technology advances, many of surgical procedures are being replaced by interventional procedures and considering that MAC and interventional procedures are inseparable, the importance of MAC will be greater.

The 3 fundamental elements and purpose of a MAC are a safe sedation, control of the patient anxiety, and pain control obtained with local anesthetics and analgesic drugs [1]. For the purpose, midazolam, propofol and dexmedetomidine have been popularly used sedatives in MAC. The advantages of midazolam are rapid onset, short duration of and properties of anxiolysis and amnesia [4]. However, action duration of midazolam is unpredictable because it's active metabolite. Propofol also mainly used drug for MAC because it shows fast onset, short half-life, and rapid recovery. Compared with midazolam, cognitive function recovery is faster and the degree of postoperative sedation, dizziness, amnesia, and postoperative nausea and vomiting (PONV) are lower after propofol sedation [5]. Dexmedetomidine, an alpha2-adrenergic agonist, can also be used for MAC. It has both sedative and analgesic properties and it does not impair the respiratory drive. However, it has been shown to impair the respiratory responses to hypoxia and hypercapnia [6] and can cause hemodynamic effects such as hypertension, hypotension and bradycardia [7].Recently, an ultra-short-acting, water soluble intravenous benzodiazepine, remimazolam has been approved in the some countries. Unlike all other benzodiazepines, remimazolam contains a carboxylic ester moiety in its structure. This enables rapid metabolism to inactive metabolite by non-specific tissue esterases [8]. So, remimazolam has characteristics that a fast onset, a rapid metabolism allowing for ease of titration, a rapid recovery. Moreover, remimazolam has a reliable reverse agent, flumazenil, and a favorable side effect profile [9]. However, the studies of remimazolam to date are limited to patients undergoing bronchoscopy, colonoscopy and upper gastrointestinal endoscopy, with study designs prescribed by regulatory authorities that limit generalizability [10].

Except dexmedetomidine, other sedatives for MAC do not have an analgesic property. So, additional analgesics such as non-steroidal anti-inflammatory drugs or opioids should be needed in MAC for painful procedure. Among these drugs, an ultra-short-acting opioid remifentanil is preferred for MAC because of its rapid recovery property [11]. However, it has critical disadvantage which is significant respiratory depression. Remifentanil infusion at a rate of 0.5±0.3 μg/kg/min provided sufficient analgesia but was accompanied by a high incidence of respiratory depression at subtherapeutic levels [11].

According to the report of anesthesia closed claim project, respiratory related injury is most common complication of MAC in non-operating room anesthesia [12]. Mason et al. [13] analyzed retrospective data on 7952 cases receiving MAC for procedure from 2010 to 2018 of 39 countries. They reported that oxygen desaturation for less than one minute was the common adverse event and with followed by airway obstruction and apnea. In these contexts, ASA recommended that equipment to administer supplemental oxygen should be present when sedation/analgesia is administered, and oxygen should be administered during deep sedation without specifically contraindicated for a particular patient or procedure [2]. The most common used oxygen supplement devices for MAC are nasal cannular and simple facemask. These two are simple, comfortable, and easy to apply but they cannot supply constant oxygen [14]. For example, nasal cannula can be easily dislodged and is not as effective in patients with deviated septum or polyps and the efficacy of simple mask relies on how well it fits. Moreover, eating and drinking can be difficult with the mask on, and some patients may feel claustrophobic with the mask on [15].

High-flow nasal cannula (HFNC) is a kind of supportive oxygen therapy device that it can provide extremely high flow, heated, and humidified oxygen. This device provides more adequate oxygenation by supplying high-flow oxygen, which can rapidly wash out carbon dioxide (CO_2) in the nasopharyngeal cavity and produce a positive airway pressure (PAP) [16].

For the first time, HFNC used just an oxygen therapy device for respiratory failure [16]. However, some recent studies reported that HFNC is beneficial for procedural sedation and general anesthesia [17-19]. For example, Chung et al. [20] reported that the use of HFNC in hypoxemic patients during diagnostic and therapeutic bronchoscopy procedures has clinical effectiveness. In general anesthesia, HFNC is effective the preoxygenation of general anesthesia in morbidly obese patients and it improve the respiratory failure of patients after extubation and reduce the occurrence of complications after general anesthesia [21, 22]. Especially, Lin et al [18] reported in their randomized multicenter clinical trial that the incidence of hypoxia in HFNC group was 0% during gastroscopy under propofol sedation.

Percutaneous radiofrequency ablation (RFA) has emerged as a treatment modality for treating liver neoplasm because RFA is easy, safe, cost-effective, less invasive and reduces the length of hospital stay than surgical resection [23-28]. Moreover, RFA has been performed as an alternative treatment for unresectable primary hepatocellular carcinoma, which often occurs in hepatic reserve-impaired cirrhotic liver [29]. Traditionally, percutaneous RFA have been performed under local anesthesia. However, some patients complain of severe pain and anxiety during the procedure, which may result in lower patient satisfaction and insufficient tumor ablation [30]. MAC is suitable in this situation because MAC provides a safe sedation, reduction of patient's anxiety, and effective pain control by anesthetic specialist. Moreover, MAC can provide the cooperation of patient. In some cases, depending on the location of the lesion, interventionist need to cooperation because the facilitate the performance of the procedure via indirect liver mobilization by ensuring that the patient can take a deep breath and/or hold their breath [31].

Most of studies that the usefulness of HFNC for procedural sedation were performed on endoscopic procedure. During the MAC for RFA, respiratory instability is more common problem than endoscopy because use of opioid and position. Unlike endoscopy, which is performed on lateral position, RFA is performed on supine position. And RFA should be need opioid because RFA is more painful than endoscopy. However, there was no clinical study that identify the usefulness of HFNC during the percutaneous RFA on hepatic neoplasm under MAC.

Considering the results of previous studies in endoscopic procedures and the characteristics of HFNC, we hypothesized that HFNC is also useful in percutaneous RFA on hepatic neoplasm under MAC. The study was designed to investigate HFNC provide more oxygenation and reduce the hypoxic event in percutaneous RFA on hepatic neoplasm under MAC compare with conventional simple facemask through the analyze of arterial blood and the incidence of hypoxic events.

Methods

Study population

This prospective, randomized, controlled study was approved by the Institutional Review Board of Asan Medical Center (2021-0714) and registered at http://cris.nih.go.kr (KCT000622 1). Between July 2021 and November 2021, 1) American Society of Anesthesiologists (ASA) physical status I to II patients for 2) more than 20 years and less than 80 years, 3) who were scheduled for ultrasound (US) -guided percutaneous RFA under MAC. Written informed consent was obtained all patients prior on the day before procedure to enroll this study. If the patient wants to withdraw consent at any time of this study, all data of these patients were discarded and excluded from the study.

Patients with 1) severe chronic pulmonary disease (patients who received oxygen therapy or the first second forced expiratory volume below 50%), 2) severe cardiac disease (diagnosed heart failure by cardiologist, uncontrolled arrhythmia, and unthreatened coronary artery disease), 3) cerebrovascular disease, 4) negative modified Allen test, and 5) contraindications for remifentanil or propofol were excluded this study. And 6) emergency RFA were excluded also.

