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Original Article

Pre-oxygenation using high-flow nasal oxygen vs. tight facemask during rapid sequence induction

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Summary

Pre-oxygenation using high-flow nasal oxygen can decrease the risk of desaturation during rapid sequence induction in patients undergoing emergency surgery. Previous studies were single-centre and often in limited settings. This randomised, international, multicentre trial compared high-flow nasal oxygen with standard facemask pre-oxygenation for rapid sequence induction in emergency surgery at all hours of the day and night. A total of 350 adult patients from six centres in Sweden and one in Switzerland undergoing emergency surgery where rapid sequence induction was required were included and randomly allocated to pre-oxygenation with 100% oxygen using high-flow nasal oxygen or a standard tight-fitting facemask. The primary outcome was the number of patients developing oxygen saturations <93% from the start of pre-oxygenation until 1 min after tracheal intubation. Data from 349 of 350 patients who entered the study were analysed (174 in the high-flow nasal oxygen group and 175 in the facemask group). No difference was detected in the number of patients desaturating <93%, five (2.9%) vs. six (3.4%) patients in the high-flow nasal oxygen and facemask group, respectively ($p = 0.77$). The risk of desaturation was not increased during on-call hours. No difference was seen in end-tidal carbon dioxide levels in the first breath after tracheal intubation or in the number of patients with signs of regurgitation between groups. These results confirm that high-flow nasal oxygen maintains adequate oxygen levels during pre-oxygenation for rapid sequence induction.

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Introduction

Rapid sequence induction (RSI) is a high-risk procedure. Patients undergoing emergency surgery are more likely to develop hypoxia [1] and, therefore, pre-oxygenation before anaesthesia induction is of critical importance [2]. Administration of low-flow oxygen with nasal cannulae has been shown to extend the time until desaturation in an apnoeic patient [3-5], but the incidence of desaturation during RSI is still high [1,6] and contributes significantly to adverse events and poor outcome [7,8].

High-flow nasal oxygen can be used to prolong apnoea time up to 1 h [9] and has been used during laryngeal surgery with apnoea times up to 30 min [10,11], and during RSI [12,13]. In previous studies, high-flow nasal oxygen during RSI has been compared with pre-oxygenation conducted with a tight-fitting facemask, as this is standard practice. It was demonstrated that high-flow nasal oxygen preserved oxygen saturation to an equal extent as facemask pre-oxygenation, with some other potential benefits [12,13]. Notably, these studies were single-centre and in a limited number of patients. One of these studies was conducted during office hours only [12] and both were strictly monitored by the research groups [12,13]. It has previously been shown that cognitive performance among staff and patient outcomes can differ between day and night [14,15]. Therefore, it remains to be determined whether this technique of pre- and peri-oxygenation during RSI is safe to use more widely.

This study compared high-flow nasal oxygen with tight-fitting facemask pre-oxygenation during RSI in patients undergoing emergency surgery in several different centres in two countries and at all times of the day and night.

Methods

This international, prospective, randomised, controlled multicentre trial was conducted in six centres in Europe: Karolinska University Hospital (Stockholm); Capio S:t Göran Hospital (Stockholm); South General Hospital (Stockholm); Karlstad Central Hospital (Karlstad); Linköping University Hospital (Linköping), all in Sweden; and at the University Hospital of Bern, Switzerland, between March 2018 and February 2020. Ethical and institutional approvals were acquired in both countries before patient enrolment. Adult patients undergoing emergency surgery where RSI was planned were consecutively enrolled around the clock. Exclusion criteria were: BMI > 35 $kg.m^{-2}$; pregnancy; need for non-invasive ventilation before anaesthesia; or not reaching S_pO_2 > 93% during pre-oxygenation. Patients who had already been included and those unable to give consent were also not analysed. Patients were asked to participate during the pre-anaesthetic evaluation. Oral and written information were given, and a consent form was signed. Patients were randomly allocated to either pre-oxygenation with high-flow nasal oxygen or with a tight-fitting facemask. This was done using sealed envelopes assigned in a 1:1 ratio in block sizes of 10.

