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An Inconvenient Truth of Clinical Assessment and Indocyanine Green Angiography Precise Marking for Indeterminate Burn Excision

Apinut Wongkietkachorn, MD*
Palakorn Surakunprapha, MD*
Kamonwan Jenwitheesuk, MD*
Kant Eua-angkanakul, MD†
Kengkart Winaikosol, MD*
Pattama Punyavong, MD*
Nuttapone Wongkietkachorn, MD‡
Supawich Wongkietkachorn, MD§
A. Neil Salyapongse, MD¶

Background: The clinical assessment of indeterminate burn wounds has relatively poor accuracy. Indocyanine green angiography (ICGA) has high accuracy and can be used to mark wounds precisely so as to guide burn excision. This study aimed to assess the differences between ICGA and clinical assessment marking and compare the marking result with the long-term wound outcome.

Methods: This was a prospective, multicentered, triple-blinded, experimental study. Indeterminate burn wounds were clinically assessed, and the area to be excised was firstly marked by the attending surgeon. ICGA marking was then performed by a second surgeon. Measurement of the marked area was conducted by a third surgeon. Three surgeons were each blinded to the others' processes. The wounds were followed up to assess complete wound closures on day 21.

Results: There were 20 burn sites included in the study. There was a significant difference in the marked areas between clinical assessment and ICGA (mean, 57.3 ± 44.1%; $P = 0.001$). The maximum difference found was as high as 160.9%. The correction rate of ICGA marking to complete wound closure on day 21 was 95.0%. Over 90% of the decreased areas of excision—which were assessed by ICGA to be superficial burns but evaluated by clinical assessment to be deep burns—were completely healed on day 21.

Conclusions: ICGA contributes to a significant difference versus clinical assessment in the marking for excision of indeterminate burns and strongly associates with long-term wound outcomes. The burn wounds can be assessed precisely to reduce unnecessary excision and prevent inadequate excision. *(Plast Reconstr Surg Glob Open 2021;9:e3497; doi: 10.1097/GOX.0000000000003497; Published online 24 March 2021.)*

INTRODUCTION

During burn excision, a decision as to whether or not to excise the area with indeterminate burn depth is difficult.[1] The accuracy of clinical assessment can be as low as 50%–75%, even though it is performed by burn experts.[2–5] There is thus a high possibility of unnecessary surgery if the indeterminate wound is inaccurately excised. The problem can be addressed by using indocyanine green angiography (ICGA).[2,6,7] Among other effective burn assessment modalities,[8] ICGA is unique in enabling real-time interpretation of results through high-quality images, which allow the wound to be precisely marked to better guide burn excision.[9] There is, however, little data on either how well ICGA marking can improve burn excision when compared with clinical assessment marking, or of the long-term wound outcomes of the

*From the *Division of Plastic and Reconstructive Surgery, Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; †Division of Plastic and Reconstructive Surgery, Department of Surgery, Khon Kaen Hospital, Khon Kaen, Thailand; ‡Division of Plastic and Reconstructive Surgery, Department of Surgery, Q Clinic, Bangkok, Thailand; §Department of Surgery, Faculty of Medicine, Princess Naradhiwas University, Naradhiwas, Thailand; ¶Department of Surgery, University of Wisconsin, Madison, Wis.*

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ICGA markings.[9] The current trial is the first study to assess the differences, and to compare the marking results with long-term wound outcomes.

METHODS

Study Design

This was a prospective, multicentered, triple-blinded, experimental study. The study was conducted, and data were reported following the Transparent Reporting of Evaluations with Nonrandomized Designs statement.[10] This study was a collaboration between Srinagarind Hospital and Khon Kaen Hospital, both in Thailand, and the University of Wisconsin in the USA. The study protocol was approved by appropriate ethics committees and was funded by the Faculty of Medicine, Khon Kaen University, Thailand (Grant Number IN63261). This trial was registered in the Thai Clinical Trials Registry (number TCTR20200117001).