Randomization

All patients were randomly allocated to 2 groups (Mask group; using simple mask and HFNC group; using HFNC). The randomization was performed with sealed envelope randomization services (available at http://www.randomizer.org) with allocation ratio of 1:1 and block size of 2. On the morning of procedure before inducing anesthesia, allocation envelopes were opened by a nurse or anesthesiologist in a blind manner who then prepared either simple mask or HFNC for oxygen supply. None of the other anesthesiologists involved in post-procedural data collection were aware of the group assignment.

Anesthetic Management

All patients fasted for more than 8 hours and were not premedicated. After the patient entered the procedural room, anesthetic monitoring includes noninvasive blood pressure, pulse oximeter, electrocardiography (ECG), and bispectral index (BIS) were placed all patients. After then, we sampled pre-procedural arterial blood for arterial blood gas analysis (ABGA) at radial artery after modified Allen's test. After sampling, the patients who allocated in Mask group received 6 L oxygen using a simple facemask and patients who allocated in HFNC group received high flow heated (34 °C) and humidified nasal oxygen is given with the OptiFlow System (Fisher & Paykel®, Aukland, New Zealand) using a flow of 30 liter/minute [32] and an inspiratory oxygen fraction (FiO_2) of 1.0. We could not apply same FiO_2 because our HFNC system could not control this.

MAC was induced and maintained via the continuous infusion of propofol and remifentanil using a target-controlled infusion (TCI) pump. To determine the proper depth of sedation, the effect-site propofol concentration by Marsh model was adjusted using steps of 0.1–0.2 μg/ml and the remifentanil dose was adjusted to maintain the mean blood pressure to within 20% of the baseline. The appropriate level of sedation was 3 points on the Modified Observer's Assessment of Alertness/Sedation scale (Table 1) and 65 to 80 points on BIS [33]. At this level of sedation, patients seemed comfortable, lost consciousness, and maintained spontaneous breathing. However, when the interventionist or anesthesiologist requested patient cooperation, the patient immediately became alert and followed the request [34, 35].

Pulse oximeter was placed on the 4th finger of the opposite arm around blood pressure cuff. If peripheral oxygen saturation (SpO_2) <95%, we applied the triple airway maneuver immediately to maintain the airway at any time of the procedure. If there was no improvement despite of these maneuvers, we applied bag-valve mask for ventilation.

Intra-procedural ABGA was performed at the 5-minute after ablation at same radial artery because the ablation times for hepatic were 8 to 12 minutes. All anesthetic drugs were discontinued immediately after end of RFA. All patients were delivered post anesthesia care unit and received close monitoring includes blood pressure, heart rate, SpO_2, and ECG for up to 30 minutes. If the patient showed stable vital signs during recovery phase, check the computed tomography to confirm the success of procedure.

Table 1. Modified Observer's Assessment of Alertness/Sedation Scale [33]

Responsiveness	Score
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal lone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

RFA for Hepatic Neoplasm

In Asan Medical Center, conventional US-guided percutaneous RFA technique has been previously described in detail [36, 37]. In brief, tumor ablation was performed by 1 of 3 interventional radiologists with >5 years of experience in a blind manner. After planning sonography, all patients received local anesthesia at insertion site. If interventionist need artificial ascites, additional local infiltration for ascites needle. Artificial ascites was made by 5% dextrose 500 to 1000 ml, as appropriate. Interventionist used single electrodes with an internally cooled tip (Cool-tip™; Covidien, Burlington, MA, USA), cooled wet tip (Jet-tip®, RF Medical Co., Ltd., Seoul, Korea), and multitined expandable tip (Proteus®, STARmed Co., Ltd., Goyang, Korea), as appropriate. The RFA current was elevated 20 W/min starting from 60 W with internally cooled tip and multitined expandable tip, or 30 W/min starting from 50 W with wet tip using the automatic impedance control method and 200-W generator (Mygen M-2004 Radiofrequency System; RF Medical Co., Seoul, Korea) for 8 to 18 minutes. Like conventional RFA, US-guided percutaneous microwave ablation also performed by 1 of 3 interventional radiologists with >5 years of experience in a blind manner. Interventionist used the only single 13-G antenna. The microwave current was 70 W to 100 using 150 W generator (Emprint™ HP ablation generator; Covidien, Burlington, MA, USA) for 6 to 10 minutes.

Data Collection

Preprocedural clinical data were collected for all patients using our computerized patient record system (Asan Medical Center Information System Electronic Medical Record). Collected data included demographics such as age, sex, height, weight and body mass index, comorbidities such as hypertension, diabetes milltus, asthma and others, reason for RFA, tumor location, tumor size, smoking history, and current medication.

Intraprocedural data such as pre-procedural arterial blood gas analysis (ABGA), noninvasive blood pressure, heart rate (HR), respiration rate (RR), BIS value, total ablation time, sedation time, use of artificial ascites technique, type of ablation tip, maximal energy, total remifentanil dose, total propofol dose, hypoxic event, and intraprocedural ABGA were collected by anesthesiologist. Intraprocedural vital signs were measured and recorded at 5-minute intervals.

Post-procedural data such as procedure or anesthesia related complications and Iowa Satisfaction with Anesthesia Scale (ISAS) (Table 2) were collected by blinded anesthesiologist who did not participate in patient's procedure [38]. Collected complications were incomplete ablation, pneumonia, pleural effusion, bleeding and PONV. ISAS was assessed the day after the procedure.

Pre-procedural ABGA was performed at immediate after initial vital signs monitoring. Intra-procedural ABGA was performed at the 5-minute after ablation. Bloods for ABGA were sampled from same radial artery after modified Allen's test. We could not analyze blood sample immediately because only one anesthesiologist was attended in procedure room. So, we sealed ABGA samples immediately after sampling to avoid contact with room air and immediately stored on ice during procedure. After the end of procedure, stored blood samples were delivered laboratory by anesthesiologist.

Table 2. The Iowa Satisfaction with Anesthesia Scale [38]

Order	Statement
1	I threw up or felt like throwing up
2	I would want to have the same anesthetic again
3	I itched
4	I felt relaxed
5	I felt pain
6	I felt safe
7	I was too cold or hot
8	I was satisfied with my anesthetic care
9	I felt pain during surgery
10	I felt good
11	I hurt

Outcome Evaluation

The primary outcomes of this study were 1) intraprocedural partial pressure of arterial oxygen (PaO_2), 2) the difference of pre- and intraprocedural PaO_2, and 3) the incidence of hypoxic event. Intraprocedural PaO_2 and the difference of pre- and intraprocedural PaO_2 reflects whether the oxygen contents were improved by oxygen delivery system. And the incidence of hypoxic event reflects how effective the changing oxygen contents by oxygen delivery system. We defined hypoxic events as a SpO2 <95% according to world health organization's training manual [39]. And we defined severe hypoxic event as a SpO_2 < 90% despite of triple airway maneuvers.