On arrival in the operating theatre, ECG, pulse oximetry and blood pressure measurement, invasive or non-invasive, were applied. A majority of the centres used monitors and S_pO_2 sensors manufactured by Philips (Intellivue MX800 with X2 or X3 and M1191B glove sensor or FAST S_pO_2, Amsterdam, The Netherlands). One centre (Capio S:t Göran Hospital) used the Carescape monitor B650 (Datex Ohmeda, Helsinki, Finland) and the TrueSignal SpO_2 sensor (GE Healthcare, Helsinki, Finland) while another (Linköping University Hospital) used a monitor manufactured by Masimo (Masimo Corporation, Irvine, CA, USA). An intravenous line was secured, and a standard infusion of electrolyte solution was started. Patients were then placed supine in a reverse Trendelenburg position. Rapid sequence induction was performed according to local routines at each hospital [16]. Drugs and doses used were determined by the anaesthetist in charge. Pre-oxygenation was conducted for a minimum of 3 min. High-flow nasal oxygen was administered using specifically designed cannulae (Optiflow TM, Fisher and Paykel Healthcare, Auckland, New Zealand) with 30–50 $l.min^{-1}$ of heated and humidified oxygen. Patients could breathe with an open or closed mouth. Once apnoea occurred, oxygen flow was increased to 70 $l.min^{-1}$ and administered continuously until the tracheal tube was in place. In the standard group, patients breathed 100% oxygen via a tight-fitting facemask with a fresh gas flow of 10 $l.min^{-1}$ delivered via a circle system [2]. In both groups, chin lift and/or jaw thrust was used during apnoea to maintain an open airway.

Conditions at tracheal intubation, such as: Cormack-Lehane laryngoscopy grade; number of attempts; need for airway equipment other than the Macintosh laryngoscope size 3; and signs of gastric regurgitation, were recorded. During induction of anaesthesia, the duration of apnoea (apnoea time) and the time needed to intubate the trachea (intubation time) were measured. Apnoea time was defined as start of apnoea until a carbon dioxide trace was visible with capnography. The time needed to intubate the trachea was measured from when the laryngoscope passed the teeth until a carbon dioxide trace was visible with capnography. The lowest S_pO_2 from start of pre-oxygenation until 1 min after intubation was noted. Patients not reaching S_pO_2 > 93% during pre-oxygenation were not included. If a patient desaturated before intubation, the

anaesthetist decided whether to start mask ventilation. The lowest saturation before mask ventilation was then noted.

In both groups, end-tidal carbon dioxide ($ETCO_2$) was measured immediately before the start of pre-oxygenation via a tight occluding facemask delivering room air. In the facemask group, $ETCO_2$ and end-tidal oxygen (ETO_2) were also measured at the time of induction. In both groups, $ETCO_2$ and ETO_2 were measured in the first breath after tracheal intubation (Aisys Carestation, GE Healthcare, Waukesha, WI, USA or FLOW-i, Maquet Critical Care AB, Solna, Sweden/Avance CS^2, GE Healthcare, Waukesha, WI, USA). Collection of data ended 1 min after intubation. Office hours were defined as Monday to Friday, 07.30 to 16.00. All other times were defined as on-call hours.

Primary outcome was the number of patients who developed oxygen saturation <93% from the start of pre-oxygenation until 1 min after intubation. Our secondary outcomes investigated end-tidal gas concentrations in the first breath after intubation and number of patients with signs of gastric regurgitation. We also explored differences between centres as well as the effect of office hours vs. on-call hours.

