

Tissue Oximetry as a Potential Alternative to Indocyanine Green (ICG) Perfusion Assessment in Colorectal Anastomotic Cases

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Introduction: Anastomotic margin tissue perfusion is recognized as critical to successful colorectal anastomosis creation. Near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) is the most common modality used by surgeons as an adjunct to clinical assessment in confirming the adequacy of tissue perfusion. Tissue oxygenation as a surrogate for tissue perfusion has been described in a variety of surgical specialties but its use in colorectal surgery has been limited. Here, we report our experience using a handheld tissue-oxygen meter, IntraOx, for the evaluation of colorectal tissue bed oxygen saturation (StO₂) and compared its utility with NIR-ICG in identifying the viability of colonic tissue before anastomosis in a range of colorectal procedures.

Materials and Methods: This was an institutional review board–approved multicenter trial consisting of 100 patients undergoing elective colon resections. After specimen mobilization, a clinical margin was chosen based on the oncologic, anatomic, and clinical assessment as per the clinicians’ standard technique. The IntraOx device was then used to take a baseline reading of colonic tissue oxygenation on a normal segment of perfused colon. Following this, measurements were taken circumferentially at 5 cm intervals along the bowel proximally and distally to the clinical margin. A StO₂ margin was then determined based on the point at which the StO₂ dropped off by ≥ 10 percentage points. This was then compared with the NIR-ICG margin using the Spy-Phi system.

Results: StO₂ was found to have a sensitivity and specificity of 94.8% and 93.1%, respectively, and a positive predictive value and negative predictive value of 93.5% and 94.5%, respectively when compared with NIR-ICG. At the 4-week follow-up, no significant complications or leaks were reported.

Conclusions: The IntraOx handheld device was found to be similar to NIR-ICG in identifying a well-perfused margin of colonic tissue while having the added benefits of high portability and reduced costs. Further studies looking at the effect of the IntraOx on preventing colonic anastomotic complications such as leak and stricture are warranted.

Key Words: tissue oximetry, ICG, NIR, colon, leak

(*Surg Laparosc Endosc Percutan Tech* 2023;33:207–210)

Received for publication December 6, 2022; accepted February 7, 2023. From the *Department of Advanced Minimally Invasive Surgery, Maimonides Medical Center, Brooklyn; and †Department of Surgery, Northwell Health, New Hyde Park, NY.

Vioptix provided the IntraOx devices.

D.S. is a consultant for Vioptix. The remaining authors declares no conflicts of interest.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s website, www.surgical-laparoscopy.com.

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Anastomotic leak (AL) is one of the most dreaded complications in colorectal surgery with an associated mortality of 6% to 22%.¹ Many factors affect the incidence of the AL but inadequate tissue perfusion most likely plays a significant role. Traditionally, surgeons have assessed the viability of the colonic anastomotic site clinically using such subjective indicators such as bowel color, temperature, mesenteric pulsations, and marginal artery bleeding. Near-infrared (NIR) imaging of fluorescent dye such as indocyanine green (ICG) has come to the forefront as an important adjunctive tool to assess bowel perfusion before anastomosis.² Although rapidly becoming incorporated by many surgeons into their standard workflow, many institutions still lack this technology. This is particularly true in community hospitals and institutions outside of the United States.

Additional limitations of NIR include—ICG saturation of the tissue leading to limited reevaluation cycles and allergy to ICG. Most importantly though, NIR angiography is not a functional assessment of oxygen delivery or tissue viability but rather simply provides visualization of dye flow to tissue. To address this shortcoming surgeons have developed individual, subjective parameters of acceptability when assessing NIR uptake including pulsatility of the ICG fluorescence, subjective brightness of the fluorescence, and time to visualization of fluorescence. Because of this, and the multifactorial etiology of AL, there remains significant variability in the literature regarding the effect of NIR-ICG on prevention of AL.

The utility of tissue oximetry (TO) to assess tissue health has been described previously in the reconstructive plastic surgery literature, but reports on its value in assessing bowel viability have been limited.³ As described previously, reflectance oximetry estimates oxygenation saturation (StO₂) based on the differential absorption of light of varying wavelengths induced by the ratio of oxygenated and deoxygenated blood within the tissue bed.⁴ In a previous report, we described our experience comparing a handheld reflectance oximetry meter with NIR in an initial cohort of 32 patients undergoing colon and rectal surgery.⁵ In that initial review, we found that StO₂ compared favorably with NIR in assessing bowel viability. The current study aimed to look at the data of an additional 68 patients for a total of 100 patients to enable data extraction from a larger set of patients.

