

Real-Time Intraoperative Ureteral Identification in Minimally Invasive Colorectal Surgery: A Systematic Review

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Abstract

Background: Although colorectal surgery (CRS) has currently almost entirely standardized surgical procedures, it can still show pitfalls such as the intraoperative ureteral injury. Intraoperative ureteral identification (IUI) could reduce the ureteral injuries rate but evidence is still lacking. We aimed to analyze the utility and the effectiveness of real-time IUI in minimally invasive CRS.

Materials and Methods: A systematic review was performed examining available data on randomized and nonrandomized studies evaluating the utility of intraureteral fluorescence dye (IFD) and lighted ureteral stent (LUS) for intraoperative identification of ureters in CRS, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards. Primary endpoint was ureteral injuries rate. Secondary endpoints included acute kidney injury, hematuria, urinary tract infections (UTI), and fluorescence assessment.

Results: After literature search, 158 studies have been recorded, 36 studies underwent full-text reviews and 12 studies met inclusion criteria. Overall, out of a total of 822 patients who successfully received IUI, 3 (0.33%) patients experienced ureteral injury. Hematuria was reported in 689 (97.6%) of patients following LUS-guided surgery and in 1 (2%) patient following IFD-guided surgery, although transient in all cases. UTI was reported in 15 (3.3%) LUS-guided resections and in 1 (2%) IFD-guided resections. Acute kidney injury occurred in 23 (2.5%) LUS-guided surgery and 1 (1%) IFD-guided surgery.

Conclusions: Real-time ureteral identification techniques could represent a valid solution in complex minimally invasive CRS, safely, with no time consuming and always reproducible by surgeons. Prospective studies will be needed to confirm these findings.

Keywords: intraureteral fluorescence, indocyanine green, lighted ureteral stent, ureteral injury, colectomy, colorectal surgery

Introduction

ALTHOUGH COLORECTAL SURGERY (CRS) has currently almost entirely standardized surgical procedures, it can still show pitfalls. One of the most feared complications is the intraoperative ureteral injury, especially during complex resections for cancer, diverticulitis, inflammatory bowel disease (IBD), and endometriosis.

The overall incidence of ureteral injury is estimated to be between 0.3% and 1.5%¹⁻⁴ and 9% occurs during colorectal resections.⁵ However, the rate of ureteral lesions is higher for

colonic resections in the context of diseases such as acute diverticulitis, endometriosis, locally advanced tumours, reoperation, previous radiation or pelvic surgery, obesity, fistulas, and Crohn's disease.^{6,7} Compared to traditional surgery, in laparoscopic and robotic era, it is necessary to compensate for the partial or total loss of tactile feedback.

While minimally invasive approaches have demonstrated numerous benefits, the rate of iatrogenic ureteral injury is higher for laparoscopy than with open surgery, which could be contributing to the observed overall rise in iatrogenic ureteral injury rate.^{1,8,9}

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Intraoperative ureteral identification (IUI) could reduce the ureteral injuries rate but evidence is still lacking.

The first use of light ureteral stent (LUS) during major laparoscopic colectomy for identifying ureters was reported in 1994,¹⁰ with no ureteral injuries, ureteral catheter complications, or instances of delayed renal function postoperatively. However, the results of ureteral stent placement in laparoscopic surgery are not convincing and several studies associated it with more complications, including urinary tract infection (UTI), urinary retention, hematuria, and perforation, in addition from added operation time.^{11–13}

Intraureteral fluorescence dye (IFD) for ureteral identification with optical dye administration is an alternative to traditional ureteral stent placement for IUI during minimally invasive CRS. This method may obviate the need for stent placement and allow for precise ureteral visualization during a minimally invasive approach that otherwise lacks tactile feedback.⁸ Fluorescence of ureters can be visualized in real-time using cystoscopy-guided indocyanine green (ICG) dye instillation or intravenous methylene blue (MB) administration. Intravenous MB was successfully first used in humans in 2013 demonstrating its feasibility for open pelvic surgery.¹⁴

The aim of this study is to perform a systematic review to analyze the utility and the effectiveness of real-time IUI in minimally invasive CRS.

