Journal of Plastic, Reconstructive & Aesthetic Surgery (2021) 74, 504–511

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Impact of opioid-free anesthesia on complications after deep inferior epigastric perforator flap surgery: A retrospective cohort study

Harold Mulier[a], Bob De Frene[b], Lara Benmeridja[b,c], Florian Vanhoorebeeck[d], Bruno Denis[d,f], Bob Casaer[b], Fabrice Jacques Rogge[b], Kris Leleu[d], Jan Mulier[a,d,e,*]

[a] *KU Leuven – University of Leuven, Herestraat 49, B-3000 Leuven, Belgium*
[b] *Department of Plastic and Reconstructive Surgery, AZSint Jan AV Brugge-Oostende, Campus Brugge, Ruddershove 10, B-8000 Brugge, Belgium*
[c] *Department of Plastic and Reconstructive Surgery, Ghent University Hospital, B-9000 Ghent, Belgium*
[d] *Department of Anesthesiology, Intensive Care and Reanimation, AZSint Jan Brugge-Oostende, Campus Brugge, Ruddershove 10, B-8000 Brugge, Belgium*
[e] *UGhent – University of Ghent, B-9000 Ghent, Belgium*
[f] *Department of Anesthesiology and Acute Pain Service, Cliniques Universitaires Saint Luc, University Catholic of Louvain, av Hippocrate 10, B-1200 Brussels, Belgium*

Received 4 January 2020; accepted 27 September 2020

KEYWORDS
Opioid-free anesthesia;
DIEP flap surgery;
Clavien-Dindo classification;
Breast reconstruction

Summary This study measured the number of complications after deep inferior epigastric perforator (DIEP) flap reconstruction performed under opioid-free anesthesia (OFA) combined with goal-directed fluid therapy or opioid anesthesia with liberal fluid therapy (OA). This retrospective cohort study consisted of 204 patients who underwent DIEP flap reconstruction at AZSint Jan Brugge between April 2014 and March 2019. Primary outcomes were complications, according to the Clavien-Dindo classification and the length of hospital stay (LOS). The secondary outcomes were flap failure, postoperative nausea and vomiting (PONV), postoperative pain, postoperative opioid consumption, and postoperative skin flap temperature. OFA included

Name and address of the department or institution to which the work should be attributed: AZSint Jan AV Brugge-Oostende, Campus Brugge, Ruddershove 10, 8000 Brugge, Belgium.
Details of any meeting at which the work was presented, wholly or in part: Lecture at the 3rd international OFA meeting in Bruges, Belgium on 8 November 2019 as a short lecture from the Bruges research group. Abstract proposed as a poster for the ESA meeting on 30–31 May 2020 in Barcelona, Spain and presented virtually on 28 November 2020.
* Corresponding author at: Department of Anesthesiology, Intensive Care and Reanimation, AZSint Jan Brugge-Oostende, Campus Brugge, Ruddershove 10, B-8000 Brugge, Belgium.
E-mail addresses: Jan.mulier@azsintjan.be, janpaul.mulier@gmail.com (J. Mulier).

https://doi.org/10.1016/j.bjps.2020.09.004

a combination of dexmedetomidine, lidocaine, and ketamine without any opioid administered pre- or intraoperatively. OA included a combination of sufentanil and remifentanil. OFA patients received strict goal-directed fluid therapy, whereas OA patients received liberal fluids to maintain perfusion pressure. All patients except 7 (TIVA with remifentanil) received inhalation anesthesia combined with an infusion of propofol. Of the 204 patients, 55 received OFA and 149 received OA. There were no differences in major complications, but fewer minor complications in the OFA group (17.9% vs. 51.4% and $P < 0.001$). Flap failure occurred in three patients of the OA group. Six patients developed flap thrombosis (five OA patients and one OFA patient). OFA was associated with fewer postoperative opioids, shorter LOS, less PONV, and less pain. In patients without previous nausea, the PONV incidence was higher in the OA group than in the OFA group (12.7% vs. 43.6% and $P < 0.001$). Patients with previous nausea more frequently required postoperative opioids and had a nausea rate of 60.87%.

