Application of Indocyanine Green in Flap Surgery: A Systematic Review

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J Reconstr Microsurg 2018;34:77–86.

Abstract

Background The vascularization of the distal portions of transferred tissue represents the most critical factor in the success of reconstructive surgery. In recent years, indocyanine green (ICG) fluorescence imaging techniques have been applied during surgery to evaluate flap perfusion. However, this investigation has found that there is little consensus regarding the standard dose of ICG as well as the pre-operative requirements of ICG allergy testing. The aim of this study is to summarize the applications of ICG to tissue transfers and safe dosing practices and to provide insight to the possible adverse effects of ICG on flap surgery with the goal of helping clinicians apply ICG safely and efficiently to tissue transfer procedures.

Methods A literature search was performed using, Wiley InterScience, and Springer with the key words, 'Flap,' 'indocyanine green,' 'surgery,' and related mesh words for all publications between 2005 and 2015. Title and abstract screening was performed using predefined in- and exclusion criteria.

Results Seventy-three articles were included. These were classified as "application of ICG in flap surgery" and "the security of applying ICG in flap surgery".

Conclusions ICG fluorescence imaging preoperatively facilitates the detection of perforators in tissue flaps with thickness <20 mm, aids in the evaluation of flap microcirculation and perfusion, and allows surgeons to select dominant cutaneous nerves while evaluating the quality of vascular anastomoses and locating thromboses. The literature also concluded that potential allergic reactions to ICG should be taken into consideration.

Keywords
- indocyanine green
- fluorescence imaging
- flap surgery

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received
December 12, 2016
accepted after revision
July 31, 2017
published online
October 9, 2017

DOI https://doi.org/10.1055/s-0037-1606536.
ISSN 0743-684X.

The vascularization of distal portions of transferred tissue represents the most critical factor for the success of reconstructive surgery. The flap selection represents a careful balance between blood supply (random, axial, or perforator based) and geometry of tissue needed.[1] Although practitioners have successfully applied several methods, including ultrasound, magnetic resonance imaging (MRI), and computed tomographic angiography (CTA), to detect perforators and main vessels in transferred tissue, these procedures are unreliable in predicting the degree of flap blood perfusion.[2–4] Currently, the evaluation of flap vascularization, regardless of type, is based on clinical experience and subjective evaluation of tissue color, flap temperature, capillary reperfusion, and assessment of arterial bleeding on flap edges. Objective methods such as oxygen partial pressure, capillaroscopy, laser Doppler flow measurement, thermography, and photoplethysmography have been evaluated clinically,[1] but these techniques have never been applied systematically to the operative process due to high cost, complexity, low sensitivity, and a high rate of false positives and false negatives. Our field is still searching for a protocol that describes an effective, reliable, and stable process to evaluate flap blood perfusion.

In the past few decades, a near-infrared fluorescence imaging device, used in medical diagnostics, has been used by plastic surgeons during procedures. This method uses indocyanine green (ICG) as contrast agent. When protein-bound ICG is exposed to light at wavelengths of 750 to 810 nm, ICG emits fluorescence that peaks at ~840 nm. The light needed for excitation is generated by a near-infrared light source attached directly to a camera equipped with a special filter. A digital video camera allows the absorption of the ICG fluorescence to be recorded in real time, allowing perfusion to be assessed and documented. ICG is used as a marker to assess the perfusion of tissues and organs, including retinal blood vessels, liver and lung tumors, and lymphedema.[5,6] ICG fluorescence imaging has also been proven to significantly improve the accuracy of flap blood perfusion evaluation.[7] It has been reported to be useful in identifying the best perforator during operations and in reducing the incidence of postoperative complications, such as flap necrosis and congestion.[8,9]

However, a standardized protocol for the use of ICG in tissue transfers remains elusive. There is no consensus about the routine dose of ICG and the requirement for preoperative allergy testing. Clinical institutions apply ICG differently from procedure to procedure. ICG may be used to design the flap, to assess flap perfusion, to evaluate the patency of microvascular anastomoses, to monitor the flap postoperatively, and to check lymphatic system function.[1,10–12] The aim of this study is to summarize the utility of ICG in tissue transfer surgery and to evaluate the maximum safe dose, routine dose, pre-operative allergy testing protocols, relevant contraindications, and the potential adverse effects in flap surgery; all of which will assist clinicians in applying ICG safely and efficiently.