The primary outcome was difference in number of patients developing oxygen saturation <93% on a peripheral pulse oximeter. In a previous study of RSI, none of the patients pre-oxygenated with high-flow nasal oxygen desaturated to <93% vs. 12.5% in the facemask group [12]. In accordance with this, we based the sample size calculation on the assumption of 10% desaturation in the facemask group and 2.5% in the high-flow nasal oxygen group. Using a type-1 error of 5% and a type-2 error of 20% (power 80%), a sample size of 326 was estimated. In order to adjust for a slightly different result and dropouts, we aimed to include 350 patients.

Differences between the groups were investigated using an unpaired two-sample t-test or a Mann–Whitney U-test depending on the distribution. Categorical data were analysed using a Chi-square test or, in case of sample size assumption violation, a Fisher's exact test. The primary outcome was analysed using a chi-square test. A value of $p < 0.05$ was considered statistically significant. All tests were performed using SPSS Statistics® 26 (IBM®, Armonk, NY, USA).

Results

A total of 350 patients were randomly allocated to either pre-oxygenation with high-flow nasal oxygen or facemask (Fig. 1). One patient was not included because of a protocol violation (the ventilator was mistakenly set to deliver room air). Due to difficulties with tracheal intubation and a long apnoea time, two patients were ventilated during the apnoeic phase. One patient was ventilated during the apnoeic phase without specification of the reason. All three had $S_pO_2 > 97$ % when apnoea was interrupted. These

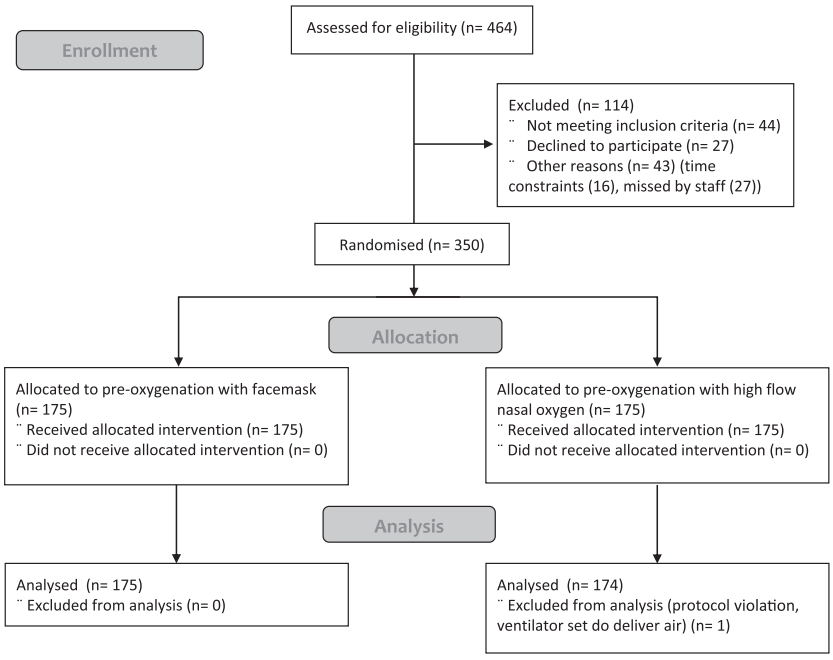

Figure 1 Study flow diagram. A total of 350 patients were eligible; 114 patients were not included. One patient was not included due to protocol violation.

three patients were included in the results and data from a total of 349 patients were, therefore, analysed. There were no differences detected in patient or airway characteristics between the groups (Tables 1 and 2). There was a slightly longer apnoea time and intubation time in the high-flow nasal oxygen group (Table 3). Other than that, conditions at intubation were similar between groups (Table 3).

No difference was seen in the number of patients developing S_pO_2 < 93% between groups from the start of pre-oxygenation until 1 min after intubation. Oxygen saturation dropped <93% in five patients (2.9%) in the high-flow nasal oxygen group compared with six (3.4%) in the facemask group (p = 0.77) (Fig. 2). There was no difference in lowest mean S_pO_2 from start of pre-oxygenation until 1 min after intubation between the groups: mean (SD) 99.1% (2.5%) vs. 99.0% (2.8%) in the high-flow nasal oxygen and facemask group, respectively.