Materials and Methods

Search strategy

A systematic review was performed examining available data on randomized and nonrandomized studies evaluating the utility of IFD and LUS for intraoperative identification of ureters in CRS, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards (Fig 1).¹⁵ Eligible studies were identified using three distinct databases through December 2020: Medline (PubMed), Web of Science, and Scopus.¹⁶ The following terms have been used for the research: “intraureteral fluorescence” and “lighted ureteral stent,” combined with “colectomy,” “colorectal surgery,” “injury” and “indocyanine green,” without any language or publication restrictions. Full-text articles were independently screened by 2 authors (G.M. and E.M.M.) for eligibility. Reference lists of eligible studies were assessed manually so that no relevant article was missed.

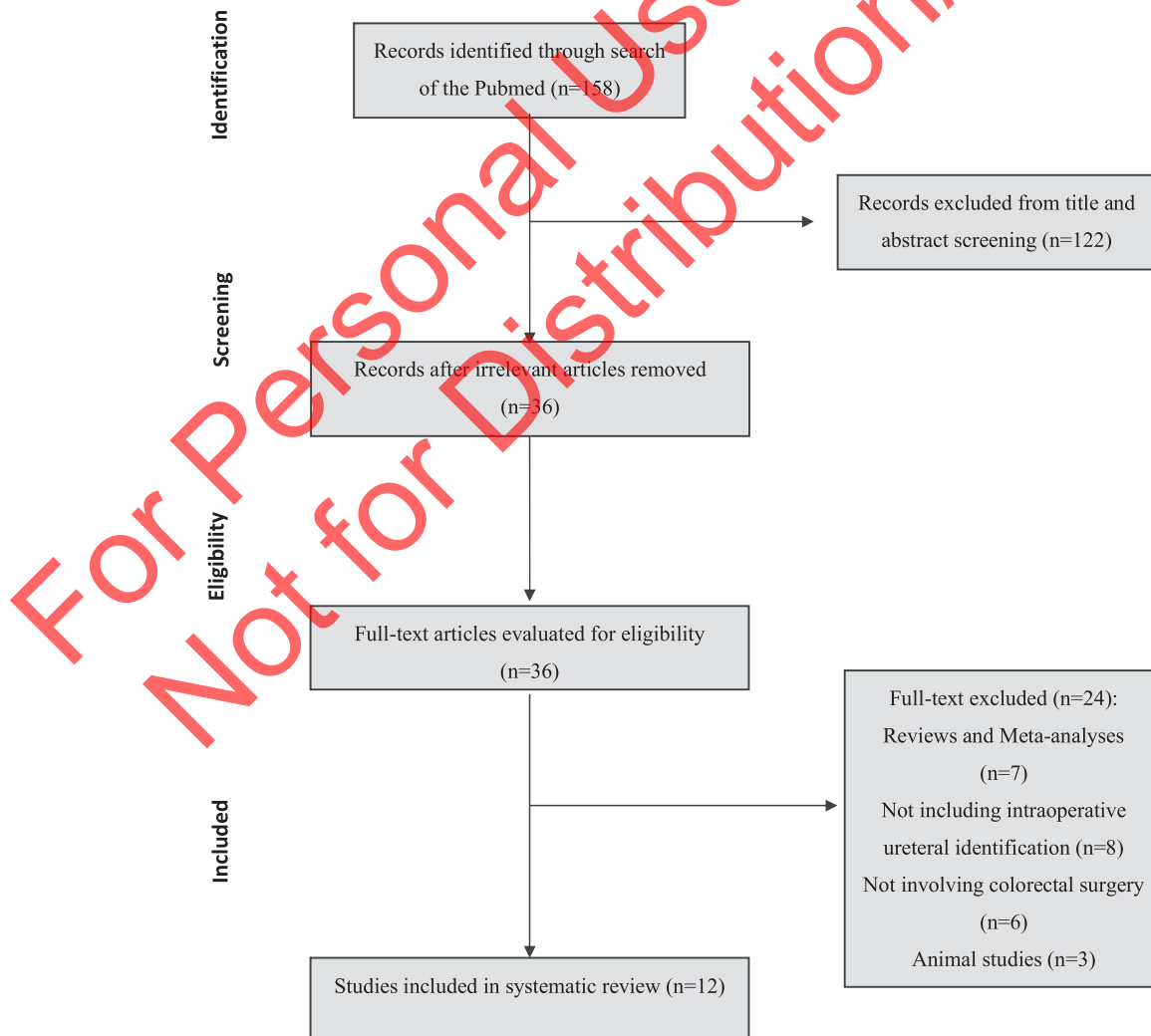


FIG. 1. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Inclusion and exclusion criteria