Introduction

The reconstruction of deep inferior epigastric perforator (DIEP) flaps[1,2] involves the transfer of free abdominal tissue to the breast using microsurgery.[3,4] Reducing perioperative opioids may enhance recovery after surgery (ERAS), as measured by the number of minor and major complications and the length of hospital stay (LOS), and is therefore one of the principles of ERAS.[5] Opioid-free anesthesia (OFA) reduces postoperative nausea and vomiting (PONV),[6] the most common minor complication affecting flap perfusion.[7] Major complications such as flap failure are rare but can have devastating effects.[5] Many perioperative factors, including low cardiac output, hypothermia, and surgical stress, may cause vasoconstriction or thrombosis, thereby reducing flap blood flow.[8] OFA may more effectively lower perioperative stress but can induce more hypotension, making the impact on flap perfusion uncertain. Dexmedetomidine[9,10] and lidocaine,[11,12] which are common components of OFA, have anti-inflammatory and vasodilatory effects that may improve free-flap perfusion.

This study tested the hypothesis that OFA combined with goal-directed fluid therapy for DIEP flap surgery is associated with fewer complications.

Patients and methods

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 their consent to allow retrospective data analysis. The study protocol was approved by our institutional review board and registered at http://clinicaltrials.gov. 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 prophylactically as a risk reduction strategy, and the decision regarding the 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 with three-dimensional image reconstruction for an assessment of the lower abdominal wall perforators and recipient vessels by an experienced radiologist.

Methods

All DIEP flap reconstructions were performed by senior surgeons using a standard technique.[4] These surgeons routinely preserve the superior inferior epigastric vein for "supercharging" if venous congestion occurs.[13] 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.

The choice of OFA or OA was at the discretion of the attending anesthesiologist, only some of whom were experienced with OFA. OFA was defined as the administration of no opioids either pre- or intraoperatively until wound closure, and opioids were only given when the patient was fully awake and had been administered nonopioid analgesics previously. OA was defined as the administration of any opioid during the pre- or intraoperative period. Postoperative opioids (after OFA or OA) were defined as the administration of opioids from the time of wound closure until discharge from the hospital.

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. Seven patients in the opioid group received total intravenous anesthesia (TIVA with remifentanil) without inhalation. Neuromuscular blockade (NMB) was achieved by the administration of rocuronium or cisatracurium in a continuous infusion to achieve periods of deep NMB when required.

Table 1 Patient characteristics.

Characteristic	OFA ($n=55$)	OA ($n=149$)	*P*-value
Age (years)	53.92±2.76	50.32±1.75	**0.045**[a]
Body mass index (kg/m^2)	25.01±0.83	25.33±0.65	0.609[a]
ASA physical status class	1.24±0.16	1.13±0.06	1.0[a]
Hypertension (%)	9.1	6.0	0.444[b]
Smoker (%)	9.1	3.4	0.092[b]
Motion sickness or previous PONV (%)	10.9	12.8	0.722[b]
Simplified Apfel score	2.42±0.18	3.01±0.08	**<0.001**[a]
Bilateral (%)	38.2	34.9	0.664[b]

Statistically significant *p* values are indicated in bold.
[a] Kolmogorov–Smirnov test.
[b] $\chi 2$ test.Data are presented as mean ± standard deviation except where indicated otherwise.ASA, American Society of Anesthesiologists; OA, opioid anesthesia; OFA, opioid-free anesthesia; and PONV, postoperative nausea or vomiting.

The method by which OFA was administered consisted of combining sympatholytics based on monitoring the analgesia nociception index (ANI).[14] Dexmedetomidine was administered as follows: 0.3 mcg/kg 15 min 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 maximal bolus doses of 10 mg lidocaine, 1 mg ketamine, and 1 mcg dexmedetomidine administered every 15 min on an as-needed basis.

