

Clinical Study

Xenon Anesthesia Improves Respiratory Gas Exchanges in Morbidly Obese Patients

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Background. Xenon-in-oxygen is a high density gas mixture and may improve PaO₂/FiO₂ ratio in morbidly obese patients uniforming distribution of ventilation during anesthesia. **Methods.** We compared xenon versus sevoflurane anesthesia in twenty adult morbidly obese patients (BMI > 35) candidate for roux-en-Y laparoscopic gastric bypass and assessed PaO₂/FiO₂ ratio at baseline, at 15 min from induction of anaesthesia and every 60 min during surgery. Differences in intraoperative and postoperative data including heart rate, systolic and diastolic pressure, oxygen saturation, plateau pressure, eyes opening and extubation time, Aldrete score on arrival to the PACU were compared by the Mann-Whitney test and were considered as secondary aims. Moreover the occurrence of side effects and postoperative analgesic demand were assessed. **Results.** In xenon group PaO₂-FiO₂ ratio was significantly higher after 60 min and 120 min from induction of anesthesia; heart rate and overall remifentanyl consumption were lower; the eyes opening time and the extubation time were shorter; morphine consumption at 72 hours was lower; postoperative nausea was more common. **Conclusions.** Xenon anesthesia improved PaO₂/FiO₂ ratio and maintained its distinctive rapid recovery times and cardiovascular stability. A reduction of opioid consumption during and after surgery and an increased incidence of PONV were also observed in xenon group.

1. Introduction

Arterial oxygenation may decrease during anesthesia with mechanical ventilation [1, 2]. This phenomenon is more evident in obese than in normal-weight patients [3, 4]. Increase in body mass index (BMI) is directly related to the impairment of arterial oxygenation, which is mainly attributable to development of ventilation-perfusion (V/Q) mismatches and intrapulmonary shunt (i.e., atelectasis); in fact this is more common during laparoscopy [5, 6]. For these reasons in morbidly obese patients, various strategies have been proposed to improve gas exchange during general anesthesia [7, 8]. Xenon is a N-Methyl-D-Aspartate (NMDA) receptor blocking agent which has become an alternative to the currently used inhaled anaesthetics [9, 10]. The element xenon is a noble gas, has no harmful environmental effects, is associated with cardiovascular stability [9–11], and owns

organoprotective properties, being able to interact with a variety of molecular targets. Several experimental studies have demonstrated a reduction in cerebral and myocardial infarction size after xenon inhalation and the up-regulation of several genes involved in cellular surviving pathways in several tissues [12–15]. Xenon has the lowest blood-gas coefficient (0.115) of all known anaesthetics making induction and recovery from anesthesia very fast [16]. Furthermore, “xenon in oxygen” is a high-density mixture that increases airway pressure and resistance by a rising the Reynold’s number [17], but this reproducible effect does not assume certain clinic implications [18]. On the contrary, as elegantly described by Wood et al., breathing gas mixtures with increased density may cause a reduction of alveolar-arterial oxygen difference (AaDO₂) and improves respiratory performances and distribution of ventilation, minimizing V/Q variances [19]. Despite arterial oxygen partial pressure

(PaO₂), hemoglobin oxygen saturation (SaO₂) and AaDO₂ are clinical indices commonly used for assessing lung function, as described by Zetterström et al.; the ratio of PaO₂ to the inspired oxygen fraction (PaO₂/FiO₂ ratio) seems the most accurate and independent off all extrapulmonary variables [20, 21].

In this paper, we present for the first time intra and postoperative data on respiratory function, hemodynamic status, and recovery times from morbidly obese patients (BMI > 35) receiving xenon-remifentanyl (XR) or sevoflurane-remifentanyl (SR) anaesthesia. In particular, we tested the hypothesis that xenon anaesthesia is able to improve PaO₂/FiO₂ ratio. Furthermore, we tested the hypothesis that xenon, even in morbidly obese patients, maintains its pharmacologic properties characterized by cardiovascular stability and rapid recovery times. The incidence of side effects and the postoperative analgesic demand were also assessed.