MATERIALS AND METHODS

This study was a prospective institutional review board–approved prospective trial consisting of 100 patients who underwent elective colon resection for benign and

malignant disease at 2 centers. Subjects were selected by the participating surgeons and enrolled in the study after obtaining informed consent. Intraoperative data, demographics, indications for surgery, and postoperative complication rate was collected

The patients in this study underwent either laparoscopic or robotic colon resection. In each case, the distal margin was divided and a proximal margin was chosen based on oncological principles (if relevant), pathologic considerations (if relevant) and vascular anatomy. The mesentery and marginal artery were then divided in preparation for transection of the proximal margin and to eliminate alternative sources of perfusion. The specimen was then exteriorized. The surgeon then made a final designation of the clinical margin based on clinical assessment of the tissue as per the clinicians' standard practice.

The IntraOx device (ViOptix Inc.) was then used to evaluate StO₂ circumferentially around the bowel at 4 points (12, 3, 6, and 9 o'clock position) at 5 cm intervals on the externalized colon and a mean of each point recorded. The highest mean StO₂ value obtained from these measurements was designated as baseline StO₂. After the baseline was determined, the mean StO₂ was measured at progressively distal 5 cm intervals towards the devascularized margin. A decrease of >10 percentage points from baseline was designated as the TO margin (Video 1, Supplemental Digital Content 1, <http://links.lww.com/SLE/A364>). NIR-ICG imaging using the Spy-phi system (Stryker) was then used for perfusion assessment (Video 1, Supplemental Digital Content 1, <http://links.lww.com/SLE/A364>). The junction where pulsatile ICG flow was visualized was designated as the NIR margin. As per protocol, this NIR margin was used as the site of transection and ultimately as the site of anastomosis. The distance between the clinical margin, TO margin, and NIR margin was recorded.

For the purposes of assessing sensitivity, specificity, and negative and positive predictive values, NIR-ICG was considered the gold standard for colonic perfusion. We assigned true positive as any StO₂ measurement within 10 percentage points of baseline StO₂ in an area of colon which also showed ICG perfusion. True negative was recorded where the delta StO₂ exceeded 10 percentage points and ICG showed no perfusion. We assigned a false positive to any StO₂ measuring within 10 percentage points of baseline StO₂ in an area of colon which showed no ICG perfusion and false negative was recorded where the StO₂ delta exceeded 10 percentage points below baseline and ICG showed perfusion.

RESULTS

Patients undergoing elective colon resection for benign and malignant disease of the colon and rectum were included in the study (Table 1). A total of 101 patients undergoing colectomies were enrolled in this study. One subject was excluded due to an unexpected intraoperative finding of locally advanced disease and the operation was terminated. An additional 5 cases were excluded from final data analysis due to incomplete data sets secondary to a probe malfunction in 2 cases and anatomic limitations in 3 cases for a total of 95 cases analyzed. Table 2 shows patient demographics.

Mean StO₂ of the normally perfused colon was found to be 71.30 and the difference of StO₂ across the NIR margin from baseline StO₂ was found to be 20.3 (Fig. 1).

TABLE 1. Surgical Characteristics

Surgery type	
Right hemicolectomy	16
Sigmoidectomy	67
Low anterior resection	17

Intraoperatively 87 of the 95 (92%) cases had a StO₂ decrease of >10 across the NIR margin correlating directly with NIR. In the remaining 8 cases, the TO indicated a greater length of viable bowel than that indicated by NIR extending up to 5 cm from the NIR margin. By 10 cm from the NIR, the correlation of NIR to TO was 100%. As per the study protocol, the final transection point was determined by the NIR margin. In 3 cases, NIR indicated a more proximal margin of tissue viability than that planned as the clinical margin. In those cases, the transection site was moved more proximally. In those 3 cases, the TO correlated with the more proximal NIR margin.

The IntraOx device had a sensitivity of 96.1% and a specificity of 92.0%. The positive predictive value was 89.1% and the negative predictive value was 97.2% when compared with NIR-ICG (Table 3).

No significant postoperative complications were observed immediately after the procedure and at the 4-week follow-up, no leaks or other complications were reported.

