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CLINICAL RESEARCH

Xenon Anesthesia Reduces TNFα and IL10 in Bariatric Patients

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Abstract
Background Anesthesia is able to modulate the balance between proinflammatory and anti-inflammatory cytokine production during surgery. The aim of this study is to assess the effect of three anesthesia approaches, total intravenous anesthesia (TIVA), inhalation anesthesia, and xenon anesthesia, on sieric levels of nitric oxide (NO), IL6, IL10, and TNFα in obese patients undergoing Roux-en-Y laparoscopic gastric bypass.
Methods Thirty adult morbidly obese patients (BMI>35) scheduled for Roux-en-Y laparoscopic gastric bypass were randomly recruited and allocated to TIVA (N=10), inhalation anesthesia (SEV, N=10), and xenon anesthesia (XE, N=10). Exclusion criteria were ASA IV, age <18 or >60 years, and Mallampati IV. Opioid dosage and ventilation parameters were standardized. Sieric levels of NO, IL6, IL10, and TNFα were assessed at T0 (before induction of anesthesia), T1 (end of surgery), and T2 (12 h after the end of surgery). We compared the relative cytokine level variations (delta) at T1 and T2 and the cytokine exposure levels calculated as the area under the curve (AUC) between T0 and T2 in the XE and non-XE (SEV+TIVA) groups.
Results At T1, we found a significant ΔIL10 (reduction) and ΔTNFα (reduction) between XE and SEV (p<0.05) and XE and TIVA (p<0.05) groups. At T2, ΔIL10 was still significant. Furthermore, we found a reduced AUC value for TNFα in the XE group.
Conclusions Xenon anesthesia seems able to inhibit postoperative proinflammatory cytokine imbalance in morbidly obese patients undergoing Roux-en-Y laparoscopic gastric bypass; the reduced ΔTNFα at T1 and the reduced global exposition to TNFα in the XE group may explain the reduced ΔIL10 at T1 and T2.

Keywords Xenon anesthesia · Bariatric surgery · Cytokines · TNFα

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Introduction

The ability of anesthesia to modulate the immune system has been suggested in the early twentieth century [1]. Many studies in vitro and in vivo emphasize the immunomodulatory abilities that endovenous or inhalational anesthetics can achieve [2–15]. The cell response to surgery comprises various aspects: duration, type and invasiveness of surgery [16], anesthesia techniques, pharmacologic treatments, and appropriate management of pain and anxiety [17]. Both proinflammatory and anti-inflammatory cytokines seem to

Table 1 Baseline data

	XE	TIVA	SEV
Age (years)	41 (23–49)	43 (22–50)	47.5 (19–57)
BMI	53 (42–83)	52 (45–81)	50.5 (39–71)
Sex (males/females)	8/2	8/2	6/4
Heart rate (bpm)	85.5 (56–100)	86 (56–98)	87.5 (65–110)
Oxygen saturation (%)	95.5 (89–98)	94 (89–99)	95 (91–100)
Systolic pressure (mmHg)	137.5 (115–175)	140 (125–170)	160 (120–168)
Diastolic pressure (mmHg)	87.5 (75–95)	88 (80–95)	86 (65–100)

Data are presented as median (range) for continuous variables. No significant differences ($p<0.05$) were found

have a function, and both are often induced [18–20]. Because of different experimental conditions and little overall in vivo and in vitro work performed, the results have been contradictory and, in particular, cytokine modulation during obesity surgery is still an issue to discover. Furthermore, obesity has been widely shown to elicit an inflammatory state, but its intensity cannot be merely studied, predicted, and compared. The aim of this study was to assess the effect of three anesthesia approaches, total intravenous anesthesia (TIVA; propofol and remifentanil), inhalation anesthesia, (sevoflurane and remifentanil), and xenon anesthesia (xenon and remifentanil) on sieric levels of IL6, IL10, and TNFα in obese patients undergoing Roux-en-Y laparoscopic gastric bypass. Also, changes in sieric levels of nitric oxide (NO), which is able to modulate cytokine imbalance [21], were evaluated.