The secondary outcomes included 1) the intraprocedural PaO_2 to FiO_2 ratio (PaO_2/FiO_2), 2) the difference of pre- and intraprocedural partial pressure of arterial carbon dioxide ($PaCO_2$), 3) RR change during procedure, and 4) ISAS score after RFA. We defined the intraprocedural PaO_2/FiO_2 as secondary outcome because the FiO_2 of simple mask is unpredictable which is depending on the patient's respiratory pattern, and how much mouth breathing occurs [40]. The difference of pre- and intraprocedural $PaCO_2$, and the change of RR reflects the stability of ventilation during procedure and ISAS reflects comfortability. ISAS is known as a reliable, valid, and useful questionnaire for measuring patient satisfaction with MAC [41].

Sample size calculation

The sample size estimate for this study was based on the study by Heinrich et al.[22]. The power analysis was performed with G*power which is a free-to use software used to calculate statistical power.

According to Heinrich's study, the mean PaO_2 after 5 min of preoxygenation by high-flow nasal cannula was 405 ± 71.3 mmHg and a facemask was 339 ± 82.3 mmHg. Assuming a β-error of 5% and an α-error of 20%, the overall target sample size was calculated to be 24 participants per group. We added 10% to the calculated sample size in consideration of the expected loss of patients during follow-up, and thus, the final target sample size was set at 52 participants. We did not perform any interim analyses.

Statistical Analysis

Continuous variables are presented as the mean±SD or median with the interquartile range, and the categorical variables are presented as number of patients and percentages. Continuous data such as age, body mass index, tumor size, ABGA data, total ablation time, sedation time, total dose of propofol, total dose of remifentanil, and ISAS were analyzed using the paired t-test or Mann–Whitney rank-sum U test. Categorical data such as sex, comorbidities, ASA classification, tumor type, procedure type, use of artificial ascites, and hypoxic event were tested using the Pearson x^2 or Fisher exact test, as appropriate. Repeated measures data such as RR were analyzed using repeated measured analysis of variance (ANOVA) with post-hoc analysis. Statistical analyses were performed using SPSS (version 21.0; SPSS Inc, Chicago, IL). For all comparisons, $P < 0.05$ is considered statistically significant.

Results

Study population

Between July 2021 and November 2021, total 136 patients were received RFA under MAC. We screened all these patients, and 84 patients were excluded because did not meet the inclusion criteria such as ASA physical status and age over 80 (n = 80), patients refuse (n = 39), and other reasons such as change the therapeutic plan (n = 5).

52 patients were randomly allocated to mask groups or HFNC group. In these cases, 3 cases (1 case of mask group and 2 cases of HFNC group) were excluded for final analysis because blood samples were clotted. Thus, 49 patients (25 patients of mask group and 24 of HFNC group) were included in final analysis (Fig. 1).

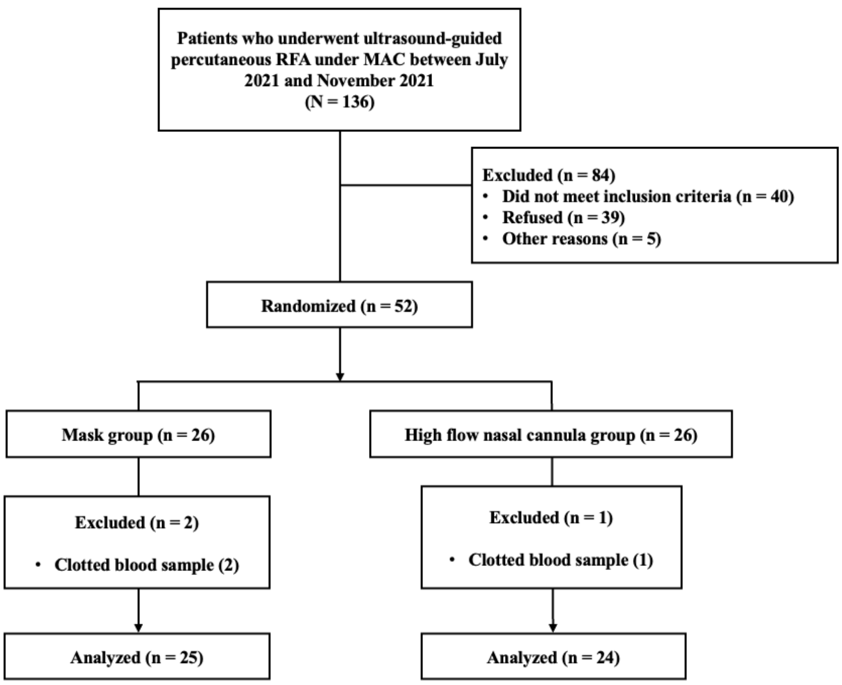

Figure 1. Study design according to the CONSORT statement.

RFA, radiofrequency ablation; MAC, monitored anesthesia care

Baseline and procedural characteristics were not significantly different between two groups (Table 3). And intraprocedural characteristics and technical data were not significantly different also between two groups (Table 4).

Table 3. Baseline characteristics and intraprocedural variables

	Mask (n = 25)	HFNC (n = 24)	*p*
Age (y)	62.1 ± 8.8	63.3 ± 8.2	0.645
Sex (male/female)	20 (80.0)/5 (20.0)	20 (83.3)/4 (6.7)	0.697
Body mass index (kg/m^2)	24.7 ± 3.8	25.2 ± 3.4	0.680
Diabetes	5 (20.0)	10 (41.7)	0.181
Hypertension	10 (40.0)	8 (33.3)	0.751
COPD	2 (8.0)	1 (4.2)	0.606
ASA classification			0.606
	2 (8.0)	1(4.2)	
	24 (92.0)	23 (95.8)	
Tumor type			1.000
HCC	24 (96.0)	22 (91.7)	
Metastatic	1 (4.0)	2 (8.3)	
Tumor size (cm)	1.72 ± 0.49	1.44 ± 0.56	0.110
ABGA			
pH (mmHg)	7.42 ± 0.02	7.42 ± 0.02	0.839
$PaCO_2$ (mmHg)	37.4 (34.8 – 40.2)	37.4 (31.8 – 38.9)	0.235
PaO_2 (mmHg)	88.3 ± 15.6	98.5 ± 17.2	0.055
HCO_3^- (mmol/l)	24.1 ± 2.8	23.1 ± 3.1	0.279

Data are expressed as the means ± standard deviations, median (interquartile range), or number of patients (percentage), as appropriate.

HFNC, high flow nasal cannula; COPD, chronic obstructive pulmonary disease; ASA, American society of anesthesiologist; HCC, hepatocellular carcinoma; AGBA, arterial blood gas analysis; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen.

Table 4. Intraprocedural characteristics and technical data

	Mask (n = 25)	HFNC (n = 24)	*p*
Total ablation time (min)	13.1 (6.0 – 17.25)	10.5 (6.0 – 13.0)	0.286
Sedation time (min)	37.1 (27.5 – 42.5)	33.0 (25.6 – 39)	0.287
Total dose of propofol (mg)	83.5 (62.5 – 91.9)	82.0 (56.9 – 99.4)	0.681
Total dose of remifentanil (ng)	90.0 (69.7 – 104.8)	88.5 (62.6 – 96.5)	0.390
Type of procedure			0.536
Conventional	15 (60.0)	11 (45.8)	
Microwave	10 (40.0)	13 (54.2)	
Use of artificial ascites	8 (32.0)	9 (3757)	1.000

Data are expressed as the mean ± standard deviation, median (interquartile range), or number of patients (percentage) as appropriate.

