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Intraoperative tissue oxygenation and postoperative outcomes after major non-cardiac surgery: an observational study†

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Editor's key points

- It is important to identify perioperative factors that contribute to mortality and major morbidity.
- Low levels of tissue oxygenation may be an important determining factor in outcome.
- Minimum perioperative peripheral tissue oxygenation was found to relate to subsequent major postoperative problems.
- The relationship between tissue oxygenation and outcome is complex and needs further study.

Background. The relationship between tissue oxygen saturation (StO_2) and serious postoperative complications remains unclear. We tested the hypothesis that perioperative StO_2 in patients undergoing major non-cardiac surgery is inversely related to serious surgical outcomes.

Methods. We enrolled 124 patients, ASA physical status ≤IV, having elective major non-cardiac surgeries with general anaesthesia. An InSpectra Model 650 StO_2 monitor (Hutchinson Technology, Hutchinson, MN, USA) was used to measure StO_2 at the thenar eminence throughout surgery and for two postoperative hours. Our primary outcome was a composite of 30 day mortality and serious in-hospital complications. The secondary outcome was an *a priori* subset of the primary composite outcome representing infectious and wound-healing complications. Multivariable logistic regression was used to evaluate the associations between our primary and secondary outcomes and time-weighted average (TWA) and minimum StO_2.

Results. Patients were 61 (12), mean (SD) yr old. The minimum StO_2 was inversely associated with our primary composite outcome (P=0.02). The estimated odds ratio (97.5% CI) of having any major postoperative morbidity was 0.82 (0.67, 1.00) for a 5% increase in the minimum StO_2. In contrast, TWA StO_2 was not significantly associated with major postoperative morbidity (P=0.35). Furthermore, neither TWA (P=0.65) nor minimum (P=0.70) StO_2 was significantly associated with wound complications.

Conclusions. Minimum perioperative peripheral tissue oxygenation predicted a composite of major complications and mortality from major non-cardiac surgery. This is an observational association and whether clinical interventions to augment tissue oxygenation will improve outcomes remains to be determined.

Keywords: hypoxia; oxygen; postoperative complications; postoperative period; tissues

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Tissue oxygenation reflects the balance between supply and utilization of oxygen, with hypoxia being defined by inadequate cellular oxygen. Tissue oxygenation is always considerably lower than arterial oxygenation because a gradient is needed to drive oxygen molecules from capillaries to the surrounding cells.[1 2] Depending on regional perfusion and other factors, the relationship between arterial and tissue partial pressures can differ considerably.[3]

Copious previous work links tissue oxygenation—as distinct from arterial partial pressure—to surgical site infection (SSI) and wound-related complications,[4] presumably because oxidative killing of bacteria by neutrophils is one of the primary

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defences against SSI[5] and because killing efficacy depends on the partial pressure of oxygen over the entire physiological range of tissue values.[6 7] For example, patients with low tissue oxygen partial pressure[3] or saturation[8] are more susceptible to wound infection and bowel anastomotic leaks after colorectal surgery.[9] Consistent with these observational data, supplemental inspired oxygen (which roughly doubles peripheral tissue oxygen partial pressure) reduces the risk of SSI in some,[10 11] but not all,[12] randomized trials.

Tissue oxygenation correlates with outcomes in non-surgical settings such as heart failure.[13] Low or inadequate tissue oxygenation is also associated with specific perioperative complications including acute postoperative kidney injury,[14] septic shock, and acute systemic inflammatory conditions.[15] Because adequate tissue oxygenation is fundamental to cellular function, tissue hypoxia may be a root cause of many serious perioperative complications.

The relationship of tissue oxygen saturation (StO_2) to immediate postoperative serious morbidity and mortality has not been fully characterized. We therefore tested the primary hypothesis that intraoperative and immediate postoperative tissue oxygen saturation in patients undergoing major non-cardiac surgery, as measured at the thenar imminence with near-infrared spectroscopy (NIRS), is inversely related to a composite of serious postoperative complications and 30 day mortality. Our secondary hypothesis was that there is an inverse relationship between StO_2 and a composite outcome of SSI and wound-healing complications.