Participants

The inclusion criterion was that patients must be admitted to the hospital with indeterminate burn wounds on any part of the body. Included patients were aged over 18 years and were hemodynamically stable (mean arterial pressure ≥ 65 mm Hg, urine output of 0.5-1 mL/kg/h, and adequate conscious to understand the study protocol); so they could make a decision as to whether to participate in this study or not. Written or fingerprint informed consent was obtained from all participants. The exclusion criteria were allergy to ICG and/or iodides, pregnancy, bleeding tendency, and psychiatric disorder. Indeterminate wound areas that contained scars, moles, or tattoos were also excluded.

Intervention

The study flow diagram is presented in Figure 1. Burn wounds with indeterminate depth were clinically assessed, and the area to be excised was marked by the first attending surgeon. The marked area was measured using a 3-dimensional wound measurement device (inSight®, eKare Inc, Fairfax, Va.), which has high accuracy and provides both inter- and intra-rater reliability of >0.99.[11–13]

ICGA precise marking was performed by the second surgeon.[9] A single 0.5 mg/kg dose of indocyanine green (ICG) (Diagnogreen Injection, Daiichi Sankyo Propharma, Japan) was intravenously injected to the patient. The Fluobeam 800 clinical system was used to capture images during 1–5 minutes after the injection. The real-time video of ICGA occurred on the monitor. The percent of maximal perfusion could be captured and was autogenerated.

ICGA Objective Interpretation and How to Predict Viability

Thirty-three percent of maximal perfusion was used as the cut-off point between superficial and deep second-degree burns.[5,9,14–19] The cut-off point was derived from the previous diagnostic study using ICGA in indeterminate burn and reported to provide high accuracy.[5] Superficial second-degree burns were defined as burns with maximal perfusion of more than 33%, deep second degree burns were defined as burns with maximal perfusion of <33%.[2,14,19] Thus, the areas with maximal perfusion of <33% were painted with methylene blue to indicate the area to be excised in the operating room.[9] There was no need to compare the burn area with the unburned area. An example of ICGA objective interpretation is illustrated in Figure 2.

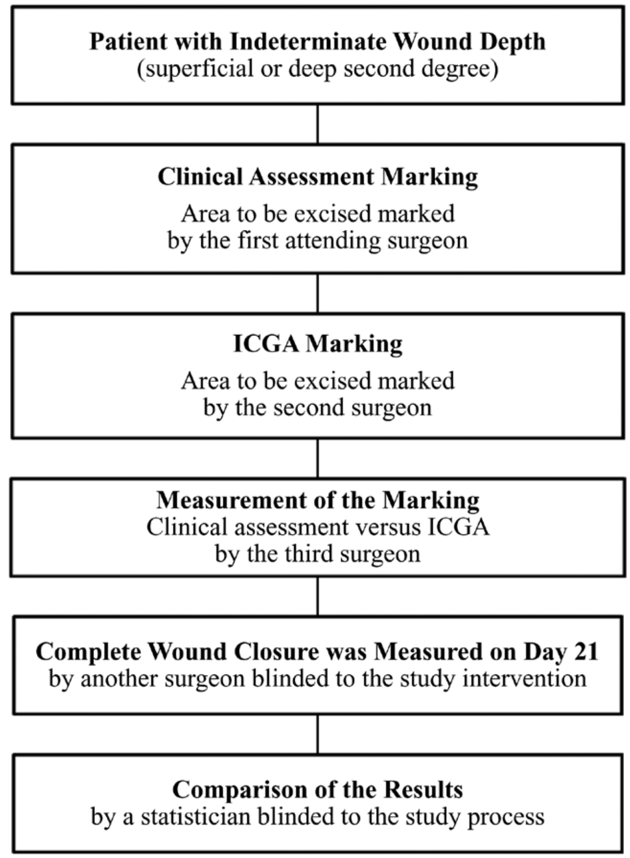

Fig. 1. Study flow diagram.

