A novel quantitative evaluation of lower-limb ischaemia with intraoperative fluorescence angiography by intravenous indocyanine green

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Article points

1. Patients with diabetic foot gangrene and ischaemic skin ulcers were treated with a new 'ultrahigh' technology approach. Intraoperative indocyanine green angiography visualised the extent of the feeding vessels for a quantification of the local tissue blood flow
2. The result led to an immediate diagnosis for the determination of the extent of ischaemic leg amputation and debridement of necrotic tissue.

Key words

- Angiography
- Ankle-brachial index
- Indocyanine green
- Intraoperative fluorescence
- Limb ischaemia
- Skin perfusion pressure

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Patients with diabetic foot gangrene and ischaemic skin ulcers were treated with a new 'ultrahigh' technology approach. Intraoperative indocyanine green angiography visualised the extent of the feeding vessels for a quantification of the local tissue blood flow. This result led to an immediate diagnosis for the determination of the extent of ischaemic leg amputation and debridement of necrotic tissue. Imaging of the local tissue blood flow was successful in all patients, and toe amputation surgery and skin grafting could be performed as part of wound-closure measures after debridement.

Fluorescence imaging with indocyanine green (ICG) is used in plastic surgery to evaluate the anastomosis of lymphatic venules in lymphoedema, and also for the evaluation of skin-flap survival areas in breast reconstruction. Intraoperative fluorescence angiography (IA) is now part of the guidelines for surgical policies of the treatment of those lesions. The authors used the IA method, during surgery, so they could evaluate the range of suitable debridement options for necrotic tissue in cases in which severing of a diabetic gangrenous foot was applicable. The IA method visualised the feeding artery area of necrotic tissue and helped provide a quantitative evaluation of the local blood flow. A number of lower-limb ischaemia cases were examined with this new 'ultrahigh' technology approach using an IA by intravenous ICG.

Methods

A total of 22 cases of ulcers and/or gangrene in the toes or lower legs of 19 patients were included in this study. They were treated at the department of plastic surgery at the Saga University Hospital, Japan, between April 2011 and June 2012. The authors encountered 11 cases of ischaemic ulcer and 11 cases of diabetic gangrene. If lower-limb blood flow was determined to be insufficient at the pre-surgery meeting of a given case, an angiology specialist would revascularise the site. Once completed, the plastic surgeons performed debridement and stump plasty.

In a private room attached to the central operating theatre with a room temperature of 25℃, the patient was asked to lie supine with the knee on measurement side slightly bent. After about 15 minutes in that position, the patient was given an injection of 0.2 mg/kg of ICG (10 mg/observation) from right elbow vein. Prior to debridement, the blood flow of the ulcer or gangrene was watched with IA by a camera system with an integrated microscope (OPMI® Pentero®, Zeiss). A naked-eye observation of the stump ulcer was also made before debridement, and, if necessary, additional debridement was conducted after an evaluation of the blood flow.

After an ICG injection and before debridement, the local blood flow was video-recorded for 5 minutes with the foot slightly raised. And the data were saved on DVD. We made a quantitative assessment of the absolute values of change in brightness with software specific to absorbance analysis. With each lesion, the following four regions of interest (ROIs) were set as measurement

sites of ICG fluorescence photography: entire affected area; centre of affected area (1 cm × 1 cm in size); proximal portion of affected area (1 cm × 1 cm in size); and distal portion of affected area (1 cm × 1 cm in size) (*Figure 1*).

Results

Intraoperative macroscopic evaluation

In all 22 instances of foot lesions in patients with skin ulcers or gangrene in lower leg or foot, the local blood flow of the target tissue was visualised. As part of the post-debridement wound closure process, a skin graft or toe amputation was performed.

Intraoperative quantitative evaluation

Perfusion time refers to the time that elapsed between an ICG injection at right elbow vein and the time at which skin tissue of the affected area fluoresced. Durations of perfusion time were classified as follows: group I — within 30 seconds; group II — 30–60 seconds; group III — 60–120 seconds; and group IV — 120 seconds or more. The measurement results gave six cases in group I, 12 in group II, three in group III, and one in group IV. The numbers of refractory cases showing delay in wound healing were: group I — two cases were refactory out of the six cases in which perfusion time was within 30 seconds; group II — two out 12 cases were refactory; group III — two out of three cases were refactory; and group IV — one out of one case was refactory.