Table 1 Characteristics of 349 patients pre-oxygenated with high-flow nasal oxygen or facemask for rapid sequence induction of anaesthesia. Pulmonary comorbidity included asthma (19), obstructive sleep apnoea syndrome (10), chronic obstructive pulmonary disease (7), pleuritis/pneumonia (5), lung cancer (3), pulmonary embolism (2), pneumothorax (1), pulmonary fibrosis (1), pleural effusion (1). Three patients had no condition specified and three suffered a combination of pulmonary diseases. Surgery specified as 'other' included ear, nose and throat and neurosurgery. Values are mean (SD) or number (proportion).

	High-flow nasal oxygen n = 174	Facemask n = 175
Sex; male	86 (49.1)	89 (50.9)
Age; year	52.1 (20.7)	50.3 (18.7)
BMI; $kg.m^{-2}$	25.1 (4.1)	25.5 (4.3)
Smoker	34 (19.5%)	32 (18.4%)
ASA physical status		
1	44 (25.3%)	57 (32.6%)
2	76 (43.7%)	59 (33.7%)
3	45 (25.9%)	43 (24.6%)
4	9 (5.2%)	15 (8.6%)
5	0	1 (0.6%)
Pulmonary comorbidity (other)	23 (13.2%)	32 (18.3%)
Pre-operative O_2 treatment	12 (6.9%)	10 (5.7%)
Type of surgery		
Abdominal	132 (75.9%)	119 (68.4%)
Intervention/endoscopy	17 (9.8%)	19 (10.9%)
Gynaecological/urological	8 (4.6%)	13 (7.5%)
Orthopaedic	13 (7.5%)	16 (9.2%)
Other	4 (2.3%)	7 (4.0%)

The number of patients developing S_pO_2 < 93% did not significantly differ between centres (Fig. 3). There was, however, a higher incidence of patients developing S_pO_2 < 93% in Switzerland (7%) compared with Sweden (1.6%) (p = 0.009). The same could be seen when only looking at the high-flow nasal oxygen group where one out of 124 (0.8%) Swedish patients desaturated <93% while 4 out of 50 (8%) Swiss patients did (p = 0.024). Furthermore, Swiss patients having high-flow nasal oxygen had longer apnoea and intubation times than those in Sweden: mean (SD) 125.6 s (66.9 s) and 64.2 s (60.8 s) vs. 102.2 s (35.7 s) and 47.2 s (24.2 s) (p = 0.004, p = 0.013).

A total of 214 patients were anaesthetised during office hours and 135 during on-call hours. Of the 11 patients developing S_pO_2 < 93%, 10 did so during office hours and only one during on-call hours (p = 0.06). No difference in levels of $ETCO_2$ in the first breath after intubation could be seen between the groups (Table 3). There were, however, higher levels of ETO_2 seen in the first breath after tracheal intubation in the facemask group (Table 3).

The person intubating the trachea was responsible for inspecting the pharynx for any signs of regurgitation. This was seen in one patient in the high-flow nasal oxygen group and in none of the patients with facemask. The anaesthetist in charge decided what drugs and doses were to be used

Table 2 Airway characteristics for 349 patients pre-oxygenated with high-flow nasal oxygen or facemask for rapid sequence induction of anaesthesia. Values are number (proportion).