Methods

Data Source and Search Strategy

A literature search was performed using, Wiley InterScience, and SPRINGER. Searches were based on the following key words: "Flap," "Indocyanine green," "Surgery, and the related mesh words. Due to the large increase in publications in the previous 10 years, the search focused on studies published during the period June 1, 2005 to June 30, 2015. Title and abstract screening was performed using predefined inclusion and exclusion criteria. Publications identified by the prior criteria were screened individually on a full-text basis. The selection process of the articles is shown in ►**Fig. 1**.

Inclusion and Exclusion Criteria

A total of 881 articles were obtained by the search query. All articles were screened manually for relevance by the authors following the inclusion and exclusion criteria. The inclusion criteria covered the articles related to the key words, "'Flap," "Surgery," and "Indocyanine green." The exclusion criteria included duplicates, animal experiments, and non-English articles.

Results

Application of ICG in Flap Surgery

Pre-Operative Application of ICG

Pre-Operative Identification of Perforators

The location of perforators is important for preoperative flap design as the preoperative identification of perforators can significantly shorten operation times and improve surgical outcomes.[13,14] The most common methods to locate perforators include CTA and Doppler ultrasound.[15] Onoda et al[16] combined multidetector-row computed tomography (MDCT), Doppler flowmetry, and ICG fluorescent angiography to preoperatively identify perforator vessels of flaps for reconstruction in 50 patients. Then, they dissected and verified the test results during procedures. They found that MDCT had a 100% (35/35) positive predictive value and a 70% (35/50) sensitivity in detecting perforators. Doppler flowmetry had an 80% (40/50) positive predictive value and a 100% (50/50) sensitivity in detecting perforators. ICG fluorescent angiography had an 84% (42/50) positive predictive value and a 76% (38/50) sensitivity in detecting perforators. In consideration of the low positive predictive value and insensitivity, this evidence suggests that using ICG dye alone to mark a perforator is not an optimal approach. ICG fluorescent angiography seems better utilized when limited to a final confirmation of the perioperative position of the perforator after identification by MDCT or Doppler ultrasound and when restricted to evaluating the dominant perforating branch of a previously identified vessel. Onoda et al also suggest that ICG fluorescent angiography should be used to confirm the detection of perforators when tissue thickness is <20 mm. Pestana and Zenn[17] did not consider ICG fluorescent angiography suitable for preoperative location of perforators, but found the method useful for intraoperative evaluation of blood perfusion, particularly when comparing the efficacy of ICG fluorescent angiography with CTA.