Quantitative evaluation at ROIs using software specific to absorbance analysis

The authors made a quantitative evaluation of the absolute values of change in brightness at ROIs after surgery, using the video-recorded data taken between ICG injection and debridement. In the analysis, the rate of increase in brightness was expressed by the gradient between rise in the graph and peak value, which defined perfusion index (Zimmermann et al, 2012). The 22 cases were then examined in terms of the correlation between perfusion time and measured index. In cases where perfusion time was short, the index ranged from low to high values, but in cases in which perfusion time was long (groups III and IV), their perfusion indices showed low values (*Table 1*).

Case 1

This case centred on a 74-year-old female with diabetic gangrene in her right second toe. Artery palpation of the foot was good and she had an ankle-brachial pressure index (ABPI) at 1.08; her skin perfusion pressure (SPP) was too low to do stump plasty, with 31 mmHg at dorsal right foot and 44 mmHg at plantar right foot. After review by IA, dorsal skin colour of right second toe was poor (duller than or not as bright as the

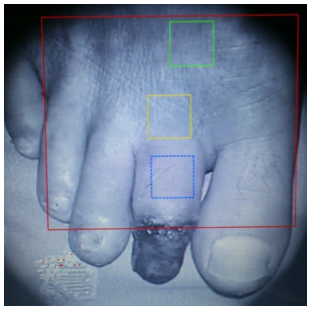

Figure 1. The following four sites were chosen for measurement for ICG fluorescence photography. a) the entire affected area (red square); b) centre of affected area 1 × 1cm; c) central side of affected area 1 × 1 cm; d) distal to affected area 1 × 1 cm.

Figure 2 (bottom left). a) preoperative; b) A foot dorsal side; colour tone of the second toe is bad; c) A plantar side; colour tone of the second toe is good; d) 8 months after surgery; wounds not separated and no recurrence. Figure 3 (bottom right). a) Preoperative; b) Blood flow in the skin ulcer was confirmed to be good at around intraoperative IA.c) Upon completion of the surgery, the patient underwent NPWT. d) We performed split-thickness skin grafting at 18 days after initial surgery. d) At 1 month after surgery, engraftment of skin graft is good. No recurrence.

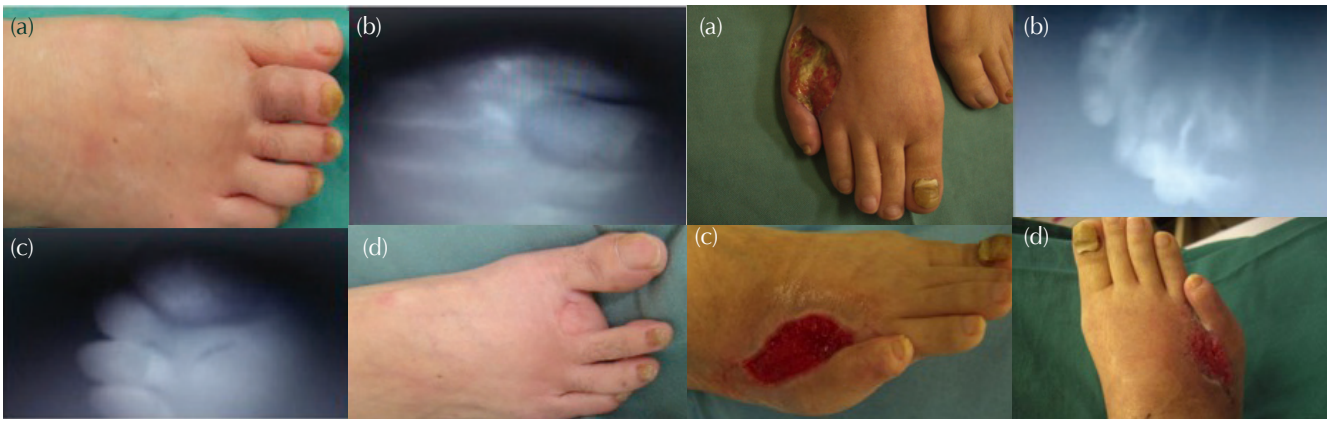

Table 1. The relationship of treatment and results perfusion index and perfusion time.