	High-flow nasal oxygen n = 174	Facemask n = 175
Modified Mallampati score		
1	78 (46.4%)	73 (44.8%)
2	63 (40.5%)	62 (38.0)
3	22 (13.1%)	25 (15.3%)
4	5 (3.0%)	3 (1.8%)
Thyromental distance		
>7 cm	112 (64.7%)	116 (66.7%)
6–7 cm	49 (28.3%)	48 (27.6%)
<6 cm	12 (6.9%)	10 (5.7%)
Mouth opening		
>4 cm	145 (83.8%)	151 (86.3%)
2–4 cm	28 (16.2%)	24 (13.7%)
<2 cm	0	0
Neck movement		
Normal	164 (94.8%)	164 (93.7%)
Limited	9 (5.2%)	11 (6.3%)

Table 3 Condition at intubation, secondary outcomes and drugs used for 349 patients pre-oxygenated with high-flow nasal oxygen or facemask for rapid sequence induction of anaesthesia. Intubation adjuncts included use of Eschmann introducer, Macintosh #4 or video laryngoscope. Some patients were given a combination of drugs from each group, represented in the table as 'combination'. Values are number (proportion), median (IQR [range]) or mean (SD).

	High-flow nasal oxygen n = 174	**Facemask n = 175**	**p**
Condition at intubation			
Cormack–Lehane grade			0.46
1	126 (73.3%)	115 (66.1%)	
2	37 (21.5%)	49 (28.2%)	
3	7 (4.1%)	9 (5.2%)	
4	2 (1.2%)	1 (0.6%)	
Intubation attempts	1 (1–1 [1–4])	1 (1–1 [1–4])	0.83
Intubation adjuncts	84 (48.3%)	82 (46.9%)	0.61
Intubation time; s	52.1 (39.0)	47.6 (41.4)	0.015
Apnoea time; s	108.9 (47.8)	97.3 (53.4)	0.001
Secondary outcomes			
$ETCO_2$ in first breath after intubation; kPa	4.64 (0.8)	4.56 (0.8)	0.33
ETO_2 in first breath after intubation (%)	76.7 (16.1)	84.9 (7.7)	<0.001
Patients with signs of regurgitation	1 (0.6%)	0	0.50
Drugs			
Induction drug			0.17
Propofol	104 (59.8%)	102 (58.3%)	
Thiopentone	58 (33.3%)	68 (38.9%)	
Ketamine	4 (2.3%)	0	
Etomidate	1 (0.6%)	0	
Midazolam	0	0	
Combination	7 (4.0%)	5 (2.9%)	
Opioid			0.88
Fentanyl	96 (55.8%)	94 (54.3%)	
Alfentanil	59 (34.3%)	59 (34.1%)	
Remifentanil	8 (4.7%)	8 (4.6%)	
Sufentanil	0	1 (0.6%)	
Combination	10 (5.8%)	11 (6.4%)	
Neuromuscular block			0.86
Succinylcholine	116 (66.7%)	118 (67.4%)	
Rocuronium	58 (33.3%)	56 (32.0%)	
Combination	0	1 (0.6%)	

for each patient. In most cases, anaesthesia was accomplished by using three different agents: one opioid, one agent for induction and one neuromuscular blocking drug. Even though the regimen varied between centres, the drugs and doses did not differ between the two groups (Table 3).

Discussion

In contrast with our previous paper [12], this study was multicentre and conducted in all suitable patients requiring RSI irrespective of the day or time. It showed no difference in the number of patients desaturating <93% between pre-oxygenation using high-flow nasal oxygen vs. tight facemask.

More patients from the Swiss centre desaturated compared with Sweden. We also observed longer mean intubation and apnoea times among the Swiss patients in the high-flow nasal oxygen group compared with the Swedish patients pre-oxygenated with high-flow nasal oxygen. Differences in the routines regarding RSI or not sufficiently maintaining an open airway during apnoea