2. Methods

The study was a prospective randomised partially blinded controlled trial. The protocol was approved by the local ethics committee, and all patients gave their informed consent before participation. A total of 20 adult morbidly obese patients scheduled for roux-en-Y laparoscopic gastric bypass were randomly recruited. Exclusion criteria were ASA IV, age <18 or >60 yr, Mallampati IV. Monitoring included ECG, pulse oximetry, invasive arterial pressure, temperature, end-tidal carbon dioxide, oxygen and xenon concentrations. All intraoperative continuous variables were recorded every 3 min. Arterial blood gas analysis was performed in the preoperative assessment, at 15 min after the induction of anaesthesia, and every 60 min during surgery. The A-line ARX index (AAI) was also monitored (AEP monitor, Alaris Medical Systems, Inc, San Diego, CA) to provide information about depth of anaesthesia. Monitoring was performed to ensure AAI values <30, and data were recorded every 5 min. After preoxygenation with O₂ 100% for 5 min, anaesthesia was induced in all patients with propofol 2 mg/kg i.v. dosed on real body weight (RBW) and remifentanyl 0.5 mcg/kg/min dosed on ideal body weight (IBW) according to Lorenz's formula (Ideal weight = [height in cm-100] - [height in cm-150]/2) by i.v. infusion over 60 sec. All patients were submitted to direct laryngoscopy for intubation. Since mask ventilation was uncomplicated an i.v. bolus of cisatracurium 0.2 mg/kg IBW was given and intubation performed. All patients received remifentanyl continuous infusion after intubation starting with 0.25 mcg/kg/min IBW and cisatracurium 0.02 mg/kg IBW every 40 min titrated to clinical needs. No cisatracurium was given after the end of 2nd anastomosis (30 minutes before end of surgery). In both groups, a closed-circuit anaesthesia machine (Felix Dual, Taema, France) was used for gas delivery. Xe (LenoXe, Airliquide) administration started after accurate patient's denitrogenation (FiO₂ >97%, FeO₂ >92); midazolam 0.05 mg/Kg IBW was given in order to keep AAI <30 for the time, 7 to 10 minutes, occurring to reach 40% FeXe in closed circuit. Hypnosis was then maintained using

Xe 60–65% in oxygen. In SR group, hypnosis was maintained with sevoflurane 1 MAC in a mixture of oxygen-air. In both groups, ventilation was pressure-controlled (PCV), with FiO₂ 35%, Peep 5, Vt 8–10 ml/kg IBW in order to maintain an end-expiratory carbon dioxide partial pressure (EtCO₂) at 4.8–6.0 kPa. Haemodynamic parameters were maintained within 20% of preoperative values by adjusting remifentanyl infusion accordingly. Normothermia (35.5–37.0°C) was achieved using warming blankets. AAI <30 was kept until the bandaging of the surgical fields were completed then anaesthesia was discontinued. The eyes opening time started with the closure of gas delivery and ended with eyes opening on command. When an adequate spontaneous ventilation, with an EtCO₂ at 5.3–6.6 kPa, was maintained, the trachea was extubated and the patient was transferred into the post anaesthesia care unit (PACU). A patient-controlled analgesia (PCA) device was then connected to a venous line delivering morphine on command.

2.1. Statistics and Sample Size Calculation. We decided to consider as clinically relevant a difference of 60 on PaO₂-FiO₂ ratio among the groups, measured at 120 minutes after induction. Assuming a mean PaO₂-FiO₂ ratio (standard deviation) of 370 (55) in xenon group and 310 (35) in the other group, we estimated a sample size of 10 patients per group enough to detect a difference of 60, at 5% level of significance with 80% power. We verified the existence of no significant differences in patient's demographic characteristics (age, sex, BMI), preoperative clinic characteristics, and duration of anaesthesia using the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables. Differences in intraoperative and postoperative data including heart rate, systolic and diastolic pressure, oxygen saturation, plateau pressure, eyes opening and extubation time, and Aldrete score in the PACU were compared by the Mann-Whitney test and were considered as secondary aims. The existence of a significant difference on morphine consumption after 72 hours between the two groups was compared, and the occurrence of adverse events (hypertension, hypotension, bradycardia, PONV, postoperative headache, awareness) was finally evaluated. Statistical analysis was performed using Stata, version 9.2, on a Mac OS X operating system. Results were considered significant with a *P* value < .05. All data are presented as median (range).

3. Results

The two groups were comparable as shown in Table 1. No significant difference was recorded in anaesthesia duration among the two groups, 150 (120–190) min in SR group and 152.5 (120–220) min in XR group; *P* = .849. Intraoperative data are shown in Table 2: there was no difference among the two groups in PaO₂-FiO₂ ratio at 15 min after the induction of anaesthesia, but in XR group, PaO₂-FiO₂ ratio was significantly higher after 60 and 120 min. Heart rate was significantly lower in XR group, while systolic pressure was significantly lower in SR group. No significant differences were recorded in diastolic pressure and oxygen saturation among the two groups; plateau pressure was significantly

TABLE 1: Baseline data.

	SR	XR	<i>P</i>
Age (yr)	47.5 (19–57)	41 (23–49)	.272
BMI	50.5 (39–71)	53 (42–83)	.519
Sex (males/females)	6/4	8/2	.628
Heart rate (bpm)	87.5 (65–110)	85.5 (56–100)	.570
Oxygen saturation (%)	95 (91–100)	95.5 (89–98)	.623
Systolic pressure (mmHg)	160 (120–168)	137.5 (115–175)	.178
Diastolic pressure (mmHg)	86 (65–100)	87.5 (75–95)	.705
PaO ₂ -FiO ₂ ratio (on air)	350 (307–394)	325.5 (302–392)	.449

Data are presented as median (range) for continuous variables; the number of males and females in each group is reported. *P* < .05 with Mann-Whitney test was considered significant.