Sufentanil was administered as the OA at a dose of 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 a dose of 0.20-0.35 mcg/kg/h. Since 2014, various adjunct medications (e.g., clonidine, dexmedetomidine, ketamine, and lidocaine) have been administered as a single dose to reduce the total dose of intraoperative opioids, and this still classifies as receiving OA. Both groups received paracetamol and ketorolac postoperatively.

All patients undergoing OFA were managed with goal-directed fluid therapy, receiving fewer than 1200 mL of intravenous (iv) fluids intraoperatively. Patients undergoing OA received more liberal fluid therapy. The OFA group consists therefore of a combination of zero intraoperative opioids with goal-directed fluid therapy.

Data collection

The following demographic data were retrieved: age, BMI, the American Society of Anesthesiologists (ASA) physical status class, history of hypertension, current or recent smoking, motion sickness, or previous PONV.

The presence of perioperative complications during the first postoperative month was graded according to the modified Clavien-Dindo (CD) classification.[15] The CD grades were converted to six categories for use in the statistical analysis, with grades 1, 2, 3a, 3b, 4a, and 4b converted to categories 1, 2, 3, 4, 5, and 6, respectively.[16] LOS was calculated as the number of nights spent in the hospital postoperatively.

DIEP flap failure was defined as the need for a revision procedure with a failure to preserve the initial flap. 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[16] (based on nonsmoking 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) and opioid usage during the first 24 h 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.[17] Postoperative flap skin temperature was measured every hour for the first 24 h after surgery and compared to the temperature of the surrounding skin (reference temperature).

Statistical analysis

The demographic data and clinical outcome parameters are expressed as the means and standard deviations, and were either analyzed using the Kolmogorov–Smirnov test or expressed as a percentage of cases and analyzed using the $\chi 2$ test. A multiple linear or logistic regression analysis was used to determine the independent effects of different continuous and categorical variables. Variables with an autocorrelation were removed. Variables were chosen based on a proven or assumed effect with a maximum of one predictor variable per 10 observations in the smallest group.[18] Statistical analyses were performed using the statistical package Stata/IC 15.1 for Mac (StataCorp, TX, USA).

Results

Patient characteristics

A total of 204 patients underwent unilateral or bilateral DIEP flap surgery at our institution from January 2014 to

Table 2 Complications categorized by the Clavien-Dindo classification.

Complication	OFA ($n=55$)	OA ($n=149$)	P-value ($\chi 2$)
CD I	9	67	
CD II	0	9	<0.001
CD I or II (minor complications)	9 (17.9%)	76 (51.4%)	<0.001
	0		
CD IIIa	0	1	
CD IIIb	1	8	
CD IVa	0	0	
CD IVb	0	0	
CD V	0	0	
CD III to V (major complications)	1 (1.8%)	9 (6.1%)	0.205

Statistically significant p values are indicated in bold.
OFA, opioid-free anesthesia; OA, opioid anesthesia; and CD, Clavien-Dindo classification.

April 2019, 73 of whom received bilateral DIEP flaps. Demographic and clinical characteristics of the OFA ($n=55$) and OA ($n=149$) groups are shown in Table 1. The simplified Apfel score was higher in the OA group ($P<0.001$), whereas age was higher in the OFA group. The age distribution was differently distributed between both groups justifying the Kolmogorov-Smirnov test instead of the Mann-Whitney U test.

Complications

The observed complications (grades I-V) are shown in Table 2. Grades I and II represent minor complications, whereas grades III, IV, and V represent major complications. No patients in either group experienced grade IV or V complications. The rate of minor complications was lower in the OFA group than in the OA group ($P<0.001$).

Nine surgical revisions were performed under general anesthesia (CD IIIb complications): one in the OFA group and eight in the OA group. The single patient in the OFA group required revision for combined arterial and venous thromboses. In the OA group, revision was required for arterial thrombosis in one patient, venous thrombosis in four patients, combined arterial and venous thromboses in one patient, and nonperfusion-related indications in two patients. Three patients in the OA group developed flap failure that required additional reconstruction using a non-free flap; one of these patients had undergone bilateral DIEP flap surgery and the other two patients had received a unilateral DIEP flap. One patient in the OA group underwent wound revision under local anesthesia (CD IIIa). Five revisions were performed out of 131 unilateral procedures (3.8%) and 5 revisions were performed out of 73 bilateral procedures (6.8%); these differences were not statistically significant ($P=0.336$). The number of minor complications was not different between the bilateral and unilateral procedures (41.1% vs. 42.7%, respectively).

