Educational Benefits of Intraoperative Indocyanine Green Angiography for Surgical Beginners During Laparoscopic Colorectal Surgery

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Purpose: The aim of this study is to evaluate the safety and usefulness of indocyanine green (ICG) angiography in laparoscopic colorectal surgery and to explore its educational benefits in surgical beginners.

Methods: From July to October of 2015, a total of 21 patients with colorectal cancer underwent laparoscopic surgery using the fluorescence-guided imaging system, IMAGE1 STM (Karl Storz, Germany). Real-time ICG fluorescence images and red inversion images were juxtaposed with standard white-light images for assessment of colonic perfusion. A surgical beginner group comprised of medical students (n=11) and surgical residents (n=11) were then questioned postoperatively about the colonic transection line and mesenteric vascular integrity across various image modes to determine the most proper view for surgical decision.

Results: A total of 21 patients underwent laparoscopic colorectal surgery using ICG angiography. Mean patient age was 69.7 years (52~77 years). Mean time-to-detection for the marginal arteries and colonic wall were 26.7 (range, 4~45) and 47.3 (range, 20~77) seconds, respectively. No injection-related adverse events were observed. Rate of change in the colonic transection line across modes was 59.9% (33.3~66.7%) in the surgical beginners. Decisions made by surgical beginners on the transection line were varied with the standard image, but converged to 81.8% in the ICG with red inversion mode. Surgical beginners preferred ICG with red inversion mode for assessment of mesenteric vascular integrity.

Conclusion: ICG angiography seems to be safe and useful in evaluating colonic perfusion for transection decisions and could have educational benefits for surgical beginners in training to make surgical decisions.

Keywords: Laparoscopic colorectal surgery, ICG fluorescence angiography, Educational benefit

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INTRODUCTION

Colorectal anastomoses carry a high risk of leakage after laparoscopic colorectal surgery. Various risk factors have been

identified, including ASA status, smoking, steroid use, excessive tension and insufficient blood supply to the site of anastomosis.¹⁻⁶ Of the aforementioned risk factors, lack of anastomotic blood supply is a cause correctable during surgery.

When the anastomosis is performed in an area where there is insufficient blood flow, acute ischemia may lead to anastomotic leakage, colon necrosis, and sepsis. Chronic ischemic conditions may not show symptoms of peritonitis, but may instead lead to anastomotic stenosis or strictures that eventually end in reoperation and long term hospitalization. Even though poor vascular anastomotic perfusion is a known risk factor for complications and thus demands objective assessment, perfusion status of the colon resection site has traditionally been determined subjectively by color, temperature, peristalsis of the colonic surface, and pulsatility and hemorrhaging of marginal vessels.⁷ Most common methods used to evaluate the perfusion status of the colon are to visually observe the change in color of the colon wall with the surgeon's naked eye and to carefully observe the pulse of the colon wall. However, these methods are subjective and not always accurate. Gross visualization of blood flow is especially difficult in patients with visceral obesity, as they tend to have excess fat tissue in the mesentery and colon wall, resulting in blood vessels buried in adipose tissue. In addition, it is more difficult for surgical beginners to determine the perfusion status of ischemic colon segments. During laparoscopic colorectal surgery, there exists a significant difference between experienced surgeons and beginning surgeons in postoperative complication rates.⁸ Reported rates of anastomotic leakage are 3~6% in experienced colorectal surgeons and 3~20% overall.^{9,10} Therefore, researchers have agreed on the need for an objective evaluation process and have worked

to realize objective methods for intraoperative assessment of perfusion.¹¹ And now, with the development of a laparoscopic ICG-enhanced fluorescence-guided imaging system capable of real-time monitoring, objective assessment of blood flow to the colon has become possible.

We believed that not only surgical experts but also beginners would be able to draw safe transection lines using ICG fluorescence imaging. The aim of this study was to evaluate the safety and usefulness of ICG-enhanced fluorescence imaging in laparoscopic colorectal surgery and to explore the educational benefits of ICG fluorescence imaging in surgical beginners.

