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Perioperative hyperoxia — Long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial

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ABSTRACT

Background: Increased long-term mortality was found in patients exposed to perioperative hyperoxia in the PROXI trial, where patients undergoing laparotomy were randomised to 80% versus 30% oxygen during and after surgery. This post hoc follow-up study assessed the impact of perioperative hyperoxia on long-term risk of cardiovascular events.

Methods: A total of 1386 patients undergoing either elective or emergency laparotomy were randomised to 80% versus 30% oxygen during and two hours after surgery. At follow-up, the primary outcome of acute coronary syndrome was assessed. Secondary outcomes included myocardial infarction, other heart disease, and acute coronary syndrome or death. Data were analysed in the Cox proportional hazards model.

Results: The primary outcome, acute coronary syndrome, occurred in 2.5% versus 1.3% in the 80% versus 30% oxygen group; HR 2.15 (95% CI 0.96–4.84). Patients in the 80% oxygen group had significantly increased risk of myocardial infarction; HR 2.86 (95% CI 1.10–7.44), other heart disease; HR 1.40 (95% 1.06–1.83), and acute coronary syndrome or death; HR 1.22 (95% CI 1.01–1.49).

Conclusions: Perioperative hyperoxia may be associated with an increased long-term risk of myocardial infarction and other heart disease.

1. Introduction

Several randomised clinical trials have investigated the effect of hyperoxia to reduce surgical site infection after laparotomy procedures, but the benefits are yet not conclusive [1]. One of the largest trials, the PROXI trial, which randomised 1400 patients to 80% or 30% oxygen, found higher point estimate of 30-day mortality in patients assigned to hyperoxia [2]. Furthermore, a long-term follow-up showed significant increase in long-term mortality [3].

The long-term effects of hyperoxia are largely unknown. Oxygen generates reactive oxygen species [4] and affects the cardiovascular system by increasing the peripheral vascular resistance [5], decreasing the cardiac index [5], and decreasing coronary blood flow [6]. A study found increased 30-day mortality in patients after non-cardiac surgery with even minor increases in cardiac Troponin T levels; indicative of myocardial injury [7]. Further, a recent randomised clinical trial found increased myocardial infarct size after six months in patients allocated to eight litres of supplemental oxygen per minute during their prehospital treatment for ST-elevation myocardial infarction [8]. The combined effects of oxygen and surgery might result in an increased risk of cardiovascular disease.

We hypothesised that hyperoxia was associated with an increased risk of acute coronary syndrome after surgery and thereby could explain the excess mortality. The aim of this post hoc follow-up study was to investigate the effect of perioperative hyperoxia on the long-term risk of

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acute coronary syndrome and other heart disease after abdominal surgery.

2. Methods

2.1. Permissions

The Danish Data Protection Agency, the Danish Medicines Agency (registered with EudraCT no. 2006-001710-32), and the regional Ethics Committee approved the PROXI trial. All patients gave written, informed consent, were older than 18 years and were planned to undergo either elective or emergency abdominal laparotomy. The Danish Data Protection Agency and the Danish Medicines Agency approved a subsequent follow-up of the patients participating in the original trial without collecting further approval from the participants.

2.2. Patients and trial course

Patients were enrolled in the PROXI trial from October 8th 2006 to October 6th 2008. The exclusion criteria were: other surgery within 30 days, chemotherapy within three months, inability to provide informed consent, and $S_pO_2 < 90\%$ without supplemental oxygen [2,9]. Patients were randomised to either 80% or 30% oxygen during surgery and the first two hours after tracheal extubation [9]. Randomisation was performed by an external department (Copenhagen Trial Unit) and stratified for: trial site, diabetes mellitus, elective or emergency surgery, and body mass index (BMI) (<30 or ≥30 kg/m^2). A standardised procedure for perioperative care was described in the trial protocol [9].

Throughout the induction of anaesthesia, 100% oxygen was used until succeeded tracheal intubation. Then, patients were given either 80% or 30% oxygen throughout the surgery according to randomisation. The percentage of oxygen was increased to ensure $S_pO_2 > 94\%$, if necessary. The allocated oxygen continued for the first two hours after extubation through non-rebreathing face masks. Hereafter, supplemental oxygen was administrated at the physician's recommendations. The intervention was blinded to patients, surgeons, the staff at the wards, and outcome assessors. The classification of outcomes in this follow-up study was performed blinded to allocation, but after the termination of the original trial.