TABLE 2: Intraoperative data.

	SR	XR	<i>P</i>
PaO ₂ -FiO ₂ ratio 15 min	282 (195–320)	260 (212–302)	.272
PaO ₂ -FiO ₂ ratio 60 min	301.5 (220–318)	350.5 (234–412)	.041
PaO ₂ -FiO ₂ ratio 120 min	326.5 (234–372)	405.5 (278–432)	.002
Heart rate (bpm)	78 (59–94)	57.5 (48–71)	.001
Systolic pressure (mmHg)	106.5 (94–124)	121.5 (110–148)	.008
Diastolic pressure (mmHg)	67.5 (58–83)	69 (62–78)	.545
Oxygen saturation (%)	96 (93–97)	95.5 (94–97)	.477
Plateau pressure (mmH ₂ O)	27 (25–28)	35 (32–37)	.0001
Remifentanyl usage (mcg)	1597.5 (1080–2425)	762.5 (415–1460)	.0001

Data are presented as median (range). *P* < .05 with Mann-Whitney test was considered significant.

TABLE 3: Postoperative data.

	SR	XR	<i>P</i>
Eyes opening time (min)	7.6 (5.5–11.7)	2.7 (1.6–4.2)	.0002
Extubation time (min)	9.4 (6.7–13.7)	2.9 (1.7–4.9)	.0002
Aldrete score (PACU admission)	9 (8–10)	9 (8–10)	1.000
Morphine demand 72 hours (mg)	26 (13–41)	9.5 (0–16)	.0016

Data are presented as median (range). *P* < .05 with Mann-Whitney test was considered significant.

TABLE 4: Occurrence of adverse events.

	SR		XR	
	N. of patients reporting adverse events	N. of adverse events	N. of patients reporting adverse events	N. of adverse events
Hypertension	0	0	1	1
Hypotension	2	2	0	0
Bradycardia	1	2	2	4
PONV	1	1	4	6
Postoperative headache	1	1	2	2
Awareness	0	0	0	0

Bradycardia was intended *a* > 20% deviation from mean baseline, hypertension *a* > 20% deviation from mean systolic baseline with stable heart rate and no other signs of low depth of anaesthesia and hypotension *a* > 20% deviation from mean systolic baseline.

higher and overall remifentanyl consumption significantly lower in XR group. Postoperative data are shown in Table 3: the eyes opening time and the extubation time were significantly shorter in XR group; morphine consumption after 72 hours was significantly lower in XR group. No difference among groups was noticed in Aldrete score on admission to the PACU. Adverse events occurrence is exposed in Table 4: hypertension, bradycardia, postoperative headache occurred rarely but more frequently in XR group; PONV was more common in XR group and only nausea was noticed; no patient experienced vomiting in the two groups. Hypotension occurred rarely but more frequently in SR group. No patient experienced awareness.

4. Discussion

In this study, we verify that xenon anesthesia is associated with better arterial oxygenation and cardiovascular stability in morbidly obese patients. As argued by Wood et al [19] the effect on AaDO₂ of a high-density gas mixture may be due to a more uniform distribution of ventilation during anesthesia; however, xenon, which pharmacologically is a NMDA receptor antagonist, is not considered a biologically inert gas [12–15, 22, 23] and the improvement of PaO₂/FiO₂ ratio may be related not only to “high-density effect” of the inhaled mixture but also to its organoprotective and preconditioning effects [12–15]. Recovery times recorded after xenon anesthesia were faster according to the blood-gas coefficient of the molecule [16]; no considerable difference was noticed with respect to normal-weight patients trials, taking into account the sample size of our study [9]. Xenon anesthesia was characterized by a significant higher arterial systolic pressure and by a minimal variation from preoperative baseline (Tables 1 and 2). Heart rate was lower; more evident were bradycardia, hypertension, and incidence of postoperative nausea; airway pressure was significantly and constantly increased. All these data are aligned to normal-weight patients trials findings and experimental literature about xenon anesthesia [9, 17, 18, 24].

An unexpected and significant reduction of opioid consumption in xenon group was found. Xenon exerts a potent analgesic action due to NMDA receptor inhibition [25] which may explain the lower overall remifentanyl consumption during surgery; however, wash in and wash out of xenon are very fast [9, 13], and NMDA receptor blocking ability may not explain an effect on pain pathways up to 72 hours. Nowadays the evidence is that xenon is able to modulate long-term pathways [12, 14, 22] which are considered the end effectors producing the long-term organoprotective effects of the gas. It is possible that a long-term modulation of pain could be inserted in such scenario but further studies are required.

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