Methods

The study design was a prospective, randomized, partially blinded, controlled trial and was an extension focusing on perioperative cytokine levels of a previously published work [23]. Thirty morbidly obese adult patients (BMI>35) listed for Roux-en-Y laparoscopic gastric bypass were enrolled and randomly allocated to TIVA (N=10), inhalation anesthesia (SEV, N=10), and xenon anesthesia (XE, N=10). Exclusion criteria were Mallampati IV, ASA IV, and age <18 or >60 years. Routine monitoring (electrocardiography, temperature, pulse oximetry, invasive arterial pressure, end-tidal carbon dioxide, oxygen, sevoflurane and xenon concentrations) and the A-line ARX index (AAI; AEP monitor, Alaris Medical Systems Inc., San Diego, CA) were used. All intraoperative continuous variables were recorded every 3 min. The AAI was recorded every 5 min to assess depth of anesthesia, and the plane of anesthesia was adapted if necessary in order to ensure AAI values <30. Anesthesia was induced in all groups after preoxygenation with oxygen 100% for 5 min. Propofol 2 mg/kg i.v. bolus dosed on real body weight (RBW) and remifentanil 0.5 μg/kg/min dosed on ideal body weight (IBW) by i.v. infusion over 60 s were used in all groups. IBW was assessed using Lorenz's formula (IBW=[height in cm−100]−[height in cm−150]/2). All patients underwent direct laryngoscopy and endotracheal intubation. As mask ventilation was uncomplicated, cisatracurium 0.2 mg/kg IBW i.v. bolus was administrated and intubation performed. All patients received remifentanil 0.25 μg/kg/min IBW i.v. continuous infusion after intubation and cisatracurium 0.02 mg/kg IBW i.v. bolus every 40 min titrated to clinical needs. After the end of the second anastomosis (30 min before the end of surgery), no more muscle relaxant agents were given. In order to standardize ventilation parameters in all groups, the same closed-circuit anesthesia machine (Felix Dual, Taema, Antony, France) was used for gas and oxygen delivery. In the XE group, xenon (LENOXe, Air Liquide, Paris, France) administration started after careful denitrogenation of the patients (FiO_2>97% , FeO_2>92%), and midazolam 0.05 mg/kg IBW was administered in

Table 2 T1 data (ΔT1)

	XE	TIVA	SEV
NO (μM)	12.5 (6–43)	15.5 (11–38)	16 (10–33)
ΔNO	0 (−10 to 3)	1.5 (−29 to 3)	1 (−3 to 4)
IL6 (pg/ml)	7.25 (2.7–13.9)	6.95 (3.4–56.2)	5.4 (2.8–67.4)
ΔIL6	4.9 (1.9–11.7)	4.95 (1.5–54.3)	2.7 (−6 to 62.5)
IL10 (ng/ml)	4.3 (1.8–35.1)	3.5 (0.6–15.7)	12.55 (3.7–55.5)
ΔIL10	0.6 (−2.1 to 30.2)*	1.85 (−1.4 to 14.3)	5.95 (2.7–18.9)
TNFα (pg/ml)	9.4 (7.1–31.7)	15.05 (11.2–34.7)	15.15 (10.1–26.8)
ΔTNFα	0.25 (−5.7 to 3.4)*	1.45 (−6.4 to 12.9)	3.95 (−3.3 to 8.9)

Data are presented as median (range). ΔIL10 was significantly lower in the XE versus TIVA and XE versus SEV groups ($p<0.05$). ΔTNFα was significantly lower in the XE versus TIVA and XE versus SEV groups ($p<0.05$)

*Statistical significance ($p<0.05$) of values

Table 3 T2 data (ΔT2)