2.3. Follow-up

This was a post hoc follow-up analysis. The date of follow-up was September 28th 2011. Vital status was obtained from the Danish Civil Registration System (www.cpr.dk), which register all citizens by their unique 10 digit number [10]. All diagnostic codes were documented according to the International Classification of Diseases version 10 (ICD-10) [11] and were obtained from the Danish National Patient Registry (NPR) that records hospital contacts for all Danish patients by their 10 digit number regardless of whether the hospital is private or public [12]. In particular, NPR has proved to produce the same results in detecting myocardial infarctions after a clinical trial as an appointed adjudication committee [13]. All codes for surgical procedures were registered according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures version 1.16 [14], which was obtained from NPR.

The primary outcome of this follow-up study was acute coronary syndrome; either myocardial infarction or unstable angina pectoris according to ICD-10 as described in Appendix A.

The secondary outcomes were events of unstable angina pectoris, myocardial infarction, acute coronary syndrome or death, other angina pectoris, arrhythmia, pulmonary embolism, other heart disease, any heart disease, surgical procedures on coronary arteries, and any heart disease or death. Appendix A shows the ICD-10 and surgical codes for the secondary outcomes.

The diagnostic codes in NPR were given during hospitalisation: at discharge (inpatient), seen in the emergency department, or treated in the outpatient clinic [12]. The acute diagnostic codes were restricted to those given during hospital admissions or in the emergency room as seen in Appendix A. We collected date of all events, where the discharge date was after index surgery. Acute coronary syndrome was defined to occur on the first day of admission, and the other events were defined to occur on the median date of hospital admission. If acute coronary syndrome was diagnosed during the initial admission for index surgery, the date was set to the day of intervention.

2.4. Statistical analysis

The long-term incidence of acute coronary syndrome after abdominal surgery was illustrated as Kaplan–Meier curves. The influence of perioperative hyperoxia on long-term cardiovascular disease was analysed with hazard ratios (HR) with 95% CI from Cox proportional hazard regression models both unadjusted, adjusted for the primary stratification variables in the PROXI trial (trial site, diabetes mellitus, elective or emergency surgery, and BMI), as well as adjusted for the stratification variables and the following further covariates: age, daily smoking, ASA, hypertension, and other cardiovascular disease. All covariates were collected with less than 0.5% missing values. We considered HRs adjusted for the primary stratification variables to be the primary analysis [15,16]. However, we have made all data available. A significance level of 5% was considered significant. Analyses were performed with SAS for Windows version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Table 1
Baseline characteristics of included patients receiving 80% or 30% oxygen. Values are presented as either range or per cent in parentheses if not otherwise stated.

Characteristics	80% oxygen group, n = 678	30% oxygen group, n = 699
Age (years), median	64 (27–85)	64 (34–84)
Sex (male:female)	284:394	292:407
Height (cm), median	170 (156–186)	170 (154–186)
Weight (kg), median	71 (49–109)	72 (50–103)
BMI (kg/m^2), median	25 (18–35)	25 (19–35)
Current smoking	202 (30%)*	211 (30%)
Alcohol consumption >48 g/day	28 (4.1%)*	35 (5.0%)
Diabetes Mellitus	51 (7.5%)	53 (7.6%)
Hypertension	207 (31%)	186 (27%)
Angina	18 (2.7%)	17 (2.4%)
Ischaemic heart disease	14 (2.0%)	16 (2.3%)
Congestive heart failure	10 (1.5%)	8 (1.1%)
Atrial fibrillation and flutter	15 (2.2%)	18 (2.6%)
Other cardiovascular disease	84 (12%)	56 (8.0%)*
Renal disease	26 (3.8%)	21 (3.0%)
ASA (I:II:III:IV)	174:371:129:4	196:373:125:5
Emergency surgery	185 (27%)	194 (28%)
Pre-operative haemoglobin (g/l), median	12.7 (9.5–15.8)	12.9 (9.2–16)
Duration of surgery (min), median	128 (38–310)	132(35–295)
Dose of ephedrine (mg), median	19 (0–50)	17 (0–50)
Other vasopressor	208 (31%)	229 (33%)
Epidural analgesia	468 (69%)	496 (71%)
Type of anaesthesia (intravenous:inhalation)	504:174	491:208
Estimated blood loss (ml), median	260 (0–2200)	250 (0–1800)
Perioperative blood transfusion (no:yes)	557:121	579:120
If yes, n portions, mean	2.0 (1–6)	2.0 (1–6)
Diagnosis: Cancer	349 (51%)	361 (52%)
Benign neoplasms	63 (9.3%)	45 (6.4%)
Other	266 (39%)	293 (42%)

* Missing data for one patient.