HFNC, high flow nasal cannula

Primary Outcomes

Our primary outcomes, intraprocedural PaO_2 and the difference of pre- and intraprocedural PaO_2 were significantly different between two groups. Both parameters of group HFNC were significantly higher than mask group. Intraprocedural PaO_2 of mask group and HFNC group were 199.9 (154.3 – 224.9) and 287.0 (191.3 – 379.9) mmHg, respectively ($p = 0.009$; Fig. 2) and the differences of pre- and intraprocedural PaO_2 of mask group and HFNC group were, 111.6 (67.4 – 141.8) and 188.5 (100.1 – 280.3) mmHg, respectively ($p = 0.009$; Fig. 3).

The incidence of hypoxic event was not significantly different between two groups. (36% of mask group vs. 25.0% of HFNC group, $p = 0.505$; Fig. 4). However, the incidence of severe hypoxic event was significantly lower in HFNC group than mask group. (32% of mask group vs. 4.2% of HFNC group, $p = 0.045$; Fig. 5).

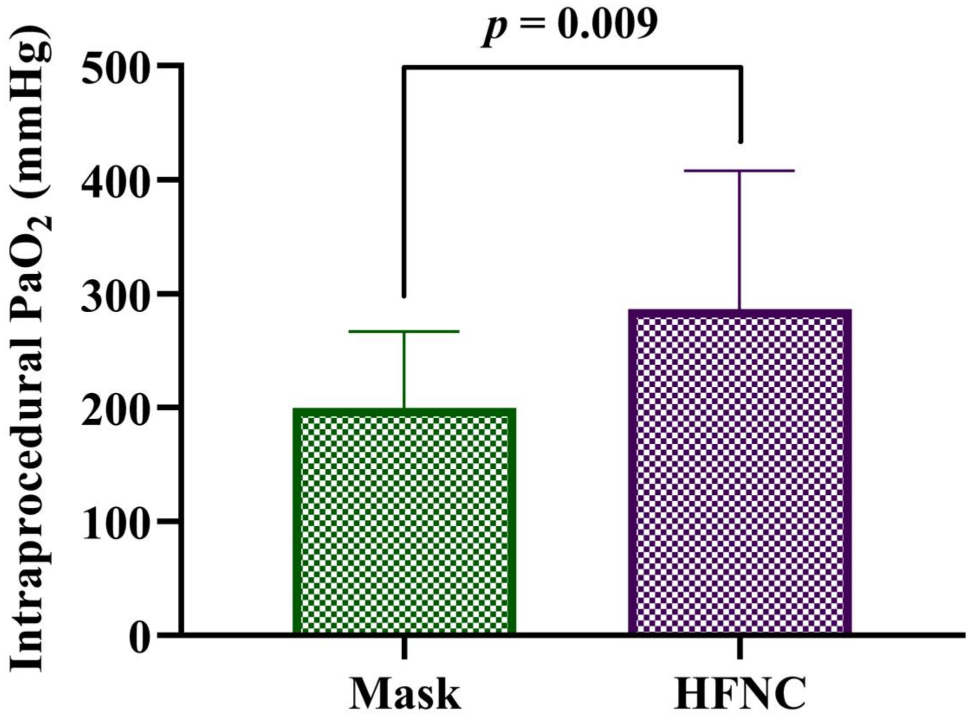

Figure 2. The difference of intraprocedural PaO_2

Data are expressed as the median (interquartile range).

Intraprocedural PaO_2 of HFNC group was significantly higher than mask group [199.9 (154.3 – 224.9) vs. 287.0 (191.3 – 379.9) mmHg, respectively ($p = 0.009$)].

PaO_2, partial pressure of arterial oxygen; HFNC, high flow nasal cannula.

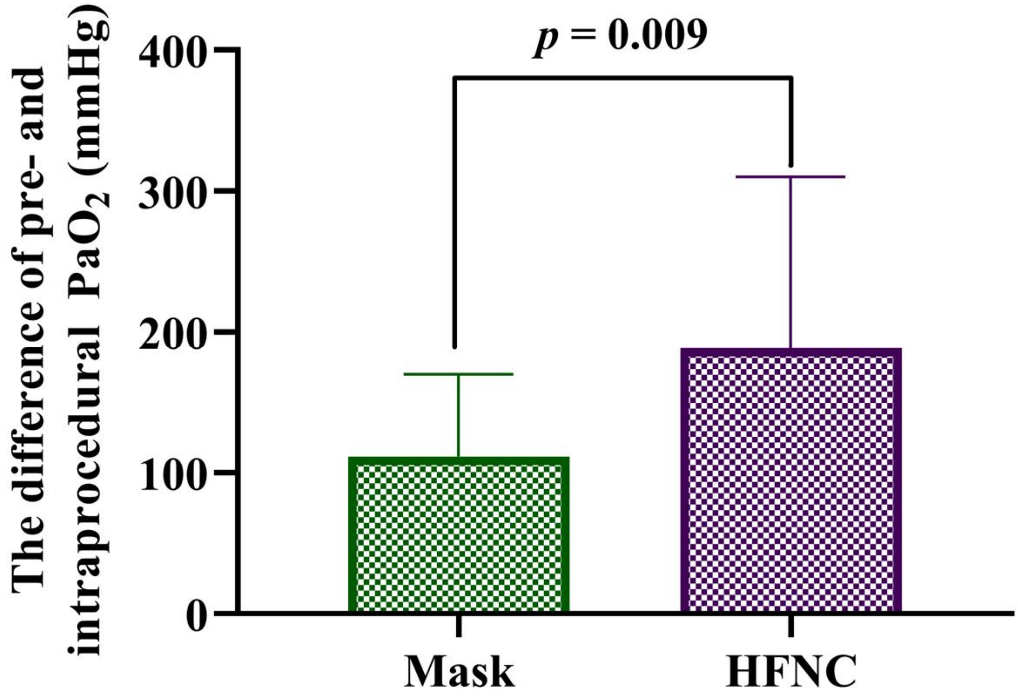

Figure 3. The difference of the difference of pre- and intraprocedural PaO_2

Data are expressed as the median (interquartile range).

The difference of pre- and intraprocedural PaO_2 of HFNC group was significantly higher than mask group [111.6 (67.4 – 141.8) vs. 188.5 (100.1 – 280.3) mmHg, respectively ($p = 0.009$)].

PaO_2, partial pressure of arterial oxygen; HFNC, high flow nasal cannula.