	XE	TIVA	SEV
NO (μM)	11.5 (7–24)	15 (8–50)	12 (7–24)
ΔNO	−3 (−20 to 4)	0 (−32 to 14)	−3 (−8 to 2)
IL6 (pg/ml)	6.65 (3.5–18.7)	8.6 (2.6–63.1)	6.15 (1.9–31.4)
ΔIL6	4.55 (2.6–16.5)	5.40 (0.9–61.2)	3.5 (−21.2 to 26.5)
IL10 (ng/ml)	3.9 (2.5–5.6)	3.55 (1.7–6.5)	4.75 (1.9–18.9)
ΔIL10	−0.2 (−2.5 to 3.2)*	1.8 (0.3–4.7)	1.25 (−11 to 2.4)
TNFα (pg/ml)	11.5 (8.1–29.1)	15.85 (8.6–32.8)	14 (9.8–20.3)
ΔTNFα	0.7 (−6.7 to 3)	1.4 (−4.5 to 8.6)	−1.55 (−9 to 6)

Data are presented as median (range). ΔIL10 was significantly lower in the XE versus TIVA and XE versus SEV groups ($p<0.05$)

*Statistical significance ($p<0.05$) of values

order to keep the AAI <30 for 7 to 10 min to obtain 40% FeXe in the closed-circuit delivery system (sedative concentration). Hypnosis was then maintained using Xe 60–65% in oxygen. In the SEV group, hypnosis was maintained with sevoflurane minimum alveolar concentration of 1 in a mixture of oxygen–air. In the TIVA group, hypnosis was maintained with propofol 5 mg/kg/h RBW. In all groups, ventilation was pressure-controlled, with FiO_2 35%, Peep 5, Vt 8–10 ml/kg IBW in order to keep the end-expiratory carbon dioxide partial pressure at 4.8–6.0 kPa. Hemodynamic parameters were maintained within 20% of preoperative values by modifying the depth of anesthesia without varying remifentanil infusion. Normothermia (35.5–37.0°C) was obtained using warming blankets. AAI <30 was kept until the bandaging of surgical fields, and then anesthesia was discontinued. After extubation, patients were transferred into the post anesthesia care unit and a patient-controlled analgesia device was connected to a venous line administering morphine on demand. For cytokine analysis, we cannulated a dedicated peripheral venous line and collected 10 ml blood samples into tubes containing 2 mM ethylenediaminetetraacetic acid at the following times: before induction of anesthesia (T0), at the end of surgery (T1), and at 12 h after the end of surgery (T2). All samples were processed within 10 min. Plasma was separated by centrifugation, aliquoted, and stored at −80°C for cytokine analysis. Commercially available enzyme-linked immunoassay kits (TEMA Ricerca s.r.l, Bologna, Italy) were used, according to the manufacturer's directives, to quantify the proinflammatory cytokines IL6 and TNFα and the anti-inflammatory cytokine IL10. NO concentration was assessed using a total NO assay kit (Assay Designs, Inc., Ann Arbor, MI). All measurements were done twice, and the results averaged.

Statistics

We confirmed the existence of no significant differences in patient's demographic characteristics, preoperative clinical characteristics, and duration of anesthesia using the Mann–Whitney test for continuous variables and the Fisher's exact test for categorical variables. To standardize the interindividual variation at T0, we compared by the Mann–Whitney test the relative cytokine blood level variations from T0 to T1 (ΔT1) and from T0 to T2 (ΔT2) and the cytokine exposure levels calculated as the area under the curve (AUC) between T0 and T2 in the XE and non-XE (SEV+TIVA) groups. Statistical analysis was performed using R, version 2.11, on a Linux operating system. Results were considered significant with a p value <0.05. All data are presented as median (range).

Results

The three groups were comparable, as shown in Table 1. No significant difference was recorded in anesthesia duration: 150 min (120–190 min) in the SEV group, 152.5 min (120–220 min) in the XE group, and 154 min (134–200 min) in