No.	Perfusion (seconds)	Class	Perfusion index	Treatment outcome
17	15	I	0.1	Healed
6	18	I	0.455	Required multiple surgeries until healed
1	20.4	I	2.298	Healed
22	23.2	I	0.344	Healed in the additional skin graft
8	23.8	I	0.287	Second operation
20	27.2	I	0.217	Healed
14	35	II	0.071	Healed
4	35.2	II	0.374	Healed
7	35.2	II	0.34	Required multiple surgeries until healed
19	35.8	II	0.316	Healed
11	36	II	0.634	Third operation
2	38.2	II	0.66	Healed
15	43	II	0.073	Healed
16	43	II	0.054	Healed
9	44.6	II	0.117	Second operation
5	45.6	II	2.551	Healed
3	56.6	II	0.109	Required multiple surgeries until healed
10	57	II	0.129	Healed
21	73	III	0.236	Healed in below-knee amputation
12	90	III	0.044	Healed
13	99.4	III	0.052	Required multiple surgeries until healed
18	123.8	IV	0.007	Required multiple surgeries until healed

surrounding area) from the base and colour was good (at least as bright as the surrounding area) at its plantar side. The flap was then formed from the sole in stump plasty. The wounds showed primary healing and blood flow was confirmed soon thereafter, while perfusion time was 20.4 seconds. At 8 months after surgery, the patient's wounds showed no dehiscence and there was no recurrence of the ulcer (*Figure 2*).

Case 2

A 65-year-old female presented with skin ulcers on her right foot. She was on oral steroids for arthritis. SPP was 54 mmHg at back right foot and 45 mmHg at bottom right foot. We confirmed that the blood flow in the skin ulcer was good at around intraoperative IA. Perfusion time was 23.2 seconds. We performed debridement and trimming at the skin ulcer margin. Upon completion of the surgery, the patient underwent NPWT. We did split-thickness skin grafting at 18 days after initial surgery. One month after surgery, engraftment of skin graft was good and there was no recurrence of the ulcer (*Figure 3*).

Discussion

ICG with a molecular weight of 774.96 is a water-soluble compound of dark blue-green colour. It combines rapidly with plasma proteins in the body. Most of it gets incorporated into liver parenchymal cells, and excreted in the bile without being metabolised. It cannot be observed with the naked eye as its peak wavelength of *in vivo* fluorescence is 845 nm in the near-infrared region. ICG is a re-agent, less toxic than other angiographic agents, that has been used worldwide for over 50 years (Miwa, 2008) and it has been approved as a medical test drug for liver and cardiovascular function.

Advantages that ICG offers are as follows: in comparison with fluorescence measurements in the visible light region, ICG is less influenced by autofluorescence; ICG makes it possible to directly obtain information from deep parts of the body; ICG makes it possible to observe lymph and blood vessels that are present at a depth of 10 mm from the body surface; and ICG also has few side effects, according to a study unertaken by Kusano (2008) — 0.08% sickness and nausea (16/21,278 cases), 0.02% shock symptoms (5/21,278), and an overall side-effect rate of 0.17% (36/21,278).

Currently, ICG is used in sentinel lymph node biopsy, such as in prostate cancer, colon cancer, gastric cancer, esophageal cancer and breast cancer. It is also used in brain surgery (Raabe et al, 2003), and ophthalmology uses it in angiography of the choroid and retina. In the cardiovascular field, ICG is intraoperatively used in angiography in coronary artery bypass graft surgery (Handa et al, 2010). ICG is used in angiography and evaluation of hepatic artery and liver tumor (Okochi, 2002; Kusano, 2008). It is also used to monitor circulating blood volume and cardiac output in anesthesiology (Iijima et al, 1997).

In plastic surgery, ICG has been used for the evaluation of skin flap survival areas of breast reconstruction and of the anastomosis of lymphatic venules in lymphoedema.

The authors surmise that local blood flow is better the sooner a lower-limb lesion site fluoresces after the administration of ICG, the reason being that ischaemia delays the time of fluorescence. The group led by Perry et al (2012), at the time of ischaemic toe amputation in a diabetic patient, resorted to IA to distinguish intact tissue from ischaemic tissue to determine which tissue was debrided. In the authors' study of 22 cases of gangrene and ulcers of the foot, the lesion was visualised in each case with ICG and examined the local microcirculation before and during surgery while observing the fluorescence angiography by near-infrared camera.

The result was that good blood flow induced fluorescence within 30 seconds, whereas in ischaemic tissue it took 100 seconds or more before one saw fluorescence. In cases where the fluorescence rate was in the 30- to 100-second middle range, it was necessary to take into account information from other means, such as Doppler auscultation and SPP before it could be determined if the local blood flow was normal or irregular. The fact remains, however, that a quantitative evaluation of limb ischaemia was possible in all cases, and that indeed enabled us to perform a minimum-range amputation and debridement. One can say that that was certainly good for the patient.