In the systematic review, we restricted the search using the following exclusion criteria: (1) animal studies; (2) studies not including IUI; (3) studies not involving CRS; and (4) reviews and meta-analyses. Randomized-controlled trials, prospective and retrospective cohort studies, case series, and case reports on patients undergoing real-time intraoperative identification of ureters during colorectal resections have been included.

Data extraction and synthesis

After reviewing the full-texts of eligible studies, 2 authors (G.M., E.M.M.) performed the data extraction and cross-checked all the results. Extracted variables included general study characteristics, patient demographics, ureteral identification, colorectal disease, and outcomes. General study characteristics included the author, journal, year of publication, study design, number of colorectal resections, and interventions with ureter detected; patient demographics included age and body mass index (BMI); ureteral identification included methods (LUS or IFD), fluorescence assessment and adverse effects; colorectal disease included cancer, diverticulitis, fistula disease, IBD, and endometriosis; finally, outcomes included ureteral injury, UTI, hematuria, and acute kidney injury. When coding the data, any disagreements were adjudicated by a third reviewer (B.P.). Data were tabulated using Microsoft Excel (Microsoft 365) and cumulative analysis was performed when possible. Categorical variables were extracted as numbers and reported as proportions.

Quality assessment

The methodological quality of all included studies is evaluated with the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies (Table 1).

Results

After literature search, 158 studies have been recorded, 36 studies underwent full-text reviews and 12 studies met inclusion criteria (Fig. 1).^{8,17-27} Study design and characteristics are reported in Table 2. Of the 12 included studies, 5 studies were retrospective, 5 were prospective, and 2 were case series or case report, published from 2002 to 2020. All studies included colorectal resections with IUI. The average patient age is 61.08 (46.7–73.4), and the average patient BMI is 27.29 (23.2–30.3). Overall, a total of 833 patients who underwent colorectal resections are present in the systematic review and 822 (94.29%) successfully received IUI. Real-time intraoperative identification was carried out with LUS in 6 studies (patients *n*=743, 90.4%) and IFD in 6 studies (patients *n*=79, 9.6%). LUS was placed in all cases preoperatively. Fluorescent dyes used were ICG in 3 studies (patients *n*=31, 39.2%) and MB in 3 studies (patients *n*=48, 60.8%).

Fluorescence assessment data were collected where possible (Table 3). The dye was injected preoperatively^{18,22} or intraoperatively,^{8,20,23} the mean dye administration time was 12.48 minutes (5–20 minutes) and mean dye visualization time was 303.5 minutes (125–489 minutes). The ICG dose injection range was 2.5–5 mg/mL and the MB dose injection range was 0.125–1 mg/kg. No adverse effects on dye injection were reported in the case studies, although MB always caused a transient decrease of the oxygen saturation.

In this literature data, 97% of patients were treated by minimally invasive surgery (80.4% laparoscopic, 16.7% robotic) and 3% of patients by traditional open surgery. Patients had both benign and malignant disease: colonic diverticulitis 477 (53.6%), colorectal cancer 239 (37.7%), IBD 18 (1.5%), colorectal endometriosis 5 (3%), fistula disease 2 (2.9%), and 28 (1.2%) others (e.g., Hartmann’s reversal, rectopexy, anterior resection syndrome). Three studies (patients *n*=64, 7.8%) did not specify the treated pathology.^{18,23,24}