DISCUSSION

The purpose of this study was to determine if the IntraOx handheld TO is a feasible alternative to NIR-ICG during colonic surgery. We previously published the results of the first 32 patients of this study and showed that 31 of the 32 patients had margins consistent with NIR-ICG.⁵ Given these promising results, the study sample size was subsequently increased to 100 participants. The goal of this study was to confirm our initial findings and determine if TO is a viable alternative to NIR-ICG as an adjunct to clinical evaluation.

The intuitive nature of NIR-ICG has led to broad adoption of this technology despite the lack of definitive evidence of its value in the literature. The PILLAR II trial, the first major prospective multicenter trial designed to evaluate the utility of NIR-ICG in preventing AL in patients undergoing left-sided/anterior resection indicated that NIR-ICG is a safe and reliable intraoperative tool to assess colonic tissue perfusion during colorectal surgery.² In the PILLAR II study, 2 leaks were reported (1.4% leak rate) and no AL in the 11 of 139 participants (7.9%) who had a change in surgical plan. The low AL in comparison to historical reports was an exciting finding and spurred intense interest in this modality. Subsequently, in a large

TABLE 2. Patient Characteristics

Demographics	Mean ± SD (range)
Sex	
Male	53
Female	47
Age	63 ± 9.0 (35-85)
BMI	29 ± 11.1 (17-67)
ASA class	2.4 ± 0.5 (2-3)

ASA indicates American Society of Anesthesiologists; BMI, body mass index.

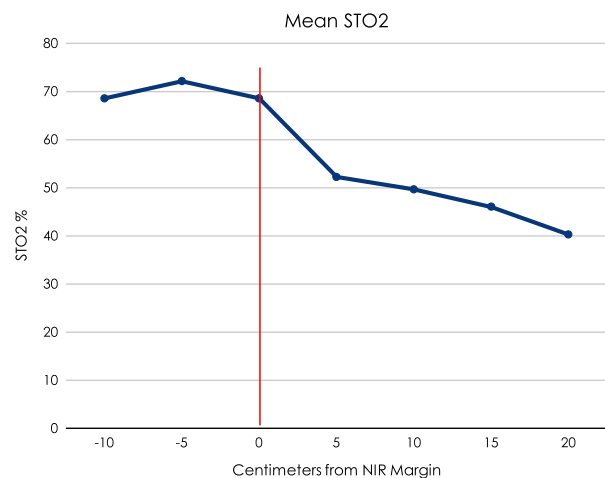


FIGURE 1. Mean tissue bed oxygen saturation (StO₂) measurements by IntraOx device at 5 cm intervals distally and proximally to the near-infrared margin.

multicenter prospective phase II study, Ris et al⁶ found that the routine use of NIR-ICG in a range of colon and rectal surgeries performed on 453 patients led to a change of surgical margin in 5.8% of cases and as compared with a historical cohort of 1173 similar operations without NIR-ICG technology, the NIR group experienced a lower leak rate (2.6% vs. 5.8% $P = 0.009$) which was statistically significant.

Several systematic reviews, meta-analyses, and a limited number of randomized studies have also been published. A systemic review of the use of NIR to assess perfusion in colorectal anastomosis determined that the surgical plan was changed in 10.8% of cases after the application of NIR and the AL rate was decreased from 7.4% to 3.4%.⁶ A meta-analysis by Shen et al⁷ also found that NIR was associated with a lower AL rate: odds ratio = 0.27 (95% CI: 0.13–0.53).

In 2019, De Nardi and colleagues performed the first RCT on this topic. This trial involved 252 patients undergoing laparoscopic left-sided colon and rectal resection randomized to intraoperative NIR or to subjective visual evaluation of bowel perfusion without NIR. NIR led to extended bowel resection in 13 cases (11%). An AL developed in 11 patients (9%) in the control group and in 6 patients (5%) in the study group ($P =$ nonsignificant).⁸ The study found that although intraoperative NIR could effectively assess vascularization of colorectal anastomosis, no statistically significant reduction of the AL rate in the ICG arm was achieved. However, in a second randomized trial conducted by Alekseev et al,⁹ the authors did find a statistically significant reduction in the rate of AL after the application of NIR in low colorectal anastomoses (4 to 8 cm

from the anal verge) but not for high anastomoses. They also reported a 19% change in the operative plan based on NIR.