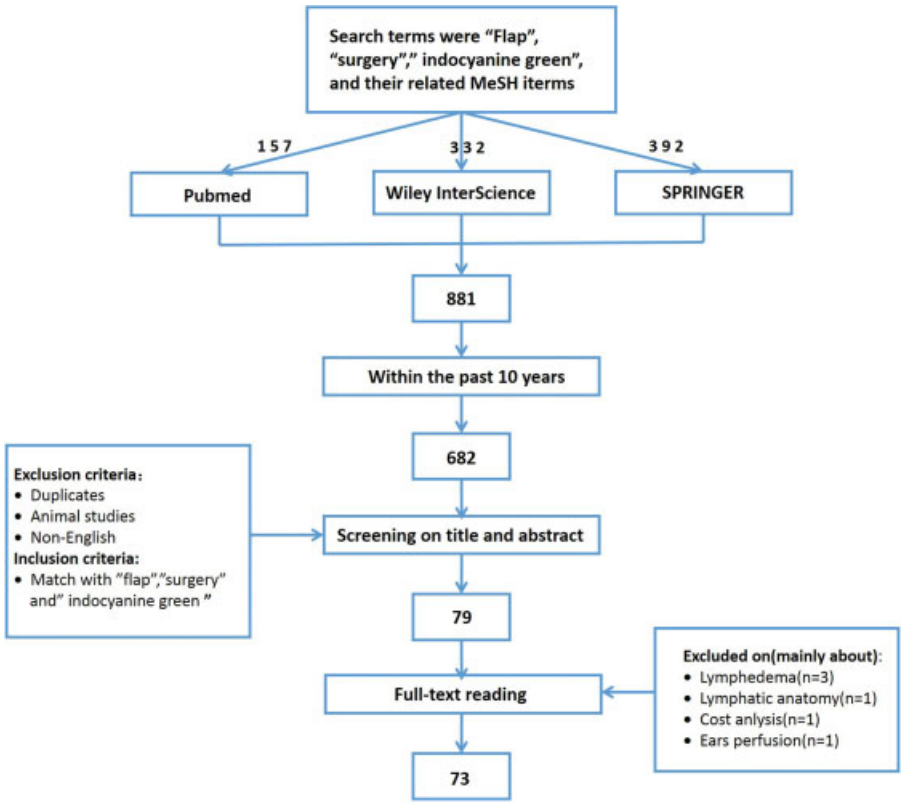

Fig. 1 Flowchart.

Prediction of Optimal Timing for Second-Stage Operations in Vascular Delay Procedures

When a large flap is harvested to cover an outsized defect, the remaining vascular network in that flap must be able to support the entire flap. To assess the vascular supply of an outsized flap, most surgeons prefer to use the vascular delay method, which contains at least two procedural stages. After the first stage operation, ischemia stimulates the dilation of constricted vessels and angiogenesis.[18] Christensen et al.[19] and Lee et al[20] used laser-assisted ICG imaging to assess perfusion in free flaps and to inform when and how to divide the target tissue. They concluded that 3 weeks following a first-stage operation was the best time for a second-stage operation. In their experience, ICG fluorescent angiography was useful in decreasing the probability of flap necrosis.

Intraoperative Application of ICG

Intraoperative Evaluation of Microcirculation Perfusion in Flaps

Adequate perfusion of flaps is essential for the postoperative survival. Compromised arterial supply and venous drainage cause postoperative complications, such as flap necrosis.[21,22] Murono et al[21] found that the intrinsic transit time of the flap, which was defined as the period from when the dye appeared at the arterial anastomosis until it reached the suture line of the venous anastomosis, was ~10 seconds in six free jejunum flaps. Holzbach et al[23] discovered that the mean transit time between arterial inflow and venous outflow was 32.8 seconds in eleven free flap cases. The intrinsic transit time of a muscle flap was 27.7 seconds as compared with 47.5 seconds in fasciocutaneous and perforator flaps. Holm et al[22] evaluated the use of ICG fluorescent angiography in 100 free-flap cases and classified intrinsic transit flow time of >90.0 seconds as venous delay. This delay suggested that microthrombi, existing in the microcirculation of flaps, might elevate the risk of postoperative flap necrosis and congestion. Though no consensus seems to exist for quantifying clinical venous congestion, 90.0 seconds is a suggested threshold for identifying venous delay and pre-emptively assisting venous drainage via supercharging. Nasser et al[24] found that ICG reliably detects venous congestion in animal models at occlusion rates ≥85%, enabling surgeons to intervene immediately.

While the above-mentioned studies focused largely on the evaluation of perfusion related to one perforator in transferred tissue, when multiple perforators are present in a single flap, surgeons must be able to select and keep the one that will ensure the highest probability of success. Douglas et al[25] dissected and applied ICG fluorescent angiography to perforators found on either the left or right side of 25 deep inferior epigastric perforator flap (DIEP) flaps. There was no significant difference between the quality of medial and lateral perforators in perfusing zone IV of DIEP flaps. Statistical analysis also confirmed that the perfusion of zone IV fat and skin was significantly higher ($p < 0.0001$) when a single perforator was used to supply the flap than that when two perforators were used. The study concluded that DIEP flaps have poor venous return, and the use of two perforators was

likely to increase the load of venous reflux, thereby leading to postoperative venous congestion. Single superior perforators provided significantly ($p < 0.0001$) better perfusion than that provided by single inferior perforators.

Following the application of ICG fluorescent angiography, SPY-Q quantitative software (Novadaq SPY Elite) is often applied to the analysis of fluorescent intensity in different segments of flaps to assist in the evaluation of the microcirculation perfusion in each zone.[26,27] While there are many ICG fluorescent angiography devices available, including handheld devices (Hamamatsu PDE) and integrated microscope systems (Mitaka, Zeiss), SPY-Q software from SPY Elite is the analytical tool of choice for measuring fluorescence intensity. Munabi et al[28] reported that absolute values (SPY-Q numbers) below 6.0 to 7.0 should be considered areas of critically low vascular perfusion and should be appropriately managed based on collective clinical experience. Moyer et al[29] demonstrated that the threshold of SPY-Q numbers for flap necrosis and stable survival were 6.30 and 12.3, respectively, through 118 cases.