TABLE 1. QUALITY ASSESSMENT OF INCLUDED STUDIES

Study	Selection			Demonstration that outcome of interest was not present at start of study	Comparability	Outcome	
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure		Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Adequacy of follow-up of cohorts
White et al. ⁸	☆		☆	☆		☆	☆
Kanabur et al. ¹⁷	☆		☆	☆		☆	☆
Mandovra et al. ¹⁸	☆		☆	☆		☆	☆
Hamilton et al. ¹⁹	☆		☆	☆		☆	☆
Barnes et al. ²⁰	☆		☆	☆		☆	☆
Boyan et al. ²¹	☆		☆	☆		☆	☆
Al-Taher et al. ²²	☆		☆	☆		☆	☆
Yeung et al. ²³	☆		☆	☆		☆	☆
Redan and McCarus ²⁴	☆		☆	☆		☆	☆
Blake et al. ²⁵	☆		☆	☆		☆	☆
Dwivedi et al. ²⁶	☆		☆	☆		☆	☆
Chahin et al. ²⁷	☆		☆	☆		☆	☆

TABLE 2. CHARACTERISTICS OF STUDIES INCLUDED IN SYSTEMATIC REVIEW

Author	Type of study	Colorectal resections n	Techniques	Ureteral identification	Ureteral injuries, n (%)
White et al. ⁸	Prospective	15	Robotic	ICG fluorescence-guided	0 (0)
Kanabur et al. ¹⁷	Case series	5	Laparoscopic	ICG fluorescence-guided	0 (0)
Mandovra et al. ¹⁸	Prospective	11	Laparoscopic	ICG fluorescence-guided	0 (0)
Hamilton et al. ¹⁹	Case report	1	Robotic	LUS	0 (0)
Barnes et al. ²⁰	Prospective	35	Laparoscopic 90% Open 10%	MB fluorescence-guided	0 (0)
Boyan et al. ²¹	Retrospective	465	Laparoscopic	LUS	0 (0)
Al-Taher et al. ²²	Prospective	5	Laparoscopic	MB fluorescence-guided	0 (0)
Yeung et al. ²³	Prospective	8	Laparoscopic 75% Open 25%	MB fluorescence-guided	0 (0)
Redan and McCarus ²⁴	Retrospective	45	Laparoscopic	LUS	0 (0)
Blake et al. ²⁵	Retrospective	100	Laparoscopic	LUS	1 (1)
Dwivedi et al. ²⁶	Retrospective	66	Laparoscopic	LUS	1 (1.5)
Chahin et al. ²⁷	Retrospective	66	Laparoscopic	LUS	1 (1.5)
Total (n = 12)		822 pts			3 (0.33)

Value are expressed as n (%).

ICG, indocyanine green; LUS, lighted ureteral stent; MB, methylene blue; pts, patients.

The outcome was reported in Table 4. Out of a total of 822 patients who successfully received IUI, 3 (0.33%) patients experienced ureteral injury.^{25–27} 2 injuries occurred during surgery for diverticulitis: the first was identified intraoperatively and was managed by leaving the ureteral stent in place for 3 weeks²⁵; the second was managed laparoscopically without conversion to open procedure by keeping the ureteral stent in place for 3 weeks.²⁶ The remaining ureteral injury was an incomplete left ureteral injury during sigmoid colectomy, recognized on postoperative day 2 with urinary ascites, and managed by reinserting the left ureteral stent temporarily. The diagnosis was made with retrograde cystoureterogram. The stent was removed on postoperative day 11, and the patient was discharged.²⁷ No case of ureteral lesion occurred during real-time IUI with fluorescence dye. Hematuria was reported in 689 (97.6%) patients following LUS-guided surgery and in 1 (2%) patient following IFD-guided surgery, although transient in all cases. UTI was reported in 15 (3.3%) LUS-guided resections and in 1 (2%) IFD-guided resection. Acute kidney injury occurred following 23 (2.5%) LUS-guided surgery and 1 (1%) IFD-guided surgery.

Discussion

To our knowledge, no previous review has evaluated the use of LUS and IFD for identifying ureters in patients who underwent colon and rectal resections.

Ureteral identification is a critical step in CRS. The objective of this systematic review was to highlight the importance of avoiding ureteral injuries, which can be a serious complication for patients. In fact, a ureteral lesion, when not recognised intraoperatively, leads to numerous postoperative complications, starting with the risk of uroseptic peritonitis, which requires a longer hospitalization period and often a nephrostomy, and even in the worst cases can lead to irrecoverable kidney damage. The technical difficulty of some challenging surgical pictures, such as locally advanced colorectal cancer, complicated diverticular disease or severe abdominal inflammation need for a strategy.