The 3-dimensional wound measurement device was later used to measure the painted area. Measurement of the marked area using clinical assessment and ICGA was conducted by the third surgeon. Three surgeons were each blinded to the other's processes. The wounds were covered with a hydrofiber with silver (Aquacel Ag+ Extra; Convatec, UK) and were followed to determine the complete wound closure on day 21, which was defined as the wound yielded 100% reepithelialization without drainage or dressing requirements.[20]

Statistical Analysis

Data were analyzed on an intention-to-treat basis using STATA/SE version 10.1. Data were reported as mean and SD for continuous variables and as number (%) for discrete variables. The difference between ICGA and clinical assessment marking was reported as the percent of difference, based on the following equation:

$$\text{Percent of difference } (\%) = \frac{(\text{clinical assessment} - \text{ICGA})}{\text{ICGA}} \times 100$$

A statistician, who analyzed and reported data, was blinded to the study process. Using one-sample *T*-test, at least 20% of the absolute percent of difference was

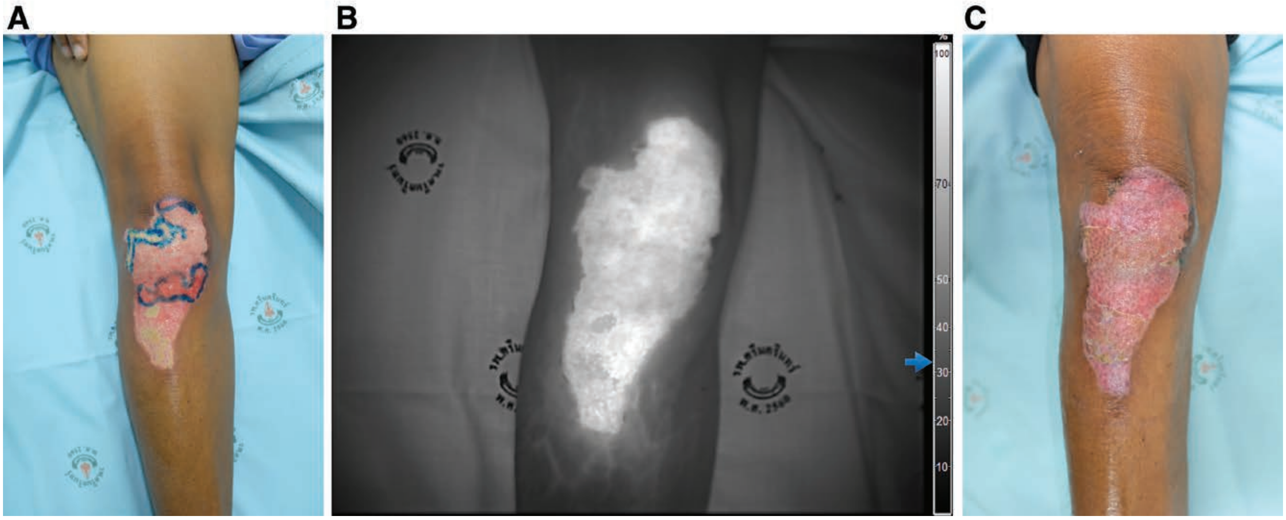

Fig. 2. An example of ICGA objective interpretation. (A) Indeterminate burn wound on the knee was clinically assessed, and the area to be excised was marked by the first attending surgeon. (B) ICGA was performed by the second surgeon. The blue arrow indicates 33% of maximal perfusion, which was used as the cut-off point between superficial and deep second degree burns. On the contrary to the clinical marking, all parts of the wound were >33% of maximal perfusion, which revealed that the wound was a superficial burn; so the wound was totally spared. (C) Outcome follow-up of the wound showing complete re-epithelialization of the wound. This confirmed the ICGA objective interpretation result that the wound was a superficial burn and could heal without unnecessary surgery.