MATERIALS AND METHODS

Laparoscopic ICG fluorescence images were obtained from 21 colorectal cancer patients who underwent surgery between July 2015 and October 2015 at Pusan National University Yangsan Hospital. Inclusion criteria were as follows: (1) patients undergoing laparoscopic colorectal surgery (2) patients aged 18 to 80 years (3) patients with ASA grade 1~2 (4) patients with ECOG grade 0~2 (5) patients who agreed to the purpose of the study and gave informed consent (6) patients who could respond to the questionnaire related to the experiment on their own or under the care of a researcher. Exclusion criteria were as follows: (1) patients undergoing surgery without ICG angiography (2) patients with hemodynamic instabil-

Fig. 1. An example image of questions given to surgical beginners. (A) Proximal good perfusion segment. (B) Proper transection line with approximation of good and poor perfusion segments. (C) Distal poor perfusion segment.

ity (3) patients with colorectal cancer undergoing emergency surgery due to intestinal perforation or obstruction (4) patients undergoing ileostomy operations without colon anastomosis after colon resection (5) patients with previous history of adverse reactions to CT contrast agents.

The operation was performed with conventional laparoscopic colorectal surgical procedures. All surgical procedures were recorded with IMAGE1 S™ (Karl Storz, Germany), the laparoscopic imaging system used in this study. ICG was diluted down to a concentration of 2.5 mg/ml with Sterile Water for Injection. After clearing the colon of the mesentery at the resection site, the colon was visualized with the standard white light (standard) image mode. After the initial visualization, the diluted ICG was slowly injected into the patient's peripheral vein over a period of 10 seconds at a dose of 0.2 mg/kg, and the patient was closely monitored for ICG-related adverse events such as urticaria, hypotension, and anaphylactic shock. We then re-visualized the laparoscopic surgical

field for about 1~2 minutes, alternating between the standard mode, ICG fluorescence mode, and ICG fluorescence with red inversion mode, and measured the time-to-detection for the colonic arteries and the colon wall. After colon anastomosis, we performed a final visualization of the colon wall across all three modes without additional ICG injection. We also recorded the time spent on ICG angiography.

After the operations, surgical procedures recorded in each imaging mode were edited in the form of still pictures. We presented the pictures of resection sites of three different patient cases to a group of 22 volunteer surgical beginners– 11 medical students and 11 surgical resident doctors– and asked them to determine a transection line that would give good perfusion (Fig. 1). We also asked if there was a preferred mode for evaluating mesenteric vessel perfusion.

Then, to evaluate the educational effects of ICG angiography, we assessed the rates of change in transection line across different imaging modes by comparing the answers in

Fig. 2. Distribution of colonic transection lines selected by surgical beginners. A total of 22 surgical beginners responded to the questionnaire in each of the three cases. The numerical values shown on each graph indicate the colonic transection lines chosen in each imaging mode.

standard white light mode to the answers in ICG fluorescence with red inversion mode. And finally, we checked the accuracy of the selection.

Statistical analyses were performed using SPSS (Ver. 21, SPSS Inc., Chicago, IL, USA) and Independent-Samples T-test for continuous variables. Categorical variables were analyzed using the chi-square test or the Fisher's exact test. p values <0.05 were regarded as statistically significant. This study was approved by the ethics committee/institutional review board (IRB no. 05-2016-169).

RESULTS

We performed laparoscopic colorectal resections with real-time ICG-enhanced fluorescence imaging in a total of 21 patients with colorectal cancer: 7 low anterior resections, 6 anterior resections, 4 abdomino-trans anal proctosigmoidectomies, and 4 right hemicolectomies. The mean age of patients with colorectal cancer ($n=21$) was 69.7 years (range 52 to 77 years) and the male to female ratio was 13:8.

There were no adverse reactions to the intravenous injections of ICG, including hypotension, skin urticaria, and anaphylactic shock.

ICG angiograms of the colon wall were performed in all patients. The average time-to-detection of ICG after injection was 26.7 seconds (4~45 seconds) in the blood vessels of the colon wall, and 47.3 seconds (20~77 seconds) in the colon wall itself. The average time required for assessment was 5 minutes (2~10 minutes). Experienced surgeons made modifications to the colonic transection line in three patients (14.3%) upon visualization with ICG.

Distribution of selected transection lines by surgical beginners are shown in Fig. 2. In each case, scattered answers given with the standard image converged to a well-perfused colon

segment with the ICG image, and to a proper transection line with good perfusion with the ICG red inversion image.

In surgical beginners, changes in transection lines were made in 59.9% of cases with ICG angiography.