Lighted ureteral stent

LUS have been introduced to enhance the visualization of the ureter with the goal of overcoming the limitations of tactile feedback.¹⁰ The risks associated with ureteric stent insertions include complications such as UTI and hematuria. However, these complications are largely self-limited and rates of UTIs with stent placement have been comparable to published rates of nosocomial UTIs after CRS.²⁸ In the largest series out of 465 cases with ureteral stent placement,²¹ no UTIs occurred, but transient hematuria was seen in all 465 cases.

TABLE 3. FLUORESCENCE ASSESSMENT

Author	Fluorescent dye	Dye injection	Dye administration time (minutes)	Dye visualization time (minutes)	Dose injection range	Adverse effects	Decrease of the oxygen saturation
White et al. ⁸	ICG	Intraoperatively	11.5	489	2.5 mg/mL	NO	—
Kanabur et al. ¹⁷	ICG	ns	16	360	2.5 mg/mL	NO	—
Mandovra et al. ¹⁸	ICG	Preoperatively	7	240	5 mg/2mL	NO	—
Barnes et al. ²⁰	MB	Intraoperatively	5	125	0.25–1 mg/kg	NO	Transient
Al-Taher et al. ²²	MB	Preoperatively	20	ns	0.125–1 mg/kg	NO	Transient
Yeung et al. ²³	MB	Intraoperatively	14.4	ns	0.25–1 mg/kg	NO	Transient

Value are expressed as n.

ICG, indocyanine green; MB, methylene blue; ns, not specified.

TABLE 4. OUTCOMES

Author	Colorectal resections n	Ureteral identification	Ureteral injuries, n (%)	Acute kidney injury, n (%)	Hematuria, n (%)	Urinary tract infection, n (%)
White et al. ⁸	15	ICG fluorescence-guided	0 (0)	1 (6)	1 (6)	1 (6)
Kanabur et al. ¹⁷	5	ICG fluorescence-guided	0 (0)	0 (0)	0 (0)	0 (0)
Mandovra et al. ¹⁸	11	ICG fluorescence-guided	0 (0)	0 (0)	0 (0)	0 (0)
Hamilton et al. ¹⁹	1	LUS	0 (0)	ns	ns	ns
Barnes et al. ²⁰	35	MB fluorescence-guided	0 (0)	0 (0)	ns	ns
Boyan et al. ²¹	465	LUS	0 (0)	19 (4.1)	465 (100)	0 (0)
Al-Taher et al. ²²	5	MB fluorescence-guided	0 (0)	0 (0)	ns	ns
Yeung et al. ²³	8	MB fluorescence-guided	0 (0)	0 (0)	ns	ns
Redan and McCarus ²⁴	45	LUS	0 (0)	ns	ns	0 (0)
Blake et al. ²⁵	100	LUS	1 (1)	0	95 (95)	6 (6)
Dwivedi et al. ²⁶	66	LUS	1 (1.5)	0	64 (97)	5 (7.6)
Chahin et al. ²⁷	66	LUS	1 (1.5)	4 (6)	65 (94.8)	4 (6)
Total (n = 12)	822 pts		3 (0.33)	24 (1.61)	690 (56.63)	16 (3.2)

Value are expressed as n (%).

ICG, indocyanine green; LUS, lighted ureteral stent; MB, methylene blue; ns, not specified; pts, patients.

In this systematic review, hematuria was reported in 97.6% of patients undergoing LUS-guided surgery, but it has always been resolved spontaneously. This hematuria was attributed to the preoperative placement of LUS.

Three (0.33%) of patients experienced ureteral injury²⁵⁻²⁷ and the placement of LUS helps to safeguard and identify ureteral injury intraoperatively.

