

The Impact of Indocyanine Green Angiography on Fat Necrosis in Deep Inferior Epigastric Perforator Flap Breast Reconstruction

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Background: The deep inferior epigastric perforator flap (DIEP) is a widely known reliable option for autologous breast reconstruction. One common complication of DIEP procedures is fat necrosis. Consequences of fat necrosis include wound healing complications, pain, infection, and the psychological distress of possible cancerous recurrence. Clinical judgment alone is an imperfect method to detect at-risk segments of adipose tissue. Objective methods to assess perfusion may improve fat necrosis complication rates, reducing additional surgeries to exclude cancer and improve cosmesis for patients.

Methods: The authors performed a retrospective review of patients who underwent analysis of DIEP flap vascularity with or without intraoperative indocyanine green angiography (ICGA). Flap perfusion was assessed using intravenous ICGA and was quantified with both relative and absolute value units of fluorescence. Tissue with observed values less than 25% to 30% relative value units was resected. Postoperative outcomes and fat necrosis incidence were collected.

Results: Three hundred fifty-five DIEP flaps were included in the study, 187 (52.7%) of which were assessed intraoperatively with ICGA. Thirty-nine patients (10.9%) experienced operable fat necrosis. No statistically significant difference in incidence of postoperative fat necrosis was found between the 2 groups ($P = 0.732$). However, a statistically significant relationship was found between fat necrosis incidence and body mass index as both a continuum ($P = 0.001$) and when categorized as greater than 35 ($P = 0.038$).

Conclusions: Although ICGA is useful for a variety of plastic surgery procedures, our retrospective review did not show a reduction in operable fat necrosis when using this technology.

Key Words: indocyanine green angiography, DIEP flap, fat necrosis

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Over the past several decades, the deep inferior epigastric perforator flap (DIEP) has become a major workhorse in autologous breast reconstruction.^{1,2} However, despite advancements in flap optimization, fat necrosis remains a problematic complication for both the patient and the surgeon. Physiologically, fat necrosis is a benign and sterile inflammatory reaction that destroys adipocytes, resulting in fibrosis and calcification through saponification.³ This reaction is instigated by the release of blood and tissue lipase due to trauma, radiation, infection, or ischemia.⁴ Clinical secondary consequences of fat necrosis include wound healing complications, pain, infection, and the psychological distress of possible cancerous recurrence. The presence of fat necrosis may result in costly diagnostic tests to rule out malignancy. In addition, if the extent of fat necrosis is significant, it may necessitate revisionary procedures.

Given these repercussions, identifying, and preventing, this complication is preferable.

In a 10-year retrospective review of 758 DIEP flaps, fat necrosis was identified in 12.9% of patients,¹ and within the literature as a whole, the incidence of fat necrosis reportedly ranges anywhere from 10.2% to as high as 62.5%.^{5–7} One proposed explanation for the incidence of fat necrosis in the DIEP flap is the mismatch of the selected perforator with the tissue transferred. As demonstrated by the persistence of this problem, clinical judgment alone is an imperfect method to detect at-risk segments of adipose tissue. However, several technologies provide the ability to quantitatively assess the transferred tissue for adequate perfusion during the initial surgical procedure.

Indocyanine green (ICG; Akorn, Buffalo Grove, Ill) laser angiography (ICGA) offers surgeons the ability to intraoperatively assess tissue perfusion zones.^{6–15} This technique introduces water-soluble, biliary-excreted ICG dye into the intravascular circulation, where it binds to plasma proteins before being excited by an 805-nm laser. In its excited state, ICG emits fluorescence and the intensity of emission is detected by a camera device, allowing for real-time assessment of tissue perfusion.^{9,16} Within plastic and reconstructive surgery, ICGA has a number of common applications, including aiding in sentinel lymph node biopsy, the evaluation of mastectomy skin flaps in implant-based breast reconstruction, and the assessment of free tissue transfer perfusion.^{16,17} Use in free tissue transfer, specifically, involves evaluation of perforator perfusion before dissection, confirmation of perfusion during dissection and after transfer, and assessment of patency of arterial and venous anastomoses.^{18–20}

Although ICG has been shown increasingly useful for these purposes, the utility of angiography to prevent fat necrosis remains incompletely elucidated; in particular, fat necrosis often involves deeper tissue that the ICGA does not assess as visualization is limited to a depth of 1.0 to 1.5 cm.²⁰ Skin perfusion, however, may be representative of perfusion quality in the deeper adipofascial layer.¹² In this study, we present the results of our efforts to diminish the incidence of postoperative fat necrosis associated with DIEP flap breast reconstruction by using intraoperative ICGA to identify and excise tissue with suboptimal perfusion.