Clinical outcomes

The clinical outcomes of both groups are shown in Table 3. There were no significant differences between groups for surgery duration, first reference skin temperature in the post-anesthesia care unit (PACU), incidence of postoperative vomiting, rate of flap failure or flap thrombosis, rate of reoperation in the first postoperative week, and LOS.

The volume of intraoperative fluids was lower in the OFA group (1.70 ± 0.30 mL/kg/h) than in the OA group (5.45 ± 0.44 mL/kg/h). Patients in the OFA group received a significantly lower number of prophylactic, as well as therapeutic, antiemetic drugs, and they had a lower incidence of postoperative nausea. They also received a lower quantity of opioids (morphine equivalents) and had a lower maximum VAS score in the first 24 h postoperatively; 40% of patients receiving OFA required opioids postoperatively in contrast to 87.3% of patients in the OA group.

When considering patients who received postoperative morphine, PONV occurred in 22.7% of patients in the OFA group and in 47.3% of those in the OA group ($P=0.034$). Patients with no history of motion sickness or PONV did not receive prophylactic antiemetics if they were in the OFA group; their rate of PONV was 6.25%. If an opioid was administered after OFA in patients with no history of PONV or motion sickness, the incidence of PONV rose to 16.67% ($P=0.042$). One or more prophylactic antiemetic drugs were always administered to patients who received OA. Even with the administration of prophylactic antiemetics in patients with no history of PONV, the incidence of PONV was 43.75% in OA patients who received no further opioids in the PACU and 46.39% in those who received additional opioids in the PACU ($P=0.419$).

Most patients (all except 2) with a history of PONV or motion sickness received an opioid postoperatively; their incidence of PONV were 50.00% and 60.87% after OFA and OA, respectively. ($P=0.659$).

Regression analysis results

Table 4 shows the results of analyses evaluating the association between various factors and PONV (logistic regression analysis), CD ranking (linear regression analysis), and LOS (linear regression analysis).

The OFA group had a lower incidence of PONV, lower CD ranking, and shorter LOS. Younger patients had a higher incidence of PONV, higher CD ranking, and shorter LOS. Higher BMI was associated with a longer LOS.

Table 5 shows the results of linear regression analysis evaluating the maximum postoperative VAS pain score and postoperative morphine consumption. OFA was associated with a lower VAS pain score and lower postoperative morphine consumption.

Table 6 shows the results of linear regression analysis evaluating the difference in skin temperature between the flap and surrounding (reference) skin. OA, high BMI, and a high first reference skin temperature in the PACU were associated with a greater skin temperature difference.

Table 3 Clinical outcomes.

Outcome	OFA ($n=55$)	OA ($n=149$)	*P*-value
Number of prophylactic antiemetic drugs	1.13±0.18	1.94±0.18	**<0.001**[a]
Postoperative nausea (%)	12.7	43.6	**<0.001**[b]
Number of therapeutic antiemetic drugs	0.14±0.12	0.57±0.12	**<0.001**[a]
Postoperative vomiting (%)	1.8	6.7	0.170[b]
Maximum postoperative VAS	1.87±0.65	4.94±0.54	**<0.001**[a]
Total morphine equivalents postoperatively (mg)	1.95±0.84	10.34±1.40	**<0.001**[a]
Intraoperative fluids (mL/kg/h)	1.70±0.30	5.45±0.44	**0.001**[a]
Duration of surgery (h)	6.42±0.95	6.73±0.32	0.854[a]
First reference skin temperature in PACU (°C)	34.96±0.41	34.90±0.35	0.186[a]
Skin temperature difference (flap - reference) (°C)	1.04±0.25	1.41±0.21	0.725[a]
Reoperation during the first week (*n*, %)	1 (1.8)	9 (6.1)	0.205[b]
Flap thrombosis (arterial or venous) (*n*, %)	1 (1.8)	5 (3.4)	0.389[b]
Flap failure (*n*, %)	0 (0)	3 (2)	0.283[b]
No opioid usage postoperatively (%)	60.0	12.7	**<0.001**[b]
Hospital LOS (days)	6.82±0.26	7.52±0.28	0.134[a]