It was also reported that hypertension reduces the probability of flap necrosis, and smoking reduces the probability of flap survival. In another study, Duggal et al[30] found that the 184 patients who underwent post mastectomy breast reconstruction using ICG angiography imaging had a lower incidence of mastectomy skin necrosis and unexpected reoperations for perfusion-related complications as compared with 184 patients without ICG angiography. This research suggested that the use of ICG angiography during post mastectomy breast reconstruction for evaluating the perfusion of flaps was beneficial and cost effective. Lohman et al[31] made a systematic analysis of 11 articles (198 cases) discussing intraoperative ICG fluorescent angiography for evaluating the perfusion of flaps. They concluded that the sensitivity of intraoperative ICG fluorescent angiography was 90.9%, and the accuracy was 98.6%. ICG has been increasingly applied to evaluate the perfusion of a variety of different types of flaps (►**Table 1**) and has made significant contributions to operative success.

Intraoperative Evaluation of Microcirculation Perfusion in Wound Closure

Assessing the intraoperative perfusion of the border area of transferred tissue has long been possible using traditional methods, such as capillary reperfusion. Deficiencies in capillary perfusion are understood to lead to an increased probability of postoperative flap necrosis. This phenomenon is related to tension in wound closure. High tension not only

Table 1 Application of ICG in different types of flaps

Types of flaps	Number of literatures	Subjects	Study
Latissimus dorsi musculocutaneous flap	2	12	Okazaki et al[80]; Kuriyama et al[63]
DIEP/TRAM	16	652	Casey et al[65]; Munabi et al[28]; Duggal et al[30]; Douglas et al[25]; Sood et al[52]; Moyer et al[29]; Losken et al[48]; Newman et al[81]; Quilichini et al[82]; Newman et al[87]; Mohebali et al[83]; Lee et al[49,84]; Komorowska[85]; Yamaguchi [91]; Holm et al[89,92]
ALT	3	30	Sacks et al[54]; Nagata et al[50]; Buehrer et al[10]
Random pattern skin flaps	1	7	Wyles et al[33]
Osteocutaneous flap[a]	3	23	Valerio et al[27]; Taylor et al[60]; Nagata et al[50]
Adipofascial cutaneous flap	1	15	Kijima et al[68]
Venous flaps	1	3	Giesen et al[72]
Jejunum flaps	1	6	Murono et al[21]
Intercostal muscle flap	1	27	Piwkowski et al[47]
Pericranial Flaps	1	22	Yano et al[59]
Superficial circumflex iliac artery perforator flap	1	12	Iida et al[71]
RF	3	22	Hayashi et al[64]; Taylor and Jorgensen[60]; Nagata et al[50]
Delayed flaps	1	2	Lee et al[49,84]
Forehead flaps	3	17	Surowitz et al[61]; Shah et al[76]; Woodard et al[26]
Sural flaps	1	1	Suzuki et al[88]

Abbreviations: ALT, anterolateral thigh flap; DIEP, deep inferior epigastric perforator flap; ICG, indocyanine green; RF, radial forearm flap; TRAM, transverse rectus abdominus myocutaneous.
[a]It is a flap combining bone and skin.

induces scar hyperplasia but also reduces perfusion in the wound.[32,33] Wyles et al[32] applied intraoperative ICG fluorescent angiography to seven cases of wound closure. Wound closures, which showed evidence of ischemia caused by undue tension, were relieved by modification of suture placement. Results showed that this intervention prevented necrosis. Furukawa et al[33] divided 17 patients into two groups. In the first group, where the microcirculation perfusion of wound closure was not evaluated with ICG fluorescent angiography, results showed 89% patients with postoperative wound dehiscence. In the second group, when ICG fluorescent angiography was applied and few suture modifications were performed, only 13% of patients had postoperative wound dehiscence ($p = 0.003$). This research suggests that intraoperative application of ICG fluorescence angiography is effective in preventing postoperative wound dehiscence.