PATIENTS AND METHODS

After institutional review board approval, a retrospective review was conducted of DIEP breast reconstructions performed by 2 of the senior authors (H.S.H. and M.W.W.) between January 2009 and October 2013. The study population consisted of 355 flaps in 224 patients. One hundred eighty-seven flaps were assessed with intraoperative ICGA (SPY Imaging System, NOVADAQ Technologies; Mississauga, Canada), and 168 flaps were performed without intraoperative ICGA analysis. Use of intraoperative ICGA was determined by availability of the machine at the time of the procedure. Data collected included patient demographics, comorbidities, and postoperative outcomes. Clinical fat necrosis was defined as a palpable mass identified on physical examination that was asymptomatic and managed conservatively. Operable fat necrosis was defined as a palpable mass that was either symptomatic or significant enough to indicate surgical intervention during a second-stage procedure. Patients were excluded from the study if they had stacked DIEP

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TABLE 1. Cohort Demographic and Comorbidities (N = 355)

Characteristic	Total (%)	Non-ICGA (n = 168), n (%)	ICGA (n = 187), n (%)	P
Age, mean	58.73	58.83	58.4	0.568
BMI, mean	30.69	30.47	30.89	0.728
Diabetes mellitus	55 (15.4)	21 (12.5)	34 (18.2)	0.139
Tobacco use	56 (15.7)	24 (14.2)	32 (17.1)	0.465
History of chemotherapy	115 (32.4)	64 (38.1)	51 (27.3)	0.029*
Preoperative radiation	110 (30.9)	69 (41.1)	41 (21.9)	0.001†

**P* < 0.05.†*P* < 0.001.

flaps, received postoperative radiotherapy, lacked complete operative records, or lacked a minimum 90-day follow-up. Unfortunately, some pertinent details including extent of resection, flap weight, and perforator count were inconsistently documented and subsequently not available for data analysis.

The DIEP flaps were harvested using standard techniques, with microvascular anastomoses to the internal mammary vessels. Preoperative assessment of perforators was performed in all patients with computed tomography angiography and hand-held Doppler device. Up to 4 perforators were maintained in each flap. After flap elevation, ICGA was used intraoperatively to assess perfusion of both the DIEP and mastectomy skin flaps. Although remaining pedicled in the abdomen, DIEP flaps were examined on both the surface and undersurface of the flap. Flaps were also occasionally evaluated after microvascular anastomoses before de-epithelialization and inset. Patients assessed with the ICGA received 5 mg of ICG through peripheral intravenous catheters after a dwell time of at least 2 minutes to allow for stabilization of fluorescent signal. Repeat dosing was infrequently performed as needed with an intermission of at least 20 to 30 minutes to allow for washout and biliary excretion of ICG. Flap data from ICGA were quantified with both relative (RVUs) and absolute (AVUs) value units of fluorescence. Tissues (skin and fat) with RVU less than 25% to 30% were resected. Flaps may have been trimmed at both donor and recipient sites if inadequate perfusion was detected. Unless absolutely necessary for shaping and volume purposes, flaps were not tailored without ICGA evaluation. For flaps undergoing repeat dosing, changes were assessed by fluorescent values of residual dye before repeat injection. Other goals of ICGA included assessing blood flow over preexisting abdominal scars, evaluating perfusion of the contralateral hemiabdomen with a single-sided flap, and examining fat in the periphery of the more obese patients. For patients not assessed with ICGA, flap viability was determined intraoperatively with observation of flap color, capillary refill, Doppler signals, and punctate bleeding, with tissue resection based on subjective analysis at that time.