Table 1. Demographic Data (n = 20)

Demographic Data	N (%) or Mean ± SD
Age (y)	48.3 ± 12.8
Gender	
Men	14 (70.0)
Women	6 (30.0)
BMI (kg/m²)	21.1b ± 2.5
Time of intervention after injury (d)	2.3 ± 0.8
Alcohol use	6 (30.0)
Smoker	4 (20.0)
Diabetes	0
Hypertension	2 (10.0)
Dyslipidemia	0
Wound location	
Trunk	7 (35.0)
Extremities	13 (65.0)
Etiology of burn	
Flame burn	16 (80.0)
Scald burn	4 (20.0)

considered to be significant. Post-hoc subgroup analysis was conducted in 2 groups: decreased excision and increased excision. The aim of the analysis was to determine how much ICGA could reduce unnecessary excision of the wounds in the decreased excision group and how much ICGA could prevent inadequate excision in the increased excision group. All test statistics were one-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

The current study was conducted between January and June 2020, and there were 20 burn sites included. Demographic data are presented in Table 1. The results are summarized in Table 2. There was a significant difference in the absolute marked areas between clinical assessment and ICGA (mean, 57.3 ± 44.1%; $P = 0.001$). The maximum difference between the 2 methods was as high as 160.9%. The median of the decreased area (or totally spared area) of excision was 57.6% [30.9, 113.7], whereas the median of the increased area of excision was 44.6% [26.4, 62.3].

The correction rate of ICGA marking to complete wound closure on day 21 was 95.0% (19 of 20 wounds). Out of the corrected 19 wounds, most of the absolute percent of difference between the 2 methods (n = 14, 73.68%) was greater than 20%.

Post-hoc subgroup analysis was conducted in 2 groups. In the decreased excision group that the area of ICGA was less than clinical assessment, there were 10 wounds and it was found that the decreased percent of difference between ICGA and clinical assessment was more than 20% with the mean difference of −82.13 and 95% CI −112.55 to −51.71 ($P = 0.001$). In the increased excision group that the area of ICGA was greater than clinical assessment, there were 6 wounds and it was found that the increased percent of difference between ICGA and clinical assessment was greater than 20% with the mean difference of 44.53 and 95% CI 24.55 to 64.52 ($P = 0.013$).

For the long-term outcome, 90.9% (10 of 11 wounds) of the decreased areas of excision—assessed by ICGA to be superficial burns compared with deep burns according to clinical assessment—were completely healed on day 21. The study process and examples of results are demonstrated in the Supplemental Video. (**See Video [online],** which displays the study process and examples of results.)

DISCUSSION

Interpretation

ICGA marking was significantly different compared with clinical assessment and strongly associated with

Table 2. Summary of Results

Wound Number	Location	Clinical Marking (cm^2)	ICGA Marking (cm^2)	Difference (cm^2)	Absolute Percent of Difference & Interpretation	Correction of the ICGA Marking to the Complete Wound Closure on Day 21
1	Right back	52.7	20.2	32.5	160.9% decreased excision	Yes
2	Back	19.8	10	9.8	98.0% decreased excision	Yes
3	Right thigh	73.7	45	28.7	63.8% decreased excision	Yes
4	Right forearm	132.7	87.7	45	51.3% decreased excision	Yes
5	Right foot	41.7	30.2	11.5	38.1% decreased excision	Yes
6	Right arm	20.1	18.4	1.7	9.2% decreased excision	Yes
7	Right knee	15.5	0	15.5	Totally spare the wound	Yes
8	Left knee	12.6	0	12.6	Totally spare the wound	Yes
9	Right chest	9.4	0	9.4	Totally spare the wound	Yes
10	Chest	33.4	0	33.4	Totally spare the wound	Yes
11	Right hand	204	43.5	160.5	369.0% The only wound for which complete wound closure was not associated with both clinical assessment and ICGA marking.*	No*
12	Left shoulder	7.7	26.4	−18.7	70.8% increased excision	Yes
13	Left leg	39.3	96.8	−57.5	59.4% increased excision	Yes
14	Right forearm	46.6	85	−38.4	45.2% increased excision	Yes
15	Left chest	143	255.2	−112.2	44.0% increased excision	Yes
16	Left back	115.2	162	−46.8	28.9% increased excision	Yes
17	Right hand	7.7	9.5	−1.8	18.9% increased excision	Yes
18	Right arm	39.1	39.1	0	0.0% equal excision	Yes
19	Left shoulder	70.5	70.5	0	0.0% equal excision	Yes
20	Back	219.9	219.9	0	0.0% equal excision	Yes