Intraoperative Evaluation of Microcirculation Perfusion in Nerves

Reconstructive surgery utilizes flaps including cutaneous nerves to restore the sensation of human body. However, few researches have demonstrated the survival and vitality of the nerves in the transferred tissue.[34] Tanaka et al[35] applied ICG fluorescence angiography to eight patients who underwent reconstructive surgery with nerve defects using free anterolateral thigh flaps. This study associated the perfusion of cutaneous nerves with the intensity of fluorescence in those nerves. Tanaka et al also showed that intraoperative ICG fluorescence angiography is a reliable and objective method for selected donor nerves.

Intraoperative Evaluation of Vascular Anastomosis

Vascular anastomosis is a critical stage during free flap transplantation surgeries.[36] Not efficient anastomosis frequently leads to flap necrosis, arteriovenous crisis, and other complications. On-time detection during surgery of poor anastomosis and immediate repairing by surgeons can increase tissue survival rates. However, the traditional methods to assess vascular anastomoses not ensure an accurate blood flow detection at the anastomotic site. Holm et al[22] applied ICG fluorescence angiography for vascular anastomosis evaluation during 50 free flaps and compared the postoperative changes. They reported that, in comparison with traditional methods, ICG fluorescence angiography resulted in higher sensitivity, and negative ICG fluorescence angiography outcomes were strongly associated with postoperative complications, such as venous congestion.

Microthrombus Detection during Free Flap Re-exploration

Pedicle tortuosity, hematoma, vasospasm, dressing compression, and thrombosis may lead to postoperative vascular complications or sudden decreases in blood supply to free flaps. According to Chen et al,[37,38] in a retrospective analysis of 1000 free flap cases, over half of the postoperative re-explorations were due to microthrombus formation. Holm et al[39] used ICG fluorescence angiography in 20 postoperative re-exploration surgeries for thrombus detection with a sensitivity of 100% and specificity of 86%. This seems to indicate that ICG fluorescence angiography is a microthrombus detection method with high accuracy.

Postoperative Application of ICG

Postoperative Detection for Arteriovenous Abnormality

Local flap necrosis is often due to abnormal arterial supply or venous reflux resulting from postoperative flap hematoma, exudation, and over-pressure.[40] The areas with abnormal blood supply or venous reflux are sometimes larger than the visible necrotic areas. Hagopian et al[12] noted that in one case of postoperative flap necrosis, ICG fluorescence angiography identified a non-fluorescent dark area larger than the visible necrotic area, and after a few days, the necrotic area was expanding to non-fluorescent dark region. His findings indicated that postoperative ICG fluorescence angiography could predict the area of arteriovenous abnormality and provide a useful information when abnormal areas have to be reconstructed. Krishnan et al[41] found two cases of venous congestion in eight tissue transfers following postoperative ICG fluorescence angiography. However, every case in this series later demonstrated adequate perfusion recovery. Though ICG fluorescence angiography is an effective method to detect arteriovenous abnormality, due to its "oversensitivity," clinical presentation should always be taken into consideration when ICG is used to evaluate flap prognosis.

Postoperative Examination of Lymphatic Recovery of Flaps and the Recipient Areas

Lymphatic circulation is often damaged in free tissue transfers. Through ICG fluorescence imaging in a patient who had received a free flap transplantation 4.5 years prior, Mihara et al[42] found that lymphatic reconnections had formed between the recipient area and the flap and that ICG injected into the proximal site of the recipient area had drained out of the flap. This showed that ICG can also be used to monitor the lymphatic tissue flap transferred. Akita et al[43] performed ICG fluorescence imaging in 13 cases of lower limb lymphedema patients who received vascularized-free lymph nodes transfers and found that lymphedema improved, and lymph flow was enhanced. This suggests that ICG fluorescence imaging can be used to evaluate the lymphatic drainage of free tissue transfer recipient areas and lymphedematous limbs.