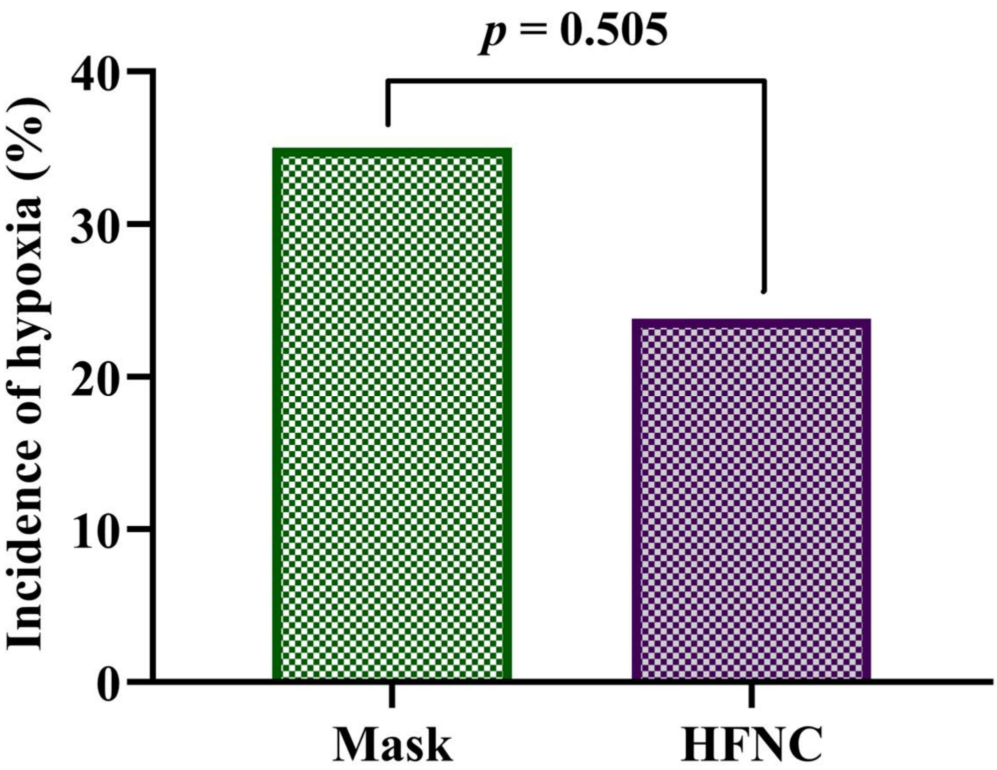

Figure 4. The difference of the incidence of hypoxic event

Data are expressed as the number (percentage).

We defined hypoxic events as a SpO_2 <95% at any time of procedure.

The incidence of hypoxic event was not significantly different between two groups (36% of mask group vs. 25.0% of HFNC group, respectively; $p = 0.505$).

HFNC, high flow nasal cannula.

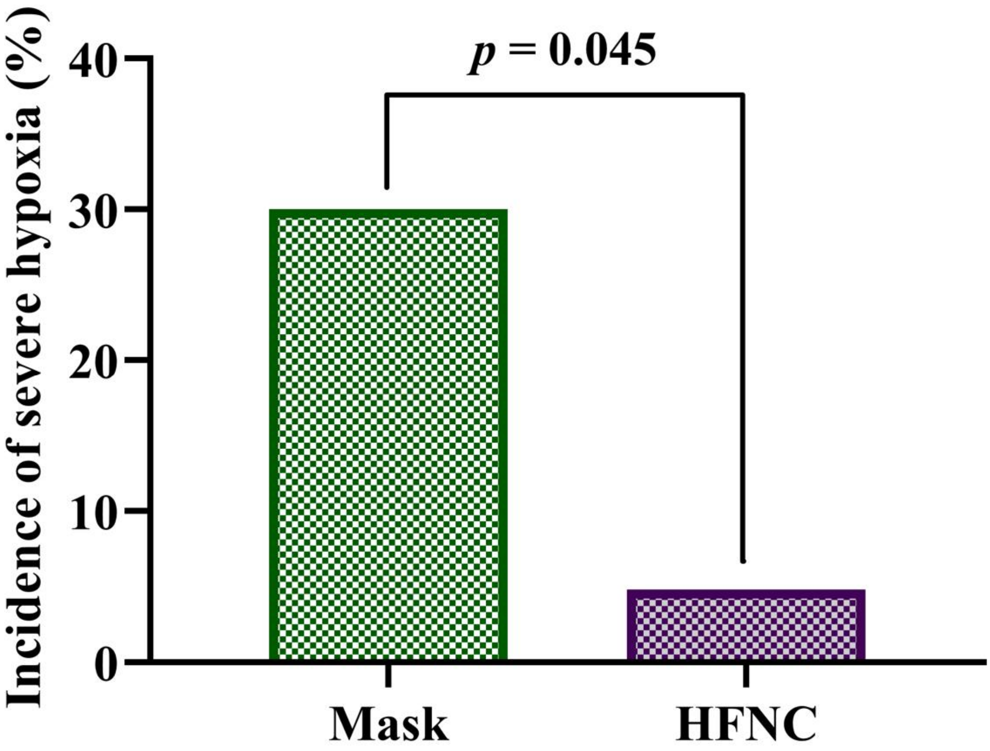

Figure 5. The difference of the incidence of severe hypoxic event

Data are expressed as the number (percentage).

We defined severe hypoxic event as a $SpO_2 < 90\%$ despite of triple airway maneuvers.

The incidence of severe hypoxic event was significantly different between two groups (32% of mask group vs. 4.2% of HFNC group, respectively; $p = 0.045$).

HFNC, high flow nasal cannula.

Secondary Outcomes

Intraprocedural PaO_2/FiO_2 were significantly different between two groups. PaO_2/FiO_2 of mask group was significantly higher than HFNC group. [399.9 (308.6 – 449.7) and 287.0 (191.3 – 379.9) mmHg, respectively ($p = 0.005$; Fig. 6).

The differences of pre- and intraprocedural $PaCO_2$ were not significantly different between two groups [12.4 (9.1 – 16.7) mmHg in mask group vs. 13.8 (10.0 – 17.8) mmHg in HFNC group, respectively ($p = 0.823$)] (Fig. 7).

Repeated measures ANOVA indicated significant differences between groups in terms of the RR ($F = 7.944$; $p = 0.08$; Fig. 8). Post-hoc analysis showed a significant reduction of RR in mask group in comparison with HFNC group during the procedure ($p = 0.001$) and post-procedure ($p < 0.001$), respectively. There were significant differences in ISAS between two groups. Patients in mask group were more satisfied than HFNC [60.6 (56.8 – 66) vs. 54.0 (44.0 – 62.0), respectively; $p =0.031$] (Fig. 9).

All patients were successfully complete the procedures and fully recovered by the end of procedure. There were no postprocedural complications in study population.