Methods

We report the results of a substudy of the DeLiT trial (ClinicalTrials.gov Identifier: NCT00433251),[16] a factorial randomized single-centre study designed to test the primary hypotheses that major postoperative morbidity is reduced by: (i) low-dose dexamethasone; (ii) intensive intraoperative glucose control; and (iii) lighter anaesthesia. Patients $\geq$40 yr of age, ASA $\leq$IV, undergoing elective major non-cardiac surgeries (open major vascular, major abdominal, major urological surgery) were enrolled. Exclusion criteria included: recent i.v. or oral steroid therapy (within 30 days); any contraindications to the proposed interventions; ASA physical status $>$IV; and procedures done under regional anaesthesia. The trial was conducted with Institutional Review Board approval and written informed consent was obtained from each participant.

All patients were given general anaesthesia, and tracheal intubation, with sevoflurane in air and oxygen mixture and i.v. fentanyl infusion after a standardized anaesthetic protocol consistent with the randomization to light or deep anaesthesia. Patients were also randomized to blood glucose concentrations of 80–110 mg dl^{-1} (intensive control) or $<$200 mg dl^{-1} (conventional control) and simultaneously randomized to receive i.v. dexamethasone (8 mg immediately before operation, 4 and 2 mg on postoperative days 1 and 2, respectively) or placebo as part of the underlying factorial study. The lungs were mechanically ventilated at the discretion of the anaesthesiologist who was blinded to the StO_2 reading to maintain end-tidal P_{CO_2} near 35 mm Hg. Typically, patients are ventilated with a tidal volume of $\sim$8 ml kg^{-1} with PEEP of 5 cm H_2O. Normothermia was maintained with forced-air warming.

There are many methods of measuring tissue oxygenation, including optodes,[17] polarographic (Clark) electrodes,[18 19] injectable tissue markers, electron spin resonance, fluorine tuned MRI,[20] and tissue blood saturation monitors. All have drawbacks. For example, the Clark-type electrode, while it is only minimally invasive, it is expensive and technically tricky. We thus chose an alternative non-invasive rapidly responsive approach, near-infrared spectrometry, which estimates tissue oxygen saturation from absorption of light by tissue chromophores in the 700–1000 mm spectrum.[21 22]

Specifically, we used an InSpectra StO_2 Tissue Oxygenation Monitor, Model 650 (Hutchinson Technology, Hutchinson, MN, USA). This FDA-approved device continuously measures tissue oxygen saturation at a depth of $\approx$15 mm under the surface from a sensor adhered to the skin. The sensor was attached to the patient's thenar eminence after anaesthetic induction, and maintained throughout surgery and for two postoperative hours. StO_2 values were recorded at 2 s intervals and downloaded into a computer for subsequent analysis; the values were not available to clinicians and therefore could not provoke changes in patient management.

Intraoperative arterial pressure was controlled to within a range of +20% to −30% of the preoperative baseline value. Heart rate was controlled to within a range of 40–90 beats min^{-1}. This was achieved through standardized protocol with consideration to the depth of anaesthesia, blood volume status assessment, and vasoactive drugs if required. These included nitroglycerine and/or esmolol for treating hypertension and/or tachycardia. Phenylephrine, ephedrine, and/or glycopyrrolate were used to treat hypotension and/or bradycardia.

The primary i.v. fluid was lactated Ringer's solution unless contraindicated. Up to 500 ml were given with induction of anaesthesia at the anaesthesiologist's discretion. Subsequently, lactated Ringer's solution was given as the maintenance crystalloid. Blood loss was replaced with lactated Ringer's solution at a 3:1 ratio, colloid at a 1–2:1 ratio, or red cells at a 1:1 ratio at the anaesthesiologist's discretion.

Red cell transfusions were controlled by protocol as well. Target minimum haematocrits (HCTs) were determined before operation based on the patient's cardiovascular status. The HCT was maintained at 25–28% in patients without substantial cardiac disease, but maintained at 30% in those with significant cardiac disease (defined as previous myocardial infarction, angina, congestive heart failure, or cardiomyopathy).

Our primary outcome was a composite of 30 day mortality and serious in-hospital complications. The secondary outcome was a subset of the primary outcome composite and included deep or organ-space SSI; sepsis; internal or external fistula formation; and bowel and surgical anastomosis stricture/obstruction or anastomotic leak (Table 1).