Data analysis was completed using R Version 3.4.1 “Single Candle.” Patients were separated into 2 groups for purposes of statistical comparison: those patients who were assessed intraoperatively with ICGA and patients who were assessed only with intraoperative clinical judgment. We performed statistical analysis of patient demographics including average age, average body mass index (BMI), tobacco use, history of diabetes, history of chemotherapy, and history of radiation. Body mass index was stratified by the World Health Organization obesity classification system: class I: BMI 30 to 35 kg/m² (obese), class II: BMI 35 to 40 kg/m² (severely obese), and class III: BMI 40 kg/m² and greater (morbidly obese).²¹ Surgical outcomes analyzed included flap loss, breast wound dehiscence, hematoma, seroma, mastectomy skin loss,

infection, clinical fat necrosis, and operable fat necrosis. χ^2 analysis was performed for all nominal variables, and a *t* test was performed for all continuous variables. Logistic regression was performed to assess potential correlations across fat necrosis, BMI, and BMI class.

RESULTS

Patient Demographics

Of 355 DIEP flaps performed on 224 patients, 187 flaps were assessed using intraoperative ICG fluorescent angiography, and 168 flaps were assessed intraoperatively using only the clinical evaluation of the senior surgeon. The 2 study groups had similar demographic profiles, although the patients in the non-ICGA group were more likely to have a history of chemotherapy (*P* = 0.029) and preoperative radiation (*P* = 0.001). The average age for all patients included in the study population was 58.7 years, and the average overall BMI was 30.7 (Table 1). The average follow-up time for all patients included in this study was 15.5 months (12.8 for ICGA patients and 19.6 for non-ICGA patients).

Surgical Outcomes

Surgical complications of DIEP procedures are shown in Table 2. Flaps were analyzed for an average of 102 seconds. The mean relative and absolute values of resected tissue were 25.8 and 24.2, respectively. The patients assessed with ICGA intraoperatively experienced statistically significant higher incidence of breast wound dehiscence (14.9%) compared with those not assessed with ICGA (7.3%, *P* = 0.03). No statistically significant differences were found for the incidence of either clinical (*P* = 0.386) or operable (*P* = 0.877) fat necrosis between patients assessed with ICGA and patients assessed clinically.

Body Mass Index and Fat Necrosis

Logistic regression analysis revealed a strong statistical relationship between BMI and incidence of fat necrosis (*P* = 0.015); no other significant predictors were identified (Table 3). Table 4 shows the incidence of fat necrosis for different BMI groups and ICGA utilization. No statistically significant difference in incidence of overall, clinical, or operable fat necrosis was found between the ICGA and non-ICGA patients within all BMI groups. However, when stratifying BMI by obesity class and removing the variable of ICGA, a separate binary logistic regression model revealed an increased risk of developing operable fat necrosis

TABLE 2. Postoperative Complications (N = 355)

Complication	Total (%)	Non-ICGA (n = 168), n (%)	ICGA (n = 187), n (%)	P
Seroma	2 (0.56)	2 (0.56)	0 (0)	NA
Hematoma	20 (5.6)	12 (7.1)	8 (4.8)	0.243
Dehiscence	42 (11.8)	13 (7.7)	29 (15.5)	0.024*
Mastectomy skin necrosis	20 (5.6)	13 (7.7)	7 (3.7)	0.103
Surgical site infection	21 (5.9)	8 (4.7)	8 (4.3)	0.168
Total flap failure	15 (4.2)	8 (4.7)	7 (3.7)	0.634
Clinical fat necrosis	49 (13.8)	26 (15.4)	23 (12.3)	0.386
Operative fat necrosis	39 (10.9)	18 (10.7)	21 (11.2)	0.877

**P* < 0.05.

NA, not applicable.

TABLE 3. Logistic Regression Analysis for Independent Predictors of Operable Fat Necrosis (N = 355)

Risk Factor	P
ICGA	0.895
BMI	0.001*
Age	0.216
Tobacco use	0.758
Diabetes mellitus	0.609
History of chemotherapy	0.170
Neoadjuvant radiation	0.832

*P < 0.01.

at BMIs greater than 35 (odds ratio, 2.48; 95% confidence interval, 1.05–5.86; $P = 0.038$; Table 5).