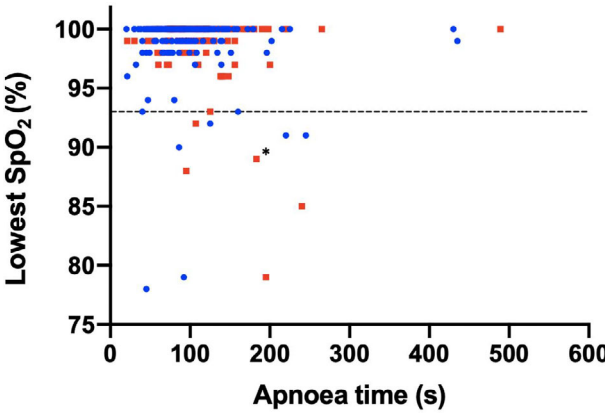

Figure 2 Oxygenation until 1 min after intubation. Lowest S_pO_2 (%) from start of pre-oxygenation until 1 min after intubation and apnoea time (s) is plotted for every patient pre-oxygenated with high-flow nasal oxygen (n = 174) or facemask (n = 175). High-flow nasal oxygen (red squares); facemask (blue dots). Desaturation was defined as S_pO_2 < 93% (dotted line). *No intubation time was noted. Therefore, this patient had the mean intubation time in the high-flow nasal oxygen group added to its apnoea time up until the laryngoscope passed the teeth.

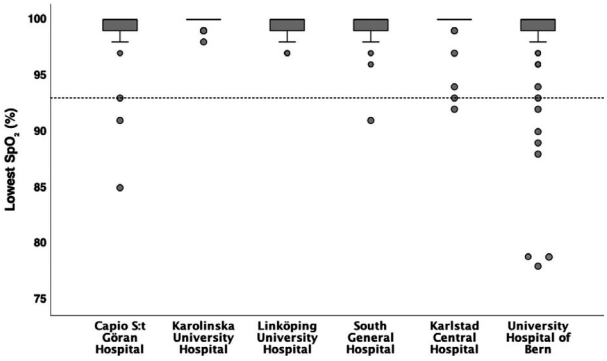

Figure 3 Lowest oxygen saturation among patients at the different centres. Boxplot comparing the lowest S_pO_2 (%) measured, from start of pre-oxygenation until 1 min after tracheal intubation, between patients from Capio S:t Göran Hospital (n = 50), Karolinska University Hospital (n = 49), Linköping University Hospital (n = 50), South General Hospital (n = 50), Karlstad Central Hospital (n = 50) and University Hospital of Bern (n = 100) when pre-oxygenated with high-flow nasal oxygen or facemask for rapid sequence induction of anaesthesia. Desaturation was defined as S_pO_2 < 93% (dotted line). No difference in number of patients desaturating below 93% could be seen between the individual centres (p = 0.15). Dark horizontal bar represents the median, the edges of the box show IQR and the whiskers the lower quartile, except outliers and extremes. Outlier and extremes are also shown.

might represent part of the explanation. Of the five patients that desaturated in the high-flow nasal oxygen group, none occurred during on-call hours. This suggests that the anaesthetist and staff that work on call correctly manage the technique of high-flow nasal oxygen including keeping the airway open.

High-flow nasal oxygen has been shown to reduce the increase in arterial carbon dioxide levels during apnoea by approximately 50%, thus allowing longer periods of apnoea [9, 10]. Recently, it has been demonstrated that high-flow nasal oxygen may cause carbon dioxide clearance by flow-dependent flushing [17]. In this study we demonstrated no difference in ETO_2 levels between the groups in the first breath after intubation even though the duration of apnoea was longer in the high-flow nasal oxygen group (Table 3). These results are in line with what has been presented in previous studies [12, 13].