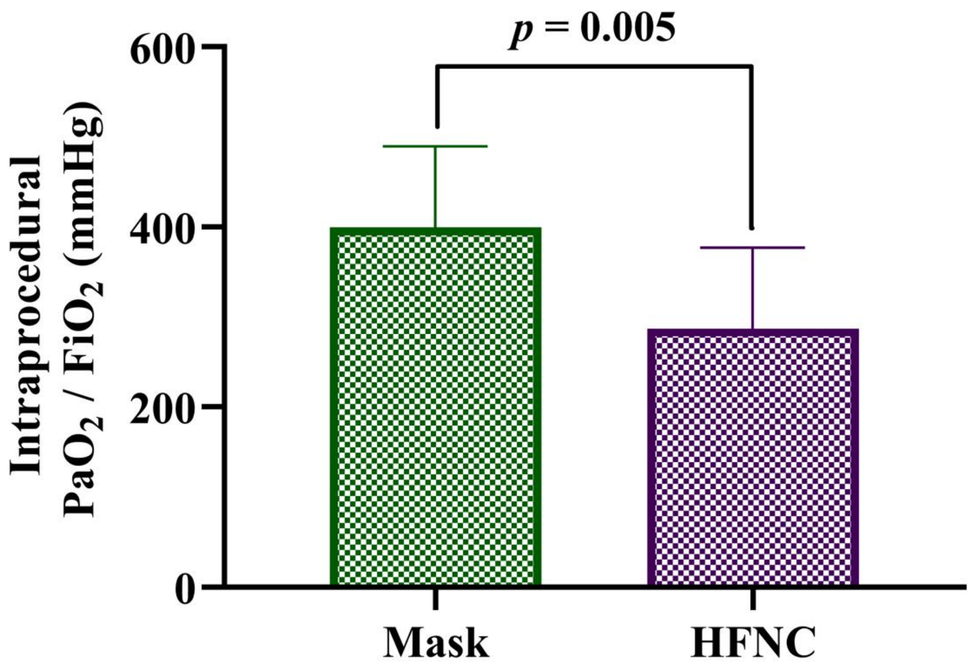

Figure 6. The difference of intraprocedural PaO_2/FiO_2

Data are expressed as the median (interquartile range).

Intraprocedural PaO_2/FiO_2 of mask group was significantly higher than HFNC group [399.9 (308.6 – 449.7) and 287.0 (191.3 – 379.9) mmHg, respectively ($p = 0.005$)].

PaO_2, partial pressure of arterial oxygen; FiO_2, inspiratory oxygen fraction; HFNC, high flow nasal cannula.

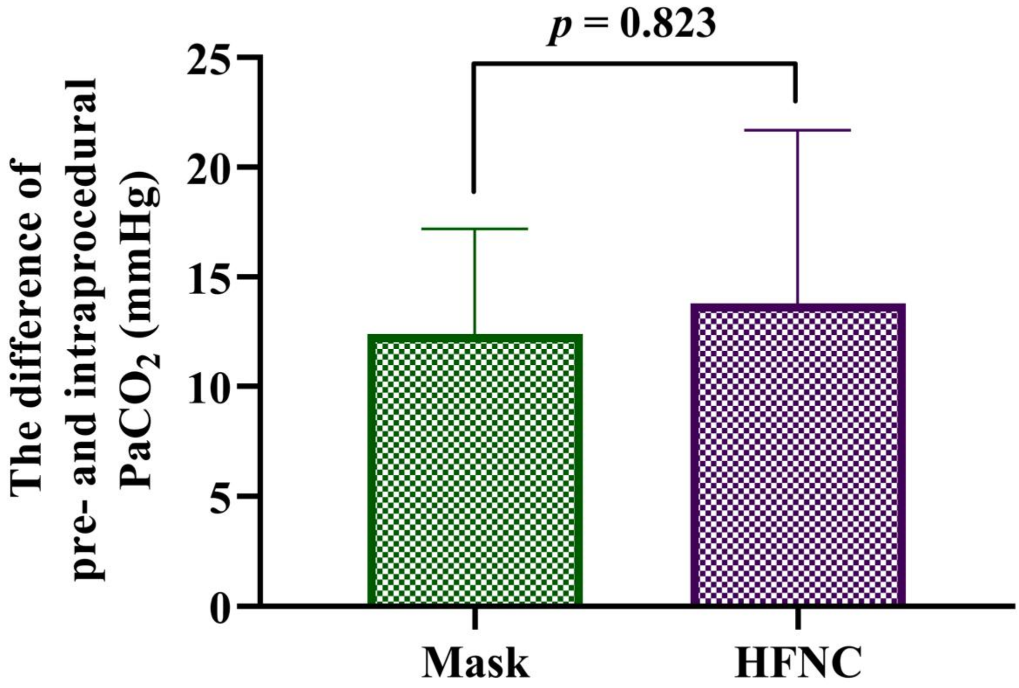

Figure 7. The difference of the differences of pre- and intraprocedural $PaCO_2$

Data are expressed as the median (interquartile range).

The differences of pre- and intraprocedural $PaCO_2$ was not significantly different between two groups. [12.4 (9.1 – 16.7) mmHg in mask group vs. 13.8 (10.0 – 17.8) mmHg in HFNC group, respectively; (p = 0.823)].

$PaCO_2$, partial pressure of arterial carbon dioxide; HFNC, high flow nasal cannula.

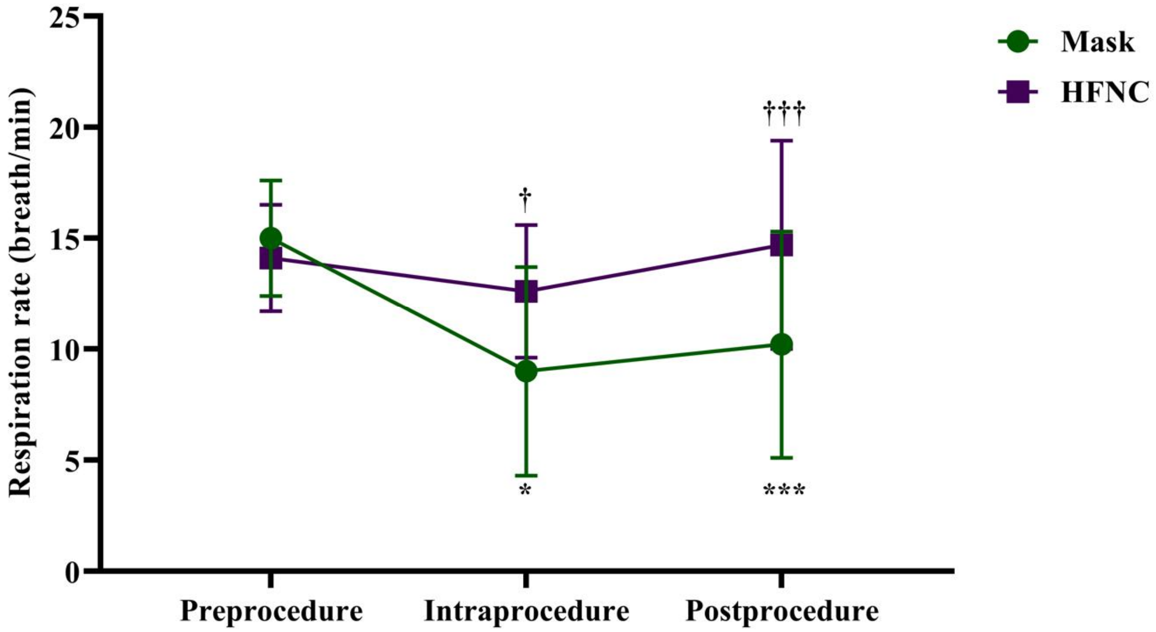

Figure 8. Change of respiration rate (RR) during procedure

Data are expressed as the mean ± standard deviation or median (interquartile range) as appropriate.

In mask group, intra- and post-procedural RR were significantly lower than pre-procedure [15.0 (13.2 – 17.0) of pre-procedure vs. 9.0 (4.3 – 12.0) of intra-procedure; †$p < 0.001$ and 15.0 (13.2 – 17.0) of pre-procedure vs 10.2 (7.0 – 12.8) of post-procedure; ††$p = 0.001$]. There were no inter-group differences in HFNC group.

