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study protocol and statistical analysis plan. Date first loaded up **Oct 15. 2019**

local name of study: **2019OSOFADIEPFLAP**

full name of study

Impact of opioid free anesthesia on the complications after DIEPflap surgery: A retrospective observational cohort study.

NCT number: NCT03202134

Methods

Patients

In this cohort study, we included all patients in our hospital database who underwent DIEP flap surgery between January 2014 and April 2019. All patients entering our hospital provide consent to allow retrospective data analysis without patient identification. The study protocol was approved by our institutional review board and registered at http://clinicaltrials.gov (registration number: NCT03202134) under the name of Jan Mulier on June 28, 2017. This manuscript adheres to the STROBE and CONSORT guidelines.

At our institution, the possibility of breast reconstruction is discussed with all women undergoing mastectomy for established breast cancer or prophylactic as a risk reduction strategy, and the decision regarding timing and type of reconstruction is based on each patient's preference and surgical options. Approximately 80% of patients requesting breast reconstruction choose a DIEP flap. When adjuvant radiotherapy is required, our breast multidisciplinary team policy is to offer delayed autologous tissue reconstruction. Patients with a high body mass index (BMI; >30 kg/m^2) are advised to lose weight and those who smoke are advised to stop smoking at least 4 weeks before surgery; however, neither of these characteristics will exclude women from being offered DIEP flap surgery. Hormone therapy, when a component of the breast cancer treatment, is stopped one week before surgery and continued after discharge. Prior to DIEP flap surgery, all women undergo computed tomography angiography (CTA) with three-dimensional (3D) image reconstruction to assess the lower abdominal wall perforators and recipient vessels by an experienced radiologist.

Surgery

All DIEP flap reconstructions were performed by senior surgeons using a standard technique. These surgeons routinely preserve the superior inferior epigastric vein for "supercharging" if venous congestion occurs. The internal thoracic vessels at the level of the third or fourth rib were the first-choice recipient vessels. End-to-end anastomoses were performed using 9-0 or 10-0 Nylon (ST&T)®, depending on the vessel caliber.

Anesthesia

The choice of OFA or OA was at the discretion of the attending anesthesiologist, only some of whom were experienced with OFA. Because the date of surgery for each patient was usually determined without knowing which anesthesiologist would be assigned to the operating room on a given day, the choice of OFA or OA was random in most cases. OFA was defined as the administration of no opioids either pre- or intraoperatively until wound closure. Opioids administered after wound closure were considered postoperative opioids. OA was defined as the administration of any opioid at any time during the pre- or intraoperative period (up to the time of wound closure). Postoperative opioid-free analgesia (OF analgesia) was defined as the administration of no opioids from the time of wound closure until discharge from the hospital, in patients who received no medium- or long-acting opioids either pre- or intraoperatively.

Most patients received a balanced general anesthetic, which was usually a combination of 0.5 MAC sevoflurane inhalation and a continuous propofol infusion at 3 mg/kg/h. Neuromuscular

blockade (NMB) was achieved with rocuronium or cisatracurium in a continuous infusion to achieve periods of deep NMB when required.

The method of OFA has remained unchanged at our institution since 2014. Dexmedetomidine was administered as follows: 0.3 mcg/kg 15 minutes before induction, 0.1 mcg/kg at induction, and an infusion of 0.1 mcg/kg/h for maintenance. Lidocaine was administered as 1 mg/kg at induction, followed by an infusion of 1 mg/kg/h for maintenance. Ketamine was administered

as 0.1 mg/kg at induction, 0.7 mg/kg (maximum, 50 mg) before incision, and an infusion of 0.1 mg/kg/h for maintenance. Postoperative analgesia was further improved by continuing very low doses of dexmedetomidine (0.05 mcg/kg/h), ketamine (0.05 mg/kg ideal body weight/h), and lidocaine (0.5 mg/kg/h) for the first few hours (maximum, 5 h) after surgery, with bolus doses of 10 mg lidocaine, 1 mg ketamine, and 1 mcg dexmedetomidine administered every 15 minutes on an as-needed basis.