*This wound was not further included in the outcome analysis of the differences between clinical assessment and ICGA marking.

positive long-term wound outcomes. The dramatic difference shows an inconvenient truth that there is too much unnecessary excision of indeterminate burn wounds by using clinical assessment alone, and this unnecessary excision could be prevented if ICGA was being used. In the current study, ICGA could totally spare 4 wounds and reduce the excision of 6. These 10 wounds accounted for 50% of our subjects, illustrating that ICGA could benefit many burn patients by saving them from unnecessary surgery.

This study fills the current gap of knowledge in using ICGA in indeterminate burns. It was found that ICGA provide high accuracy, and the number needed to treat was as low as 2.[5] Using ICGA is not only effective,[5] but this study also found that ICGA contributed to a huge difference of the burn excised area, as most of the difference (73.68%) was >20% (Table 3). The large difference was found in both subgroups, including decreased and increased excision. This means that ICGA could significantly reduce unnecessary excision and prevent inadequate excision in indeterminate burns. Moreover, ICGA provided a good long-term prediction of the wound as high as 95%.

The appropriate time to perform ICGA marking is important. This study performed ICGA interpretation approximately 2.3 days after injury. First, there could be a larger difference between clinical marking and ICGA marking if the ICGA marking was performed earlier because the characteristics of the wound (superficial or deep) became more distinct when the wound was clinically assessed later.[21] Second, ICGA should be performed on the day that the patient was adequately stable to undergo further early excision. Commonly, it was described that the time of early excision was within 1–6 days.[22] The mean of 2.3 days in this study was acceptable in the 6-days limit.[22] Third, performing ICGA at a single time point during the first 5 days after the injury is adequate to detect the difference between superficial and deep burn.[17] There was a case series that the ICGA was performed daily on the burn area for the first 5 days after the injury.[17] It was found that the percent of perfusion could be altered over time, but the difference between superficial and deep burn was still apparent.[17]

Table 3. The Absolute Percent of Difference between ICGA and Clinical Assessment Marking (n = 19)

The Absolute Percent of Difference (%)	N (%)
0%	3 (15.7)
>0%–10%	1 (5.26)
>10%–20%	1 (5.26)
>20%	14 (73.68)

Generalizability

The method used in the current study was reproducible and generalizable. The key factor was the objective criteria used for interpreting ICGA. This study is one of the very few studies,[5,14,19,23,24] for which objective criteria (33% of maximal perfusion cut-off point) were clarified and used for interpreting the results. Superficial and deep burn wounds are significantly different and easy to distinguish using ICGA[19] because the superficial burns tend to have high perfusion of the area due to vasodilatation from the inflammatory response in the burn physiology.[19,23,25] Furthermore, this study included only second degree burns, whose pathophysiology was the partial destruction of the dermis where the venous drainage of the areas was not significantly involved.[26] Thus, the high perfusion found by using ICGA in burn is not limited in the same way with flap reconstruction, which high perfusion could indicate venous congestion and may lead to flap necrosis.[27]

Limitations

ICGA marking has some limitations. An additional injection with ICG is required; so patients with allergy to iodide are contraindicated. However, the advantage of ICGA marking, which is much more precise than clinical assessment, is worthy. Whenever dealing with indeterminate burns, the use of ICGA marking is fruitful and encouraging.

CONCLUSIONS

ICGA contributes to a significant difference versus clinical assessment in the marking for excision of indeterminate burns and associates with long-term wound outcomes. The burn wounds can be assessed precisely to reduce unnecessary excision and prevent inadequate excision.

Palakorn Surakunprapha
Department of Surgery
Faculty of Medicine
Khon Kaen University
123 Mittraparp Highway
Muang District
Khon Kaen 40002
Thailand
E-mail: apinutme@gmail.com

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