Statistically significant *p* values are indicated in bold.
[a] Kolmogorov-Smirnov test.
[b] $\chi 2$ test.Data are presented as mean ± standard deviation except where indicated otherwise.OFA, opioid-free anesthesia; OA, opioid anesthesia; VAS, visual analog pain score; PACU, postanesthesia care unit; and LOS, length of hospital stay.

Table 4 Linear regression analysis for postoperative nausea and vomiting, Clavien-Dindo complications, and length of hospital stay.

Factor	PONV[a]		CD ranking[b]		LOS[b]	
	B coef	*P*-value	B coef	*P*-value	B coef	*P*-value
Type of anesthesia (OFA=1 and OA=0)	-1.821	**<0.001**	-0.536	**0.001**	-0.789	**<0.001**
Surgery laterality (unilat=1 and bilat=2)			−0.031	0.817	0.238	0.287
Age	-0.033	**0.032**	-0.015	**0.018**	0.026	**0.012**
Body mass index			0.007	0.679	0.117	**<0.001**
Smoker	-0.775	0.495				
Previous PONV	0.918	**0.050**	0.089	0.646	−0.112	0.724
Number of prophylactic antiemetics	-0.061	0.707				

Statistically significant *p* values are indicated in bold.
[a] Results of the logistic regression analysis.
[b] Results of the linear regression analysis.PONV, postoperative nausea and vomiting; CD, Clavien-Dindo classification; LOS, length of hospital stay; coef, coefficient; OFA, opioid-free anesthesia; OA, opioid anesthesia; unilat, unilateral; and bilat, bilateral.

Table 5 Linear regression analysis for maximum VAS score and morphine consumption postoperatively.

Factor	Maximum VAS[a]		Postoperative morphine[a]	
	B coef	*P*-value	B coef	*P*-value
Type of anesthesia (OFA=1 and OA=0)	-2.925	**<0.001**	-8.114	**<0.001**
Surgery laterality (unilat=1 and bilat=2)	-0.352	0.436	-0.197	0.855
Age	-0.032	0.112	−0.066	0.173
Body mass index	-0.072	0.229	0.012	0.931

Statistically significant *p* values are indicated in bold.
[a] Results of the linear regression analysis.coef, coefficient; OFA, opioid-free anesthesia; OA, opioid anesthesia; unilat, unilateral; and bilat, bilateral.

Discussion

In this study, we used a retrospective cohort to include every patient who underwent DIEP flap surgery over a 4-year period. OFA was used in approximately 25% of our patients, distributed equally over the study years. This usage was primarily based on the random availability of an anesthesiologist experienced with OFA.

The limitations of this study include the retrospective analysis and overall low incidence of major complications

Table 6 Linear regression analysis for skin temperature difference between the flap and surrounding skin.

Factor	Skin temperature difference[a] (flap – reference[b])	
	B coef	*P*-value
Type of anesthesia (OFA=1 and OA=0)	-0.586	**0.007**
Age	-0.016	0.069
Body mass index	0.058	**0.023**
Maximum postoperative VAS	-0.055	0.096
First reference skin temperature in PACU	0.143	**0.003**

Statistically significant *p* values are indicated in bold.
[a] Results of the linear regression analysis.
[b] The reference was an area of skin surrounding the flap.coef, coefficient; OFA, opioid-free anesthesia; OA, opioid anesthesia; unilat, unilateral; bilat, bilateral; VAS, visual analog pain score; and PACU, post anesthesia care unit.

and flap failures as compared to previous cohort studies. Intraoperative perfusion pressures and the total dose of vasoconstrictors were not recorded in sufficient detail to allow for analyses. Analgesics are not required intraoperatively but those that block orthosympathetic, metabolic, and inflammatory reactions or induce reflex depression, as Gray explained already in 1960,[19] are required instead. Sufficient sympatholysis was verified by using ANI monitoring (MDoloris, Lille, France) in OFA patients and if the nociceptive reaction was for more than 15 min below 50%, extra dexmedetomidine and lidocaine was given.