Recently the long-awaited PILLAR III trial was published. This was a randomized controlled trial comparing NIR to clinical evaluation alone with the primary endpoint being AL. Although the PILLAR III trial did not find a significant difference in the AL rate between the 2 groups,¹⁰ The authors conceded that this study did not achieve accrual of the predetermined sample precluding any meaningful conclusions from this data.

TO has been proven clinically useful in the plastic surgery literature, particularly for postoperative flap monitoring. Steele used a NIR spectroscopy TO to monitor free flaps. He found sensitivity, specificity, and predictive values for detecting threatened flap loss of 100%. He concluded that the NIR spectroscopy TO was a highly reliable non-invasive method for postoperative free tissue transfer monitoring.¹¹ Lin et al³ also described the use of TO to decrease flap loss rate and improved the flap salvage rate in microsurgical breast reconstruction indicating that it may help to determine vascular compromise before clinically evident. No direct NIR spectroscopy to NIR-ICG comparison was made in the plastics literature but early detection of vascular compromise of flaps with NIR spectroscopy was shown in multiple studies.^{11–15}

In this prospective study, we were able to show a high correlation between the NIR and TO margins. The IntraOx appeared easy to use with a shallow learning curve. Averaging data points from number of circumferential sites at each location of the bowel appeared to stabilize some of the noise inherent in this technology.

While the results of our study are promising, there are a number of important limitations. Some limitations include the small sample size of 100 participants and the fact that our study was conducted at only 2 centers by 2 surgeons. We chose to use 5 cm intervals for IntraOx evaluation. This protocol was designed before any significant experience was gained with this novel instrument. In retrospect, 5 cm intervals was not granular enough, we should rather have used 1 cm intervals which would have had more clinical relevance and would have been well within the resolution of the IntraOx device.

In this study, we used the NIR rather than TO margin for clinical decision-making. As the first-in-human colectomy study using TO technology, it would not have been appropriate to use anything but our standard of care for this decision. But importantly, this precludes any conclusions regarding which technology—the NIR or StO₂—is a more accurate modality for assessing tissue viability. It remains unknown whether we would have experienced an increased AL if we had used the TO margin in the 8 patients were the IntraOx indicated a more distal margin. Also in no cases did the TO demonstrate a more proximal margin than that indicated by NIR. In this study as in other published reports, we used the area of the colon with the most intense fluorescent uptake or the first proximal point of pulsatile ICG fluorescence to define the final margin of transection. We do not routinely use fluorescence quantification nor do we have a defined time from injection at which point we assess the degree of fluorescence and make our transection site decision.¹⁶ For these reasons, NIR-ICG may be too sensitive of a test. If we had, for example, waited a longer period of time from injection before deciding on a NIR margin or had used quantification we may have found that

TABLE 3. IntraOx Device Compared With NIR-ICG Fluorescence

	< 10 points from baseline	> 10 points from baseline
ICG fluorescence	TP: 172	FN: 7
No fluorescence	FP: 21	TN: 242

FN indicates false negative; FP, false positive; ICG, indocyanine green; NIR, near-infrared; TN, true negative; TP, true positive.

the NIR margin was actually more distal and correlated with the TO margin more closely. An indication of possible hypersensitivity of NIR-ICG is suggested by the findings of the 2 RCTs^{8,9} mentioned above, where they reported that the NIR-ICG arm had a change of margin that when added to the leak rate of that arm far exceeded that of the non-NIR arm. This implies that NIR may overcall hypoperfusion and lead to excessive and likely unnecessary colon resections. More study is needed on this question to clarify this.

One last note on the IntraOx, is that in its current form factor, it can only be used in cases where the colon is extracorporealized. With the increasing use of the robotic platform in colon and rectal surgery, intracorporeal anastomosis is becoming more accessible to surgeons. Because of this a laparoscopic version of this device would be desirable and is currently going through the research and development process.

Further studies which include larger sample sizes are needed to confirm our findings. This should then be followed by a randomized controlled trial comparing NIR-ICG to TO looking specifically at the prevention of AL.

CONCLUSIONS

TO using the IntraOx shows significant promise in identifying a relevant demarcation line of viable and non-viable bowel during colon and rectal surgery with comparable results to NIR-ICG. The IntraOx device has a number of benefits, including portability, it does not require fluorescent dye or specialized imaging equipment and has a lower cost of entry. Further studies looking at the effect of the IntraOx on preventing colonic anastomotic complications such as leak and stricture are warranted.

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