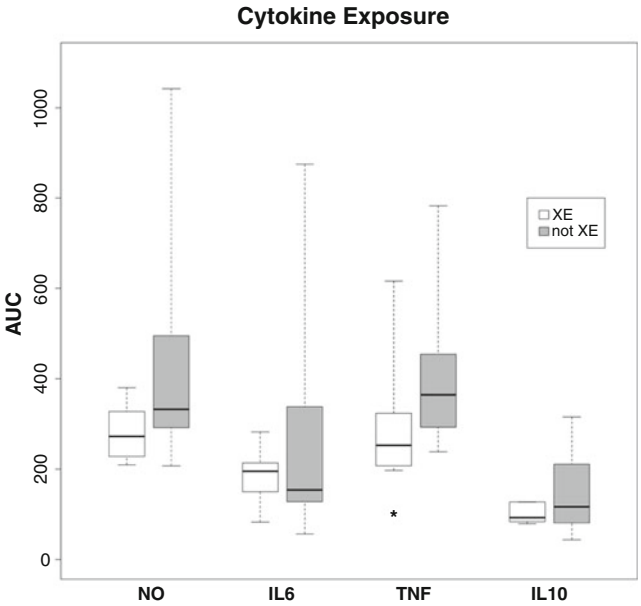

Fig. 1 AUC T0–T2

the TIVA group. T1 data (ΔT1) are shown in Table 2. There was no difference among the three groups in NO and IL6 blood levels. There was a significant ΔIL10 (reduction) and ΔTNFα (reduction) between XE and SEV ($p<0.05$) and XE and TIVA ($p<0.05$) groups. T2 data (ΔT2) are shown in Table 3. There was no difference among the three groups in NO, IL6, and TNFα blood levels. We still found a significant ΔIL10 (reduction) between XE and SEV ($p<0.05$) and XE and TIVA ($p<0.05$) groups. Furthermore, we investigated the differences between the XE group and the TIVA+SEV (non-XE) groups considered together: there was a significant difference ($p<0.05$) in the AUC value for TNFα, which was 252.8 (197–728.8) in the XE group, 364.5 (238.1–783.1) in the TIVA group, and 367.7 (263.9–522.1) in the SEV group, suggesting a reduced global exposure to TNFα for the XE group (Fig. 1).

Discussion

With this study, we assessed a significant difference in ΔIL10 (at T1 and T2), ΔTNFα (at T1), and global TNFα exposure between XE and non-XE groups; no differences were seen in other cytokine blood levels. These results validate the hypothesis that anesthetic drugs exert a modulating effect on cytokine response after surgical trauma. TNFα is an early-released major proinflammatory cytokine, which can control the production of other proinflammatory and anti-inflammatory cytokines, such as IL10 itself. TNFα is involved in the pathogenesis of systemic inflammatory response syndrome (SIRS) and septic shock; high plasma levels of this cytokine are associated with major illness and worst outcome [6, 15, 16, 22]. IL10 is able to inhibit the production of proinflammatory cytokines such as TNFα, IL-1, and IL6; this cytokine seems to be released in response to inflammatory stimuli in order to re-establish the cytokine balance. In experimental models of sepsis, recombinant IL10 can control SIRS signs, whereas during elective surgery, IL10 may be able to limit and modulate the inflammatory effects of tissue injuries [15–17, 22]. In our study, the reduced ΔTNFα at T1 and the reduced global exposition to TNFα in the XE group may explain the reduced ΔIL10 at T1 and T2. In conclusion, xenon anesthesia seems able to inhibit postoperative proinflammatory imbalance of cytokine production in morbidly obese patients undergoing Roux-en-Y laparoscopic gastric bypass. Overall benefits of xenon anesthesia in bariatric patients are documented and discussed in another study, which compared xenon with sevoflurane anesthesia [23]. These findings suggest that xenon anesthesia is a secure alternative to conventional inhalational anesthesia and offers a better intraoperative respiratory performance, exceptionally short recovery times, and a constant cardiovascular stability. On the contrary, postoperative nausea incidence and cost (which is also the most solid obstacle to extensive clinical use) are higher. Choosing xenon for bariatric patients may be a new weapon for the anesthesiologist, but this is the first investigation on xenon-related modulation of cytokine response during obesity surgery; further studies are required to correlate xenon extra-anesthetic properties with patient's outcome.

Conflict of Interest All the authors (Antonio Abramo, Claudio Di Salvo, Giacomo Baldi, Elena Marini, Marco Anselmino, Guido Salvetti, Francesco Giunta, and Francesco Forfori) declare that they have no conflict of interest.

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