Intraureteral fluorescence dye (IFD)

Today, only two fluorescent dyes, ICG and MB, are approved for clinical use by the Food and Drug Administration and the European Medicines Agency.²⁹

ICG-enhanced fluorescence was introduced in laparoscopic surgery to improve the view and provide detailed anatomical information during surgery.³⁰⁻³⁵ The dye, ICG, can be injected into the human blood stream with practically no adverse effects,³⁶ aiming for identification of anatomical structures where the dye is present, such as biliary ducts, vessels, lymph nodes, and the urinary tract. ICG is excreted by the bile, so ureters can be visualized in real-time using cystoscopy-guided ICG dye instillation. The unique property of ICG is that it binds to the proteins of the ureteric epithelium and stains them reversibly.³⁷

Intravenously administered MB is excreted renally and concentrated in the urine. It can be excited at 660 nm, and it emits light typically in the far red/near-infrared region (700 nm), in which light penetration in tissue is considerably higher than using white light alone.³⁸ In this systematic review, there were no adverse reactions following MB administration (patients n = 48). However, a transient decrease of the oxygen saturation was observed in all patients.^{20,22,23} This phenomenon is known and is caused by the principle of pulse oximetry, which is based on the red and infrared light absorption characteristics of oxygenated and deoxygenated hemoglobin, which is influenced by the transient passage of MB.³⁹ MB in low doses (<2 mg/kg) is safe, however, it can induce severe adverse effects such as arrhythmias, coronary vasoconstriction, and hemolytic anemia in patients with renal insufficiency or after the administration of higher doses.⁴⁰

Formal left ureter identification during sigmoid or rectal surgery was considered mandatory more frequently than right ureter identification during right colectomy (83.7% versus 31.7%)⁴¹ and 50% to 70% of intraoperative ureteral injury cases are not recognized during the primary procedure.⁴² Technically, the critical time is certainly the mid-lateral dissection between the mesocolic plane (Toldt's fascia) and the renal plane (Gerota's fascia), in fact in this phase, in the high-risk cases previously exposed, (diverticulitis, endometriosis, etc.) the two planes may be fused and difficult to separate due to inflammation, increasing the risk of entering the wrong surgical plane and consequently risking damaging the ureter through tractions or with energy devices. When not recognized intraoperatively, ureteral injury is difficult to identify with a significant increase in the risk of intra-abdominal sepsis.

In addition, the use of LUS and IFD may provide greater assurance for young surgeons who are about to perform colonic resections in a more difficult setting by decreasing the risk of ureteral injury. Finally, this strategy also provides a cost benefit, as the cost of a stent is much lower compared to the additional days of hospitalization for patients who suffer complications from ureteral injury and the numerous procedures they have to undergo to resolve the complications.²¹

In summary, IUI-guided CRS can have multiple endpoints to discuss and evaluate to definitively reduce the rate and/or improve the prognosis of iatrogenic lesions. Moreover, the study of fluorescence-guided intraoperative evaluation of urinary abnormalities could be of interest. Intraoperative detection of pitfalls such as ureter duplications may not only avoid injury but also reduce the conversion rate. White et al.⁸ reported 2 patients in his cohort with duplicated collecting systems, one with partial left duplication and the other with complete left duplication. Intraureteral ICG successfully facilitated the identification of both left ureters in the patient with a partially duplicated left collecting system.

It should be highlighted, however, that there are no comparative studies included in the analysis and, as the literature is still very lacking, we also included case reports or case series to provide as much available data as possible;

therefore, these could be considered limitations of our systematic review. Then, prospective randomized studies, possibly comparing the use of prophylactic versus visualized stents, are expected to validate the use of this technique.

Overall, ureteral injury is the least reported complication in IUI-guided colorectal resections.

Conclusions

Future prospective studies should focus on fluorescence-assisted CRS to improve the iatrogenic lesions impact and increase evidence. This systematic review study showed the benefit of performing the IUI to prevent ureteral injuries, identify in real-time, and manage iatrogenic lesions intraoperatively.

According to the results, real-time ureteral identification techniques could represent a valid solution in complex minimally invasive CRS, safely, with no time consuming and always reproducible by surgeons. In addition, randomized studies aiming to compare the outcomes of prophylactic versus lighted or near-infrared ureteral stents will be needed to evaluate their effectiveness and to encourage the use of new technologies to improving the benefits of minimally invasive surgery, even in complex abdominal settings.

Authors' Contributions

G.M., E.M.M., B.P., and I.A.M. designed the study; G.M. performed the research; material preparation and data collection were performed by G.M.; G.M. and E.M.M. analyzed the data; G.M. and E.M.M. wrote the article; G.M., E.M.M., B.P., S.R., S.R.D.M., and I.A.M. reviewed the article; I.A.M. supervised the study. All authors read and approved the final article.

Disclosure Statement

No competing financial interests exist.

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