

Cover page

Official Title of the study:

Effects of Remote Ischemic Preconditioning During Free Flap Reconstruction in Head and Neck Cancer Patients With Preoperative Radiotherapy

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Study protocol and statistical analysis plan

Study protocol

Without premedication, the patients were monitored using 3-lead electrocardiography, non-invasive blood pressure and pulse oxygen saturation measurements, and bispectral index monitoring. Arterial blood pressure was monitored continuously, and intermittent blood gas analysis was performed intraoperatively. General anesthesia was induced by administering an intravenous bolus dose of propofol 1.5 mg/kg and a target-controlled infusion of remifentanyl using a commercial infusion pump (Orchestra Base Primea, Fresenius-Vial, Sèvres, France). After administration of rocuronium 0.6 mg/kg for neuromuscular blockade, the patient's trachea was intubated, and the lungs were ventilated in the volume-controlled mode with a tidal volume of 6–8 mL/kg; a fraction of inspired oxygen, 0.4; and, positive end-expiratory pressure, 5 cmH₂O. Anesthesia was maintained using 1.5–2.5 vol% of sevoflurane or 4.5–7.5 vol% of desflurane, and the target-controlled infusion of remifentanyl. The effect-site concentration of remifentanyl was adjusted to 2–4 ng/mL to maintain analgesia and stable hemodynamics throughout surgery.

Remote ischemic conditioning, consisted of four cycles of 5-min ischemia and 5-min reperfusion, was applied to the patient's available arm or leg before (preconditioning) and after (postconditioning) free flap transfer in the RIC group. Ischemia was achieved by inflation of a pneumatic cuff up to 200 mmHg, and the subsequent reperfusion was followed by deflation of the cuff. In the sham group, a pneumatic cuff was applied to the arm or leg without inflation/deflation during surgery.

Statistical analyses

Data distribution was assessed using the Kolmogorov–Smirnov test or Shapiro–Wilk test, and data are presented as mean \pm standard deviation (SD) or median (interquartile range, IQR), or number (proportion) accordingly. Continuous variables were compared using an independent *t*-test or Mann–Whitney *U* test. Noncontinuous variables were compared using Pearson chi-square test or Fisher exact test. Comparisons of values obtained before and after free flap transfer were conducted using the paired *t*-test or the Wilcoxon signed-rank test. For repeated-measures variables, we used a linear mixed model with Bonferroni correction for comparison between the groups. In the mixed model, the measurement time, group, and their interactions were treated as fixed effects,

whereas the subject was considered a random effect. Plots of residuals versus fitted values were assessed to determine whether the residuals had a mean variance of zero or a constant variance. The assumption of normality for repeated measures was confirmed using histograms and quantile-quantile plots of the residuals.

All analyses were performed using the IBM SPSS Statistics (ver. 27.0; IBM Corp., Armonk, NY, USA) or R software (ver. 3.5.1; R Development Core Team, Vienna, Austria). Statistical significance was defined as a two-sided P value <0.05 .