Previous studies in bariatric surgery reported that OFA[20] and ERAS[21] reduced postoperative opioid use by 75% and improved the outcome. In the current study, OFA was associated with a more than 80% reduction in opioid consumption in the first 24 h postoperatively.

The Clavien–Dindo classification (CD) was developed by Clavien in 1992 for cholecystectomy and modified by Dindo in 2004.[22] Recently, it has been used as an objective tool for grading morbidity after free-flap surgery.[23] CD found a difference for minor complications (CD I and II), but not for major complications. The rates of flap thrombosis and flap failure were lower in this study than in previous reports.[4] The linear regression analysis of the CD ranking showed more complications for OA and younger patients.

Patients in our OFA group received less intraoperative fluids (1.70 mL/kg/h) than those in the OA group (5.45 mL/kg/h). Nelson et al. reported that less than 7 mL/kg/h of intraoperative fluids increased the risk of postoperative thrombosis above their average rate of 4%.[24] Our rate of thrombosis was lower in OFA and OA (1.8% vs. 3.4%). Dexmedetomidine causes direct vasoconstriction,[25] but its indirect sympatholytic effects are more pronounced, which results in vasodilation. Free flaps are not innervated and might therefore elicit a hypothetical steal effect. Nunes did not find an induction of vasoconstriction in denervated flaps with the use of dexmedetomidine,[26] and we could not confirm the steal effect either, suggesting the importance of reducing the levels of circulating catecholamines. ERAS might increase perioperative hypotension and bradycardia,[27] which requires additional vasoconstriction. Dexmedetomidine and lidocaine have also been reported to reduce the activation of coagulation, and might therefore be more important for the prevention of thrombosis.[28,29]

One of our patients who received 6.1 mL/kg/h of fluids intraoperatively developed fluid overload, with delayed wound healing and prolonged hospitalization. This outcome appears contrary to Nelson's recommendation to give 8 mL/kg/h.[17] The judicious use of vasoconstrictors to maintain perfusion pressure may be superior to high fluid intake to avoid wound edema.[30] A clinical trial[31] found no difference in flap failure or LOS between 2 and 8 mL/kg/h of intraoperative fluids either, when norepinephrine was used to maintain the systolic blood pressure above 100 mmHg. The ERAS pathway recommends restrictive fluid therapy, with the administration of additional fluids when the pulse pressure variation exceeds 20%; these recommendations were followed in our OFA patients.[32]

The difference in skin temperature between free flap and surrounding skin might be a measurement of quality of perfusion. No difference was found between both groups except in the regression analysis.

Kroll et al.[33] reported the use of 0.74 mg/kg morphine equivalents in the first 24 h after DIEP flap surgery, which was substantially higher than the doses in both our OA and OFA groups (0.15 mg/kg and 0.03 mg/kg, respectively). Our findings show the importance of reducing intraoperative opioids to zero. The Apfel score differed between groups, because fewer patients required opioids after OFA.

PONV is common after DIEP flap breast reconstruction surgery, which occurs in up to 76% of patients[7]. PONV begins soon after awakening and persists for several days, notwithstanding the use of multiple rescue antiemetics. Although OFA itself reduces PONV, opioid use after OFA still increases PONV. Patients with previous PONV, more frequently required a small dose of opioids for pain relief in the PACU, even after OFA, and had a high rate of PONV despite the use of more prophylactic antiemetics. Apfel measured that TIVA as compared to inhalation reduced PONV because of the antiemetic effects of propofol from 38% to 31%.[34] Three of the seven cases receiving TIVA without any inhalation still had PONV. All DIEP flap patients in this study received propofol in a continuous infusion. The incidence of 44% in the OA group is still higher than the 13% in the OFA group.