As reported by Holm et al (2002), there was a correlation between the rate of increase in IA luminance and tissue perfusion by blood flow. Terasaki and Inoue (2008) also quantified the relationship — expressed as a graph — between the rate of increase in brightness and passage of time and, considering differences found in there, they tried to determine whether they had an ischaemic limb. The above findings led the authors to form a hypothesis that the longer it took blood flow to perfuse a segment of tissue, the more ischaemic was the tissue.

The perfusion time of the 22 cases, as measured by intravenously injected ICG, showed that it took 60 seconds or less in 18 cases; and four needed more than 60 seconds. There were inevitable refractory cases in which wounds dehisced: 4/18 cases (22%) in groups I and II (fluorescent within 60 seconds); and 3/4 cases (75%) in groups III and IV (more than 60 seconds before fluorescence).

The authors acknowledge that the number of cases dealt with in this study is somewhat limited to draw a definitive conclusion, and also because the surgical techniques used by research groups were not uniform, intergroup comparisons may not be as meaningful as otherwise. That said, in cases in which perfusion time was longer, arterial blood circulation circulation turned out to be poorer (*Table 1*).

Additional to perfusion time, the authors took the rate of increase in brightness to define the perfusion index, which refers to the gradient between a rising point in the graph of brightness and its peak value.

The respective values of perfusion time and perfusion index were compared. Where perfusion time is short, perfusion index ranges from a low value to an extremely high value (*Figure 4a*). However, at least in cases in groups III and IV with higher values of perfusion time, their

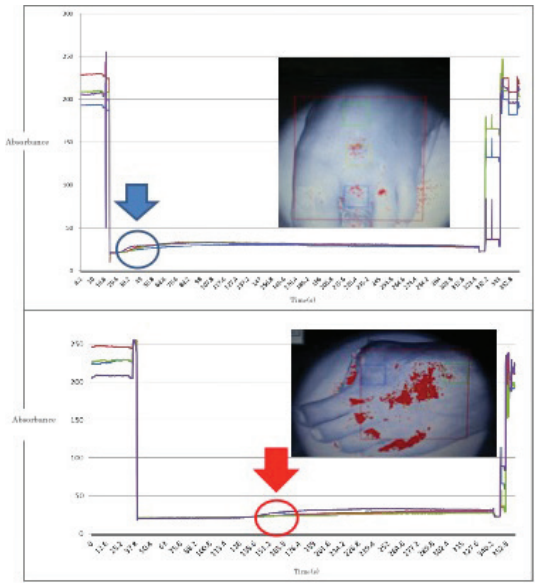

Figure 4. a) Case 17, 59-year-old man, left second toe: ischaemic ulcer. Perfusion time was 15.0 After surgery, wounds healed. Perfusion index is (29.814-23.057) / (106.8-39.2) = 6.757/67.6 = 0.09996. b) Case 13, 68-year-old man, left great toe: diabetic gangrene. Perfusion time was 99.4. After surgery, wound dehisced. Perfusion index is (28.537-22.013) / (263.6-138.4) = 6.524/125.2 = 0.05211.

perfusion indices show low values (*Table 1*). There was a tendency that when ABPI and SPP were good, perfusion time had a low value with a high perfusion index. Sporadic cases were noted where good ABPI and SPP co-occurred with a longer perfusion time and a lower perfusion index (*Table 1, Figure 4b*). Part of the reason for that may have been local infection of the foot.

It is hoped that the method introduced in this article gets serious consideration from plastic surgeons in that it could help them decide on the least invasive surgery, therefore, optimum to the patient.

In addition to the widely employed preoperative means of evaluation, such as ABPI and SPP, the introduced method can visualise and quantify, pre- or intraoperatively by use of ICG, the perfusion status of the target tissue. It is the accurate information about target tissue that constitutes a big advantage.

The 'ultrahigh' technology approach requires further research in order to gain a better idea of its efficacy. An optimal combination of perfusion time and perfusion index needs to be established so that the wound will likely heal in a timely fashion using this method.

Conclusion

The authors treated patients with diabetic foot gangrene and ischaemic skin ulcers with a new 'ultrahigh' tech approach. Intraoperative ICG angiography visualised the extent of feeding vessels for a quantification of local tissue blood flow, which led to an immediate diagnosis for the determination of the areas of ischaemic leg amputation and necrotic tissue debridement.

In addition to the widely employed preoperative means of evaluation, such as ABPI and SPP, the authors' method can visualise and quantify the perfusion status of the target tissue even during surgery. Accurate information obtained about target tissue enables the surgeon to decide on the least invasive surgery. ■

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