DISCUSSION

In our study, intraoperative evaluation of DIEP flaps with ICGA was unsuccessful in preventing fat necrosis. We certainly observed regions of hypoperfusion with regularity, particularly in the lateral subscarpal fat. As flap tailoring was almost exclusively guided by SPY data, one possibility is that these regions were within areas that would have ordinarily been excised for shaping, volume reduction, or classical fat necrosis prophylaxis. Hembd et al¹⁵ found that an additional average of 84.9 g is resected prophylactically when ICGA is not used, although fat necrosis incidence was unaffected in this component of the study. In addition, the ICGA system's primary limitation, as frequently cited by the literature, is a lack of visualization depth. Previous authors have found ICGA devices to accurately visualize perforator perfusion zones to a depth of 1 to 1.5 cm.^{20,22,23} Given that the adipose tissue in these flaps often goes deeper than 1.5 cm, this system may not be able to detect at-risk areas of hypoperfusion.

Alternatively, our method for determining tissue excision may not have been sensitive enough to predict and prevent fat necrosis. In our study, we used quantitative units of fluorescence (cutoff of RVU or AVU 25%–30%) to guide resection of hypoperfused tissue. Overall, the clinical relevance of value units of perfusion has not adequately been explored in the setting of autologous breast reconstruction.^{15,24,25} Several investigators have attempted to use both absolute and normalized scores relative to adjacent tissue, primarily in assessment of mastectomy skin flaps. These thresholds have varied widely, with analogous relative perfusion units considered more established than absolute perfusion units in predicting necrosis.^{16,24,26} This is because ICG's ability to bind to plasma proteins can be altered by plasma and vascular changes due to smoking, diabetes mellitus, and tumescent solution, thereby confounding absolute fluorescence.^{16,24,26,27} Indeed, Fourman et al²⁶ concluded

TABLE 4. Incidence of Operable Fat Necrosis Stratified by BMI (N = 355)

BMI	Total (%)	Non-ICGA (n = 168), n (%)	ICGA (n = 187), n (%)	P
≤25 (underweight)	3 (7.0)	3 (7.0)	5 (11.6)	0.72
25–29 (normal)	8 (8.5)	7 (7.4)	7 (7.4)	0.94
30–34 (class I obesity)	10 (9.8)	11 (10.8)	12 (11.8)	0.81
35–39 (class II obesity)	6 (15.8)	8 (21.1)	5 (13.2)	0.59
≥40 (class III obesity)	7 (20.0)	8 (22.9)	4 (11.4)	0.46

TABLE 5. Logistic Regression Analysis for Predicting Operable Fat Necrosis by Obesity Class (N = 355)

BMI	Odds Ratio	95% Confidence Interval	P
BMI 30–34.9	1.245	0.507–3.055	0.632
BMI ≥ 35	2.482	1.050–5.864	0.038*

*P < 0.05.

that absolute values demonstrate too much variability between each individual patient and recommended use of a normalized value instead. Relative perfusion units are considered predictive for mastectomy flap necrosis between 15.6% and 41.6%,²⁴ but a specific consensus for methods, numbers, and parameters remains lacking.

Several other studies in recent years have also explored the use of intraoperative ICGA evaluation to reduce rates of fat necrosis among DIEP flaps.^{6,9–14} A strong conclusion is difficult to obtain from these studies, however, because of unclear and variable definitions of fat necrosis,^{28,29} differing criteria for tissue resection and different technologies used by surgeons to assess intraoperative flap perfusion. In a large retrospective study of 560 DIEPs assessed using the SPY Elite (Stryker; Kalamazoo, Mich), a fat necrosis incidence of 8.5% was found in the ICGA group versus 16% in the non-ICGA group.¹⁴ In this study, however, ICGA was only used when flap vascularity was thought to be compromised, introducing inherent bias into the comparison. Fat necrosis in this study was defined as a palpable mass greater than 1 cm on physical examination or imaging studies, and subjective assessment according to the authors guided tissue excision. Two other studies used a different angiography device (Photodynamic Eye; Hamamatsu Photonics) to predict fat necrosis. A smaller study of 61 patients suggested that intraoperative ICGA evaluation reduced the incidence of fat necrosis from 59.5% to 29%.⁶ However, subgroup analysis based on flap size demonstrated a statistically significant difference in fat necrosis was only found with grade II masses, defined as 5% to 15% of the total flap. Fat necrosis in this study was assessed with clinical examination and ultrasound imaging. Surgeon judgment along with qualitative data guided excision: dark areas were excised, and gray areas were removed in thin patients. Finally, in a randomized controlled clinical trial of 51 patients, Varela et al¹⁴ reduced the rates of fat necrosis from 59.3% to 8.3% using Photodynamic Eye as a guide for excision of hypoperfused tissues. Fat necrosis in this study was assessed with ultrasound or computed tomography scans, and tissue excision was determined qualitatively—blue or dark areas were removed.