Wade et al. recently reported a higher revision rate after bilateral DIEP flap surgery (23%) than after a unilateral DIEP flap procedure (11%)[1]. We likewise observed twice the number of revisions after bilateral surgery, albeit at a much lower frequency (6.8% vs. 3.8%).

LOS was not shorter in the OFA group except when other factors were included in a regression.

With a larger database, one can discuss the value of adding more variables in the regression analysis, but this would be based more on assumptions than on a proven impact.

In summary, we observed no differences in major complications between OFA combined with goal-directed fluid therapy and OA for DIEP flap surgery. OFA and goal-directed fluid therapy were associated in a regression analysis with

less minor complications, less pain and a reduced rate of PONV, less difference in skin temperature between the flap and surrounding skin, lower postoperative opioid use, and shorter hospital LOS.

Declaration of Competing Interest

Harold Mulier: None.
Bob De Frene: None.
Lara Benmeridja: None.
Florian Vanhoorebeeck: None.
Bruno Denis: None.
Bob Casaer: None.
Fabrice Rogge: None.
Kris Leleu: None.
Jan Mulier: Personal fees, department grants, financial, and nonfinancial support to organize scientific meetings from MSD Merck, GE Healthcare, and Johnson & Johnson outside the submitted work.

Acknowledgments

We would like to thank the members of the Department of Anesthesia, Reanimation, and Intensive Care, AZ Sint Jan Brugge, for their support of this study and for demonstrating the OFA technique to visitors from around the world. We would also like to thank members of the Department of Plastic and Reconstructive Surgery, AZ Sint Jan Brugge, for their collaboration in the search for improved patient care.

Financial disclosures

None for this submitted work. No support whatsoever was obtained to perform this study.
Clinical Trial Registry and Number: Clinicaltrials.gov, NCT 03202134.

References

1. Wade RG, Razzano S, Sassoon EM, et al. Complications in DIEP flap breast reconstruction after mastectomy for breast cancer: a prospective cohort study comparing unilateral versus bilateral reconstructions. *Ann Surg Oncol* 2017;**24**:1465–74.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin* 2019;**69**:7–34.
3. Blondeel PN. One hundred free DIEP flap breast reconstructions: a personal experience. *Br J Plast Surg* 1999;**52**:104–11.
4. Allen J. The evolution of perforator flap breast reconstruction: twenty years after the first DIEP flap. *Reconstr Microsurg* 2014;**30**:121–6.
5. Batdorf NJ, Lemaine V, Lovely JK, et al. Enhanced recovery after surgery in microvascular breast reconstruction. *J Plast Reconstr Aesthet Surg* 2015;**68**:395–402.
6. Mulier J, Wouters R, Dillemans B, De Kock M. A randomized controlled, double-blind trial evaluating the effect of opioid-free versus opioid general anaesthesia on post-operative pain and discomfort measured by the QoR-40. *J Clin Anesth Pain Med* 2018;**2**:015.
7. Manahan MA, Basdag B, Kalmar CL, et al. Risk of severe and refractory postoperative nausea and vomiting in patients undergoing DIEP flap breast reconstruction. *Microsurgery* 2014;**34**:112–21.
8. Hagau N, Longrois D. Anesthesia for free vascularized tissue transfer. *Microsurgery* 2009;**29**:161–7.
9. Li, B.,Li Y., Tian S.et al. Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: a meta-analysis. *Sci. Rep.* **5**, 12342.
10. Byon H, Ok S, Lee SH, et al. Dexmedetomidine inhibits phenylephrine-induced contractions via alpha-1 adrenoceptor blockade and nitric oxide release in isolated rat aortae. *Int J Med Sci* 2017;**14**:143–9.
11. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiol Scand* 2006;**50**:265–82.
12. Gherardini G, Gurlek A, Cromeens D, et al. Drug-induced vasodilation: in vitro and in vivo study on the effects of lidocaine and papaverine on rabbit carotid artery. *Microsurgery* 1998;**18**:90–6.
13. 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. *J Plast Reconstr Aesthet Surg* 2013;**66**:67–72.
14. Gazi M, Abitagaoglu S, Turan G, et al. Evaluation of the effects of dexmedetomidine and remifentanil on pain with the analgesia nociception index in the perioperative period in hysteroscopies under general anesthesia. A randomized prospective study. *Saudi Med J* 2018;**39**:1017–22.
15. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications. *Ann Surg* 2009;**250**:187–96.
16. 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.
17. McPherson ML. *Demystifying opioid conversion calculations: a guide for effective dosing*. American Society of Health-System Pharmacists, Inc; 2009. ISBN 978-1-58528-198-5.
18. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med* 2004;**66**:411–21.
19. Gray C. A reassessment of the signs and levels of anaesthesia. *Ir J Med Sci* 1960;**419**:499–508.
20. Mulier J, Dillemans B. Anesthetic factors affecting outcome after bariatric surgery, a retrospective leveled regression analysis. *Obes Surg* 2019;**29**:1841–50.
21. Sharif-Askary B, Hompe E, Broadwater G, Anolik R, Hollenbeck ST. The effect of enhanced recovery after surgery pathway implementation on abdominal-based microvascular breast reconstruction. *J Surg Res* 2019;**242**:276–85.
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–13.
23. Miyamoto S, Nakao J, Higashino T, et al. Clavien–Dindo classification for grading complications after total pharyngolaryngectomy and free jejunum transfer. *PLoS ONE* 2019;**14**(9):e0222570.
24. Nelson JA, Fischer JP, Grover R, et al. Intraoperative perfusion management impacts postoperative outcomes: an analysis of 682 autologous breast reconstruction patients. *J Plast Reconstr Aesthet Surg* 2016;**68**:175e183.
25. Talke P, Lobo E, Brown R. Systemically administered alpha2-agonist-induced peripheral vasoconstriction in humans. *Anesthesiology* 2003;**99**:65–70.