There was significant reduction of RR in mask group in comparison with HFNC group during the procedure [9.0 (4.3 – 12.0) of mask group vs. 12.6 (10.0 – 14.5) of HFNC group; *p = 0.001] and post-procedure [10.2 (7.0 – 12.8) of mask group vs. 14.7 (11.0 – 17.5) of HFNC group; ***$p < 0.001$]

HFNC, high flow nasal cannula.

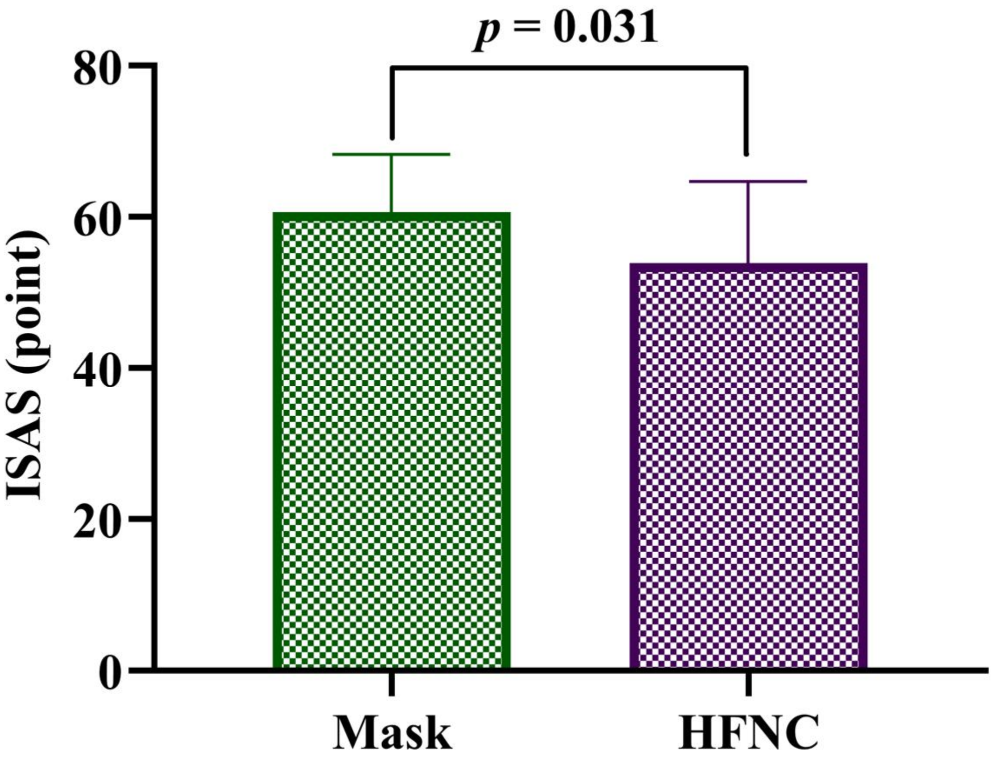

Figure 9. The difference of Iowa Satisfaction with Anesthesia Scale

Data are expressed as the median (interquartile range).

Mask group was more satisfied than HFNC group [60.6 (56.8 – 66) vs. 54.0 (44.0 – 62.0), respectively; p =0.031]

ISAS, Iowa Satisfaction with Anesthesia Scale; HFNC, high flow nasal cannula.

Discussions

This prospective, randomized, study showed that HFNC improve arterial oxygen contents during percutaneous RFA of hepatic neoplasm under MAC compare with simple facemask. Moreover, HFNC can reduce the incidence of severe hypoxic event.

Common complications of MAC are oxygen desaturation, apnea, airway obstruction, hemodynamic instability [13, 42-44]. Above all, hypoxia is the most common complication during MAC and the most common cause of hypoxia is respiratory depression [13].

The mechanism of action of propofol associated with a positive modulation of the inhibitory function of the neurotransmitter gamma aminobutyric acid (GABA) through $GABA_A$ receptors. GABA is the major inhibitory neurotransmitter in the central nerves system (CNS) [45]. As mentioned earlier, the most serious complication of propofol is respiratory depression. Propofol induces central respiratory depression by $GABA_A$ receptors mediated hyperpolarization of pre-inspiratory neurons [46]. Moreover, this respiratory depression is more serious the combination of opioids such as remifentanil [47]. Respiratory depressant effects of opioids are caused by activation of opioid receptors expressed on neurons within the respiratory networks of the brainstem [47-49]. In this context, cautious monitoring and intense patient care should be need MAC with propofol-remifentanil. To prevent hypoxia, ASA recommended that oxygen should be administered during deep sedation without specifically contraindicated for a particular patient or procedure and recommend capnography monitoring [2].

Compared with simple facemask, HFNC can improve oxygenation by several mechanisms. First, heated, and humidified oxygen may improve secretion clearance, decrease airway inflammation [50, 51] Standard oxygen therapy delivered through simple face mask delivers cold and dry gas. This cold, dry gas can lead to airway inflammation, increase airway resistance, and impair mucociliary function. Second, HFNC can improve patient's work of breathing.

Third, although some debate is existed, HFNC may improve functional residual capacity because HFNC provides positive end-expiratory pressure (PEEP) [52]. Forth, HFNC can minimize oxygen dilution by meeting flow demands. Last, HFNC can reduce dead-space. HFNC provide a continuous flow of fresh gas at high-flow rates which can replace or wash out the patient's pharyngeal dead-space. Thus, the patient receives oxygen-rich gas instead of the old gas (low in oxygen and high in CO_2) [53]. Moreover, some studies showed that the HFNC improve apneic oxygenation [54, 55]. In this context, we think that HFNC might beneficial during RFA under MAC with propofol and the incidence of severe hypoxic event of HFNC group was lower than mask group in this study.

However, HFNC did not reduce the incidence of overall hypoxic events in this study. Propofol induced hypoxia may occur not only direct action of CNS system, but also indirect effect on the upper airway tract. Propofol affects upper airway obstruction by relaxation of tongue and pharyngeal muscles, which causes narrowing or closing of the upper airway space [19, 56]. Teng et al. [57] investigate that the difference of the incidence of hypoxic event during gastroscopy under sedation according to oxygen delivery device and airway device. They reported that mandibular advancement device which mimics the jaw thrust action by holding the mandible in a forward position [58] shows lower incidence of hypoxia than conventional nasal cannula. This finding reflects that maintain the patency of upper airway tract is important to prevent hypoxia during sedation. So, we think that airway obstruction is a greater cause than respiratory depression in the occurrence of hypoxic event during RFA under MAC with propofol-remifentanil. In this study, we applied triple airway maneuvers as soon as SpO_2 <95% because the safety issue. And it means that we removed the main cause of hypoxia immediately. After then, HFNC can reduce the incidence of severe hypoxic event. It may reflect that HFNC does not reduce the airway obstruction but improve apneic oxygenation.