The Security of Applying ICG in Flap Surgery

The Conventional Dose and Maximum Safe Dose of ICG in Plastic Surgery

ICG fluorescence imaging has been applied for the assessment of a variety of flap types (►**Table 1**). However, there is no consensus about the optimal intravenous dose. Measurements of free ICG are confounded by in vivo fluorescence quenching, which makes it difficult to predict the precise working dose of ICG needed in the flap. Additionally, all patients have unique circulating plasma volumes and cardiac outputs, which complicate the achievement of consistent in vivo ICG concentration targets. Different medical institutions

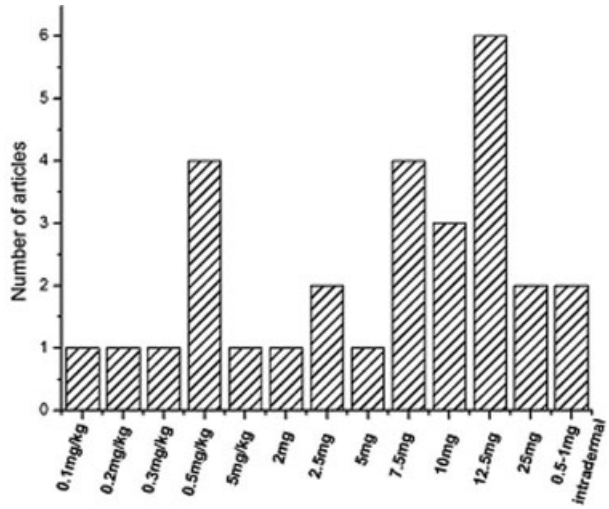

Fig. 2 Frequencies of different doses of indocyanine green reported in flap surgery. The last one is intradermal local dosage for detecting the lymphatic circulation in skin. Others are dosages of intravenous injection. mg/kg: weight of indocyanine green/weight of patients.

and different medical groups use their own experiences to determine the dosage. There is no evidence showing that diverse intravenous dosages will affect the result or the quality of ICG fluorescence imaging. We found 29 articles introducing a potential dosing protocol for ICG (►**Fig. 2**),[1,11,16,21,22,26–29,31–33,35,39,44–56] and a total dose of 12.5 mg was the most frequently used intravenous dose. The second and third most frequently used intravenous doses were 7.5 mg total and 0.5 mg/kg$_{(weight)}$, respectively. When evaluating local lymphatic function, the doses used at each injection site were 0.5 to 1 mg total. Because ICG is hepatically metabolized and excreted through the kidney with a short half-life of 150 to 180s, it can be repeatedly applied in the same operation. Lee et al[20] suggested that the maximum dose of ICG should be less than 1 mg/kg$_{(weight)}$, while in the literature we have examined that the maximum dose by weight was up to 3 mg/kg$_{(weight)}$.[57] In our clinical cases, we used a total dosage of 10 mg as the conventional dose of ICG for fluorescence angiography. According to our experience, 10 mg total ICG is adequate for assessing the supporting scope of microcirculation in diverse flaps. In the future, ICG dosing should be standardized through large series and clinical trials.

Adverse Reactions, Preoperative Allergy Testing and Contraindications of ICG

Adverse reactions to ICG were categorized into three levels: mild, moderate, and severe, depending on the duration of the reaction, the need of medical intervention, and the final outcomes. A mild reaction was defined as a transient effect that did not require any treatment with complete and rapid resolution. Nausea, vomiting, extravasation, sneezing, and pruritus were classified as mild reactions. A moderate adverse reaction was defined as a transient effect where medical treatment may have been required. Urticaria, syncope, other skin eruptions, pyrexia, local tissue necrosis, and nerve palsy were categorized as moderate adverse reactions. A severe adverse reaction was defined as one exhibiting prolonged effects that required intense treatment. A severe adverse reaction involved cardiac, respiratory, and neurologic systems.[5,58]

We have found 74 articles referring to the application of ICG fluorescence imaging in flap surgery of which, 87.8% (65 cases) did not mention preoperative allergy testing[8,10,12,16,17,19–26,29,30,32,33,35,39,42,44,45,47–52,54–56,59–93]; 9.5% (7 cases) only reported preoperative iodine allergy test[26,28,46,53,94–96]; and 2.7% (2 cases) conducted both an iodine allergy test and ICG allergy test[5,57] (►**Fig. 3**). The lack of reported preoperative ICG allergy tests may be due to the acceptance that ICG is a non-toxic contrast agent with a low rate of allergy (1:42,000–1:60,000) and does not damage blood composition and coagulation systems.[22,39,53] However, in the past 34 years, there had been reported two cases of fatal ICG anaphylaxis.[53] Though no deaths followed preoperative iodine allergy tests, 0 to 4.5% of patients reported experiencing different degrees of allergic reactions.[5,46,58] Therefore, preoperative allergy test seems warranted for ICG procedures. Because iodine allergies are the most probable source of an adverse allergic reaction in ICG procedures,[96] we consider preoperative iodine allergy test a necessary precaution. In addition to hypersensitivity to iodine, contraindications for applying ICG include closed-angle glaucoma, allergic asthma, severe hypertension, hepatic and renal function failure, and pregnancy.[5,96]