Oxygen concentration in the first breath after pre-oxygenation was higher in the facemask group than in the high-flow nasal oxygen group. It is possible that the tubes to the ventilator have not been filled with 100% oxygen during oxygenation with high-flow nasal oxygen, as occurs with use of the facemask technique. The first breath given to the patient after intubation will, therefore, contain room air. This, in turn, affects the ETO_2 concentration in the first breath after intubation. Also, during pre-oxygenation, some of the patients in the high-flow nasal oxygen group were breathing with their mouth open. The fraction of inspired oxygen could, therefore, be lower than expected due to dilution as previously shown [18]. This might have affected the amount of oxygen stored in the lungs after pre-oxygenation which, in turn, could have had an impact on the ETO_2 in the first breath after intubation. Additionally, there is some evidence suggesting that the time necessary to pre-oxygenate above ETO_2 > 90% may be longer during high-flow nasal oxygen compared to facemask [19]. The main strength with high-flow nasal oxygen lies in its ability to continuously deliver oxygen to an apnoeic patient, that is, peri-oxygenation. The capacity of high-flow nasal oxygen to store oxygen might, therefore, not have the same clinical relevance as during traditional facemask pre-oxygenation when oxygenation during apnoea ceases. End-tidal oxygen has been used as a surrogate marker of the efficacy of pre-oxygenation. This variable cannot be measured during high-flow nasal oxygen and does not take the effect of apnoeic peri-oxygenation into account. The effect of peri-oxygenation is reflected in studies comparing apnoea times when high-flow nasal oxygen or facemask is used during pre- and peri-oxygenation, where longer apnoea times at high oxygen saturation are seen using high-flow nasal oxygen [20].

Concern has been raised whether the high flow of oxygen delivered by high-flow nasal oxygen could cause gastric distension and increase the risk of regurgitation. In spontaneously breathing patients with closed mouth, it has been shown that nasopharyngeal airway pressure increases linearly with approximately 1 cmH_2O per 10 $l.min^{-1}$ of flow [21]. Recently, it has been shown that these pressures correlate relatively well with the anaesthetised patient, when the mouth is closed, and that airway pressure increases with flow rate but remains below 10 cmH_2O even with flow rates up to 80 $l.min^{-1}$. Additionally, airway pressure is virtually zero during high flows when the mouth is open [22]. Moreover, healthy volunteers using high-flow nasal oxygen up to 70 $l.min^{-1}$ in 30 min showed no signs of gastric distension or increase in gastric secretions as assessed by ultrasound [23]. Ventilating anaesthetised patients with a facemask can cause gastric insufflation at a positive pressure above 14 cmH_2O [24, 25]. Therefore, it seems unlikely that high-flow nasal oxygen, even at maximum flow, could cause gastric insufflation of gas. In the present study there was one patient in the high-flow nasal oxygen group with signs of regurgitation and none in the facemask group. This study is obviously underpowered for such a rare event, but we found it important to describe this variable in the emergency surgery population since most studies mentioned above were conducted in awake healthy volunteers with assumed normal physiology in contrast to anaesthetised emergency surgery patients.

Importantly, the purpose of RSI is to minimise apnoea time before the airway is secured. In this study, mean apnoea time was longer in the high-flow nasal oxygen group compared with the facemask group. This pattern was also seen in the study by Mir et al. [13]. Although high-flow nasal oxygen can provide an extended safe apnoea time it is important that RSI intubation is performed safely according to routine practice, and without unnecessary delay. However, a method that could prolong the time until desaturation would be beneficial when dealing with a difficult airway or critically ill patient [26]. Since patients were included during all hours of the day, selection of a special patient population was avoided. This increased the generalisability of the technique and proved that high-flow nasal oxygen can be a non-inferior substitute to facemask pre-oxygenation also during on-call hours, when staff is compromised, and time often is limited.

There are limitations to our study. It was not possible to blind and we chose to set the desaturation level to 93% for safety reasons. This is according to recommendations from most parts of the world but constitutes a higher level of saturation than some studies performed in Europe and could, therefore, be considered a weakness. We did not include obese patients and pregnant women, populations that are known to be at high-risk for desaturation during apnoea due to low functional residual capacity and high metabolic demand. Furthermore, they may in addition present a difficult airway. These patients might, therefore, also benefit from peri-oxygenation using high-flow nasal oxygen. We have shown that high-flow nasal oxygen is a suitable method for pre- and peri-oxygention to maintain adequate oxygen levels during RSI and is an alternative to traditional facemask pre-oxygenation.

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