However, many studies shows that HFNC (flow up to 50 L/minute) can generate positive airway pressure (PAP) (up to 7.1 mmHg) in the pharyngeal space [59-61]. Eastwood et al. [62] reported that up to 11.8 ± 2.7 mmHg of upstream pressure was require to maintain airway patency. In the present study, the flow rate of HFNC was 30 L/minute and it might not enough to generate adequate PAP. A randomized multicenter clinical trial by Lin and colleague [18] may support our hypothesis. They compared the incidence of hypoxia between the conventional nasal cannula group and HFNC during gastroscopy with propofol sedation and they reported that the incidence of hypoxia in HFNC group was 0%. To compare our study, the differences are flow rate of HFNC and patient positioning. Lin et al. applied HFNC flow rate up to 60 L/minute and all patients were in lateral position and in present study applied 30 L/minute flow rate and supine position. Higher flow rate might be made higher PAP in airway tract and lateral position might be helpful to maintain airway patency.

If upper airway obstruction may be a main cause of hypoxia, simple facemask has a great advantage compared to HFNC which can use of capnography. Capnography can early detect airway obstruction and hypoxia during sedation because it provides continuous, real-time, breath-to- breath feedback on the clinical status of the patient [63-65]. High oxygen flow rates during HFNC would severely dilute expired carbon dioxide and make sampling end-tidal carbon dioxide ($ETCO_2$) impossible [66].

Other finding of present study is the difference of ISAS. ISAS is known as a reliable, valid, and useful questionnaire for measuring patient satisfaction with MAC [41]. The ISAS literally measures satisfaction with the anesthetic, unlike assessments of satisfaction with the perioperative period that are the suitable options for patients who are unconscious for some or all of the period that the patient considers to be the anesthetic [38]. ISAS of HFNC group was significantly lower than simple mask group. We do not know the exact reason for the difference in ISAS between two groups why because ISAS reflects satisfaction of overall anesthesia. According the literature, most patients who receive the HFNC therapy were tolerable but, some patients might be felt uncomfortable because intense arrival of constant air associated with difficulty in expiration and chest tightness [67]. And other reason we think is that HFNC might be unfamiliar to patients than simple face mask.

This study has some limitations. First, this study was not completely blinded because these two devices were completely different. To minimize the bias, we performed blinded evaluation of postprocedural data. Second, we decided the PaO_2/FiO_2 as a secondary outcome. In this study, the FiO_2 of two devices were different. In this situation, PaO_2/FiO_2 may more accurately reflect arterial oxygenation. However, as mentioned earlier, the FiO_2 of simple mask is unpredictable which is depending on the patient's respiratory pattern. So, we inevitably had to show the calculated result with FiO_2 of simple mask as a 0.5. In this context, we think that our primary outcomes are more reflective the "real" practice condition. Third, the onset of time to onset of hypoxia and the length of desaturation was not collected. These are reflected apneic oxygenation and theoretically HFNC improve this. If we had collected these data, we could more clearly explain the relationship between the reduced the incidence of severe hypoxic event and the effect of HFNC on apneic oxygenation. Fourth, we did not collect obstruction related factor such as history of obstructive sleep apnea and nasopharyngeal pressure. And we fixed flow rate of HFNC. Because we think that propofol induced central respiratory depression is major cause of hypoxia. Last, we did not concern cost-effectiveness. Further studies that concern these limitations are needed to clarify the usefulness of HFNC on RFA under MAC with propofol-remifentanil.

Even concern these limitations, this study would be meaningful because this is the first randomized controlled study to comparing the effect of HFNC versus simple facemask in the patients undergoing percutaneous RFA under MAC with propofol-remifentanil. And our results reflect that HFNC is useful in real practice condition because it can reduce the incidence of severe hypoxic event. Moreover, we suggest that the main cause of hypoxia during RFA under

MAC may be an airway obstruction. These findings may be helpful to treat the patients who undergoing RFA under MAC with propofol-remifentanil.

Conclusion

The use of HFNC improve oxygen profile and reduce the incidence of severe hypoxic event in patients undergoing percutaneous RFA under MAC with propofol-remifentanil.

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국문 요약

연구 제목: 프로포폴과 레미펜타닐을 이용한 감시마취에서 산소공급을 위해 사용하는 고유량 비강 캐뉼라와 단순 마스크의 효과 비교

연구 목적: 경피적 고주파 열 치료는 간의 신생물에 효과적이고 안전한 치료법으로 알려져 있으나, 이 시술은 심한 통증을 동반하기에 프로포폴과 레미펜타닐을 사용한 감시마취하에 이루어진다. 하지만 두 약제의 조합은 심각한 호흡 저하를 유발 할 수 있다. 최근 몇몇 연구에서 고유량 비강 캐뉼라가 시술 중 저산소증의 발생을 줄여준다고 보고하고 있다. 이에 이 연구에서는 단순마스크와 고유량 비강 캐뉼라의 유용성을 비교해본다.

연구 방법: 이 무작위 대조군 연구에서는 정규로 고주파 열치료를 받는 환자 41명을 두 군으로 나누었다. 산소 투여 방법은 단순 마스크 (Mask group) 나 고유량 비강 캐뉼라 (HFNC group) 로 이루어졌고 이외의 진정은 두 군이 동일하게 프로포폴과 레미펜타닐을 지속 정주 하였다. 주 변수는 시술 중 동맥혈 산소분압, 시술 전 후의 동맥혈 산소 분압차, 저산소증의 발생 빈도이고, 보조 변수는 시술 중 동맥혈 산소 분압과 흡입산소 농도의 비율, 시술 전 후의 동맥혈 이산화탄소 분압차, 호흡수 변화, 환자 만족도이다.

연구 결과: 두 군간 시술 중 동맥혈 산소 분압 [199.9 (154.3 – 224.9) and 287.0 (191.3 – 379.9) mmHg; $p = 0.009$], 시술 전 후의 동맥혈 산소 분압차 [111.6 (67.4 – 141.8) and 188.5 (100.1 – 280.3) mmHg; $p = 0.009$] 는 고유량 비강 캐뉼라 군에서 유의하게 높았다. 저산소증의 발생 빈도는 두 군간 차이가 없었지만. (36% of mask

group vs. 25.0% of HFNC group, p = 0.505). 심각한 저산소증의 발생은 감소시켰다 (32% of mask group vs. 4.2% of HFNC group, p = 0.045). 시술 중 동맥혈 산소 분압과 흡입 산소 농도의 비율은 마스크 그룹에서 더 높았다 [399.9 (308.6 – 449.7) and 287.0 (191.3 – 379.9) mmHg; *p* = 0.005)]. 시술 전 후의 동맥혈 이산화탄소 분압차는 차이를 보이지 않았고 [12.4 (9.1 – 16.7) and 13.8 (10.0 – 17.8) mmHg; *p* = 0.823]. 호흡수는 두 군간 유의한 차이를 보였다 (F = 7.944; *p* = 0.08). 환자 만족도는 단순 마스크 군에서 유의하게 높았다 [60.6 (56.8 – 66) vs. 54.0 (44.0 – 62.0), *p* =0.031].

연구 결론: 고유량 비강 캐뉼라는 프로포폴을 사용한 간의 고주파 열치료의 감시마취에서 동맥혈 산소 분압을 올리고 심각한 저산소증의 발생을 줄인다.

중심 단어: High flow nasal cannula, Face mask, Hypoxia, Monitored anesthesia care