OA involved the use of sufentanil or sufentanil combined with remifentanil. Sufentanil was administered as 0.1–0.3 mcg/kg at induction, followed by additional 0.1–0.2 mcg/kg doses as needed during surgery or by a continuous infusion of remifentanil at 0.20–0.35 mcg/kg/h. Since 2014, various adjunct medications (e.g., clonidine, dexmedetomidine, ketamine, lidocaine) have been administered as a single dose at induction to reduce the total dose of intraoperative opioids. Nevertheless, as long as an opioid was given before wound closure the type of anesthesia was still classified as OA.

All patients undergoing OFA were managed with strict goal-directed fluid therapy, receiving approximately 600 to 1,200 mL of intravenous (iv) fluids intraoperatively. Patients undergoing OA received more liberal fluid therapy, with usual total intraoperative volumes between 3,000 and 5,000 ml.

Data collection

The following demographic data were retrieved: age; body mass index (BMI); American Society of Anesthesiologists (ASA) physical status class; and history of hypertension, current or recent smoking, motion sickness, or previous PONV. We also recorded the total volume of intraoperative fluids, duration of surgery, and laterality of the DIEP flap (bilateral or unilateral). The simplified Apfel score [ii] (based on non-smoking status, female sex, history of previous PONV or motion sickness, and postoperative opioid use) was calculated for each

patient, and the presence of nausea or vomiting, as well as the number of antiemetics

administered before and after PONV, was recorded. We likewise recorded the maximum

visual analog scale (VAS) pain score and opioid usage during the first 24 hours

postoperatively. Opioid usage was converted to total iv morphine equivalents as follows: 1

mg iv morphine = 1 mg iv or subcutaneous piritramide, 10 mg iv tramadol, or 2 mg sublingual

oxycodone.
hours after surgery and compared to the temperature of the surrounding skin (reference temperature). Hospital length of stay (LOS) was calculated as the number of nights in the hospital postoperatively.
The presence of perioperative complications during the first 1 month postoperatively were

Postoperative flap skin temperature was measured every hour for the first 24

[iv]
converted to 6 ranks for use in the statistical analysis, with grades 1, 2, 3a, 3b, 4a, and 4b

graded according to the modified Clavien-Dindo (CD) classification.

The CD grades were

being converted to ranks 1, 2, 3, 4, 5, and 6, respectively.
failure was defined as the need for a revision procedure that failed to preserve the flap, thereby requiring another type of flap reconstruction.

Statistical analysis

The demographic data and clinical outcome parameters are expressed as means and standard deviations and analyzed using Mann-Whitney test or expressed as percentage of cases and analyzed using $\chi 2$. A linear or logistic regression is used to analyze the independent effect of different factors on the outcome parameters. Statistical analysis was performed using statistical package (Stata/IC 15.1 for Mac, StataCorp, TX 77845 USA)

[i] Rothenberger J, Amr A, Schiefer J, Schaller H, Rahmanian-Schwarz A. A quantitative analysis of the venous outflow of the deep inferior epigastric flap (DIEP) based on the perforator veins

and the efficiency of superficial inferior epigastric vein (SIEV) supercharging. Journal of Plastic, Reconstructive & Aesthetic Surgery 2013;66,67-72.
[ii] Apfel C C, Laara E, Koivuranta M, Greim C, Roewer N. A Simplified Risk Score for Predicting Postoperative Nausea and Vomiting Anesthesiology 1999; 91:693–700.

[iii] Mary Lynn. McPherson. Demystifying opioid conversion calculations: A guide for effective dosing. ISBN 978-1-58528-198-5 . 2009 American society of health-system Pharmacists, Inc.
[iv] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindoo classification of Surgical complications. Ann Surg 2009;250:187-96.