Drawbacks and Prospect of ICG Application in Flap Surgery

Despite the high sensitivity (90.9%) and accuracy (98.6%) of ICG fluorescence imaging[31] in predicting tissue transfer survival, its limited detecting depth (<1 cm) makes the technique insufficient, when used as a standalone method, to evaluate flap microcirculation.[55] However, ICG imaging is

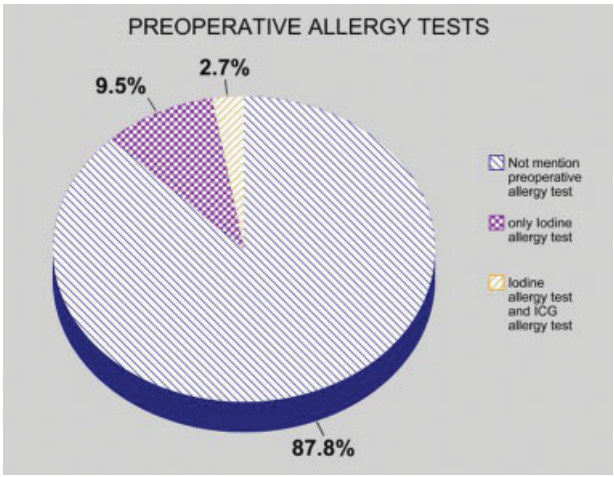

Fig. 3 Applying preoperative allergy tests before ICG fluorescence imaging. Seventy-four articles were found referring to applying ICG fluorescence imaging in flap surgery, of which, 87.8% (65 cases) did not mention preoperative allergy test; 9.5% (7 cases) only mentioned preoperative iodine allergy test; and 2.7% (2 cases) conducted both an iodine allergy test and an ICG allergy test. ICG, indocyanine green.

an important adjunctive approach when combined with clinical condition as well as the operator's subjective clinical experience.[97]

Proulx et al[98] recently developed a new formulation of ICG that is enveloped with liposomes, and animal experiments have demonstrated increased stabilization, fluorescence intensity, specific absorbance through lymphatic vessels, and ability to create deep lymphatic tissue imaging. This formulation has enhanced the potency of ICG with better imaging depth and has broadened the prospective applications of ICG imaging. In the future, more emphasis on improving the sensitivity and accuracy of ICG to reduce postoperative complications is warranted.

Conclusions

ICG fluorescence imaging may facilitate the preoperative detection of flap perforators in tissue transfer with thickness $<$20 mm and may also assist in determining the optimal timing for the second-stage surgeries of delayed flaps. Intraoperatively, ICG may help in evaluating the perfusion of flap microcirculation, assessing microcirculation in wound closures after suturing, selecting dominant cutaneous nerves, evaluating the quality of vascular anastomoses, and locating thromboses. ICG can also be used postoperatively to examine vascular abnormality and lymphatic system recovery. While there is no consensus regarding the recommended ICG dosage, the maximum dose appears to be $<$3 mg/kg$_{(weight)}$, and the total applied dosages range from 7.5 mg to 12.5 mg. Our experience suggests that 10 mg of total dose is appropriate. The prevalence of allergic reaction to ICG administration has been reported to be 1:42,000–1:60,000, and only two fatalities due to allergy to ICG have been reported. Contraindications and iodine allergies should be assessed before potential use of ICG imaging. ICG remains a low-risk contrast agent, but possible adverse reactions to the agent should be cautiously assessed and be given immediate treatment once they present.

Conflict of Interest
None of the authors has financial conflicts or interests to report in association with the contents of this paper.

Acknowledgment
This research was supported by a center of clinical medicine in Shanghai (health education in Shanghai (2012) 052).

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