Surgical beginners chose the appropriate colonic transection line with a mean accuracy of 81.8% in the ICG red inversion image mode. In comparison, the standard white light image mode gave a mean accuracy of 39.4%, which shows that ICG angiography helped to improve the accuracy of colonic blood flow evaluation (Fig. 3). ICG with red inversion imaging was the most preferred mode for the evaluation of colonic vascular perfusion (Fig. 4).

DISCUSSION

ICG is a water-soluble tricarbo-cyanine dye with a molecular mass of 775 Daltons, often mixed with $<5\%$ sodium iodide to ensure solubility. It has a half-life of 3~4 minutes, and emits fluorescence between 830~845 nm when exposed to near-infrared light. Following intravenous injection, ICG binds plasma proteins and is excreted exclusively through the biliary system without being metabolized.^{12,13} Since its approval as a fluorescent contrast agent by the FDA in 1959, it has been used in various clinical settings- from residual liver function tests to cardiac output measurements and even retinal angiography.¹⁴ Studies on ICG toxicity in cells, tissues, animals, and humans have all demonstrated excellent safety profiles.¹⁵

Because our center had just introduced brand new ICG angiographic laparoscopic equipment, we paid special attention to patient safety. Although ICG is proven to be clinically safe at recommended doses, documentation of side effects such as itching, vein pain, and hypotension do exist.¹⁵ Rare cases of death resulting from anaphylactic shock have also been re-

Fig. 3. Improvement in diagnostic accuracy of surgical beginners ($n=22$) on selection of colonic transection lines with good perfusion.

Fig. 4. Preference of image mode for evaluation of mesenteric vessel perfusion in surgical beginners.

ported and ICG use is contraindicated in patients with iodine sensitivity.^{14,15} In our study, no ICG-related adverse reactions were observed. This is most likely due to our slow infusion rate and low ICG concentration of 0.2 mg/kg, which is far below the upper limit of 5 mg/kg/day specified in another study.¹⁵ Exclusion of patients with history of adverse reactions to CT contrast agents is another likely explanation. However, if ICG angiography becomes a more common mode of visualization in colorectal surgery, various side effects are to be expected. It is therefore important to establish safety protocols in preparation for adverse events in cooperation with anesthesiologists prior to ICG angiography.

To this day, there is controversy over application of ICG fluorescence imaging to reduce anastomotic complications. Only a few studies have been published on the efficacy of ICG fluorescence angiography during colorectal surgery, and though scarce in number, they have still reached conflicting conclusions. In some previous studies, the use of ICG fluorescence angiography resulted in a 60~66% reduction of anastomotic reoperation events.^{16,17} Conversely, another multivariate analysis reported that application of ICG fluorescence imaging did not help to significantly reduce anastomotic leakage.¹⁸

In our study, we noted that surgical beginners could benefit from real-time ICG fluorescence angiography by easily obtaining objective information on colonic perfusion status. Improvements in assessment could be seen in the initial scattered selections of colonic transection planes with the standard white light laparoscopic images, which converged to a more secure and well-perfused segment of the colon in subsequent ICG-enhanced fluorescence images.

Clinical application of new medical devices that require knowledge of advanced technology is expected to have a greater effect on surgeons who have just started practicing surgery than on surgeons who have been in the field for a long time. A surgeon with little experience will have difficulty in differentiating all the shades of the colon, and the diagnostic accuracy of anastomotic perfusion status will reflect so. In our study, diagnostic accuracy of surgical beginners in standard laparoscopic image mode was 39.4%. But, accuracy improved to 81.8% when presented with the ICG fluorescence image. This improvement suggests that accuracy in clinical judgment, which can be gained through experience, can also be obtained in a short period of time by using advanced equipment. ICG with red inversion mode gave particularly good results, and was preferred by the majority over the other imaging modes. There were no significant differences between surgical residents and medical students on preference of imaging mode. In this study, 59.9% of beginners changed the colonic transection line to a more appropriate, well-perfused region following visualization with ICG angiography. According to a previous

study, changes in planned level of anastomosis occurred in 4.7~6.5% of cases with experienced surgeons.^{9,19}

Further studies are needed to confirm the relationship between the educational effects of ICG angiography and reduced complications following laparoscopic colorectal surgery. In the future, incorporation of ICG angiography into training courses for colorectal surgery will help beginning surgeons to objectively assess colonic blood flow and to determine appropriate surgical resection margins. It is our hope that the educational effect will help to establish grounds for safer colorectal surgery by effectively shortening the learning curve.

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