In addition, it is possible that technological and procedural updates to various ICGA systems over the past several years could be partially responsible for the success seen in other groups. The NOVADAQ SPY imaging system made its commercial debut in 2005 but did not see broad commercialization until 2009 through 2012 when it was upgraded to the SPY 2001 system.³⁰ Our data set, consisting of patients during this early period from 2009 to 2013, was collected and analyzed over 7 years before publication. In 2015, the product was rebranded as the SPY ELITE system and was eventually sold to Stryker Corporation in 2017. As of 2020, the SPY Elite system retains only a single (800 nm) imaging channel but has a 241.3-cm² field of view with a 1-cm depth of penetration and a 190-μm resolution.²⁴ Compared with the SPY system specifications in 2010, these are substantially improvements in field of view (56 cm²) and depth of penetration (1 mm), with resolution not specified as recently as 2016.^{22,23} As no study reported their specific SPY specifications at the time of data collection, we cannot assess what impact these updates may have had in their ability to flap perfusion. However, it is nonetheless likely that more recent studies may have used updated, more powerful imaging systems compared with when we

used the technology. Furthermore, widespread reports throughout the surgical literature over the past decade have resulted in protocol evolution and the natural progression of surgeon experience, comfort, and clinical decision making.^{7,13,16,19,21–23,31,32} Together, these factors likely account for reasonable progression in improved clinical outcomes compared with a then-immature system. However, the basic principles of the technology have not changed, and these limitations may still remain for those without the upgraded system.

One interesting trend that was observed by our study is a positive logistic relationship between BMI, particularly when greater than 35, and the incidence of fat necrosis. A systematic review of fat necrosis in autologous breast reconstruction reported 5 articles that demonstrated higher rates of the complication in obese patients³; however, this relationship was only present in patients who received pedicled transverse rectus abdominis muscle (TRAM) flaps (15.4% fat necrosis rate in obese patients vs 9% in nonobese patients). Fat necrosis rates were lower in free TRAM and DIEP flap obese patients compared with nonobese patients (7.8% vs 6.1% and 9.9% vs 11.4%, respectively). Another systemic review also failed to demonstrate a statistically significant relationship between obesity and fat necrosis for muscle-conserving flap patients.³³ The difference in fat necrosis rates for TRAM and muscle-conserving flaps may be related to the difference in vascularity between the 2 techniques. The DIEP flaps may have a higher risk of ischemia because of the lack of small vessels within the muscle fascia of TRAM flaps.² Vascularity has been proposed to play a significant role in the etiology of fat necrosis. Namely, several studies have observed decreasing fat necrosis rates with increasing perforator number.^{34–36} However, this observation has not been universal, with Gill et al¹ finding an increasing incidence of fat necrosis with increasing perforator number; this may be due to a selection bias toward incorporating additional perforators among patients with smaller, low-quality vessels lacking large dominant perforators. Further specific studies, accounting for confounders such as perforator number and flap weight, are necessary to clarify possible etiologies and patient characteristics associated with fat necrosis.

This study has several limitations. Our patient population was not randomized and therefore bias may be inherently introduced into our data. As previously discussed, the retrospective nature of our study limits the standardization of patients to better assess the utility of intraoperative angiography. Deficiencies in operative documentation neglect pertinent flap variables including flap weight and perforator count, and other nondocumented factors such as blood pressure and room temperature may also potentially influence intraoperative imaging and alter results. Finally, our inability to detect distinctions in fat necrosis incidence among the separate classes of obesity despite apparent trends and an independent association with BMI may be secondary to inadequate power within each subpopulation.

CONCLUSIONS

Intraoperative ICGA has become widely used in plastic surgery to evaluate free flap viability and prevent mastectomy skin flap necrosis in breast reconstruction; however, the available studies seem to demonstrate more the inherent clinical variability of results and technical limitations of this technology rather than generating consensus findings. Our retrospective review of a sample from 2009 to 2013 demonstrated that intraoperative evaluation of DIEP flaps with ICGA did not accurately predict fat necrosis in autologous breast reconstruction patients. However, this may change as ICGA techniques and technology improve.

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