26. Nunes S, Berg L, Raittinen LP, et al. Deep sedation with dexmedetomidine in a porcine model does not compromise the viability of free microvascular flap as depicted by microdialysis and tissue oxygen tension. *Anesth Analg* 2007;**105**:666–72.
27. Anolik RA, Sharif-Askary B, Hompe E, et al. Occurrence of symptomatic hypotension in patients undergoing breast free flaps; is ERAS to blame? *Plast Reconstr Surg* 2020;**145**:606–16.
28. Zhang Y, Liu M, Ynag Y, Cao J, Mi W. Dexmedetomidine exerts a protective effect on ischemia-reperfusion injury after hepatectomy: a prospective, randomized, controlled study. *J Clin Anesth* 2019. doi:10.1016/j.jclinane.2019.109631.
29. Ganter MT, Hofer CK, Spahn DR, et al. The effect of clonidine on perioperative blood coagulation. *J Clin Anesth* 2005;**17**:456–62.
30. Anker AM, Prantl L, Strauss C, et al. Assessment of DIEP flap perfusion with intraoperative indocyanine green fluorescence imaging in vasopressor-dominated hemodynamic support versus liberal fluid administration: a randomized controlled trial with breast cancer patients. *Ann Surg Oncol* 2020;**27**:399–406.
31. Anker AM, Prantl L, Strauss C, et al. Vasopressor support vs. liberal fluid administration in deep inferior epigastric perforator (DIEP) free flap breast reconstruction – a randomized controlled trial. *Clin Hemorheol Microcirc* 2018;**69**:37–44.
32. Forget P, Lois F, De Kock M. Goal-directed fluid management based on the pulse oximeter–derived pleth variability index reduces lactate levels and improves fluid management. *Anesth Analg* 2010;**111**:910–14.
33. Kroll SS, Sharma S, Koutz C, et al. Postoperative morphine requirements of free TRAM and DIEP flaps. *Plast Reconstr Surg* 2001;**107**:338–41.
34. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004;**350**:2441–51.