REVIEWS IN UROLOGY

Comparison of Methods for Ureteral Patency Visualization

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Abstract

Background: The most common cause of ureteral trauma occurs during open, laparoscopic, or endoscopic procedures across multiple specialties. Ureteral injuries are often unrecognized or mismanaged. Early recognition of ureteral injuries by cystoscopy allows for prompt intervention. Visualization can be enhanced using agents that color or improve the contrast of ureteral flow.

Methods: A review of the literature was performed to summarize the characteristics, safety, and efficacy of current methods and visualization aids for cystoscopic evaluation of ureteral patency.

Results: Visualization aids reviewed include intravenous, oral, and intravesical agents such as indigo carmine, methylene blue, sodium fluorescein, phenazopyridine, vitamin B_2, dextrose, mannitol, and saline.

Conclusions: Physicians should consider evidence of both safety and efficacy when selecting a visualization aid to determine ureteral patency.

Introduction

Ureteral trauma most commonly occurs during open, laparoscopic, or endoscopic procedures across multiple specialties, including urology, urogynecology, and colorectal surgery. Ureteral injuries are often unrecognized or mismanaged in the absence of urologic assessment. Clinicians must have a high index of suspicion for these injuries, and even with this level of alert, some ureteral injuries remain unrecognized. Delayed recognition can have substantial consequences for the patient. The overall incidence of iatrogenic ureteral injuries during operative procedures ranges from 0.5% to 10%.[1] A retrospective review of patients with iatrogenic ureteral injuries found that a majority (55%) occurred during gynecologic procedures, with the remainder occurring during urologic (25%), colorectal (15%), and vascular procedures (5%).[1] A systematic review by Siff et al[2] showed that urinary tract injuries had a prevalence rate ranging from 0.3% to 2.8%.[2]

Early recognition of ureteral injuries allows for prompt intervention. One of the primary methods of early recognition has been cystoscopic visualization of ureteral flow. Visualization can be enhanced using agents that color or change the density of ureteral flow.

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Though indigo carmine has been the benchmark visualization dye for ureteral patency evaluation by cystoscopy, its use has been affected by shortages since 2015.[3] During this period, alternative methods have been used to evaluate ureteral patency, including other dyes and viscosity agents. The first US Food and Drug Administration (FDA) approval of indigo carmine (Bludigo; Provepharm Inc) as a visualization tool for assessing ureteral integrity in adults occurred in July 2022, and the product was reintroduced to the market. This review presents data on the advantages and disadvantages of dyes and other techniques to evaluate ureteral patency as reported in the literature.

Indigo Carmine

Indigo carmine is a blue dye that was developed for use in coloring textiles in 1743, with its first use as a kidney diagnostic dye for visualization of the ureteral orifice and ureteral flow reported in 1903 or 1904 by Voelcker et al.[4,5] When Voelcker and colleagues were searching for a dye to use as a kidney diagnostic tool in cystoscopy by visualizing ureteral flow, they initially evaluated methylene blue but found it had a high degree of variability in its time to visualization and in its color—sometimes appearing as pure blue, sometimes lighter in color, and sometimes disappearing entirely for a while before reappearing. For these reasons, they abandoned its use, and after testing several other dyes, they chose indigo carmine as the best option for ureteral flow visualization.[4] Intravenous (IV) administration was established by Harpster[6] in 1922, and the current administration route, dose, and concentration of 5 mL of a 0.8% solution was initiated by Douglass[7] in 1944.

In 2012, the American Association of Gynecologic Laparoscopists Practice Committee reported that the risk of lower urinary tract injuries during laparoscopic hysterectomy may be as high as 3% and that most but not all of these injuries are detected at intraoperative cystoscopy. The practice committee recommended that surgeons consider cystoscopic evaluation following laparoscopic total hysterectomy as a routine procedure. A description of the recommended procedure includes visualization of the ureteral jets using indigo carmine.[8] More recently, in 2018, an American Urogynecologic Society consensus statement based on clinical evidence concluded that cystoscopy should be performed at the time of all pelvic reconstructive surgeries, with the exception of operations solely for posterior compartment defects.[9] The society commented that if efflux of urine from the ureteral orifices was difficult to visualize, adjunctive agents could be helpful, noting that IV indigo carmine was used for this purpose.

ABBREVIATIONS

FDA	US Food and Drug Administration
IV	intravenous

A large body of literature is available for indigo carmine. A meta-analysis by Siff et al[2] analyzed data on 7781 patients evaluated for ureteral patency using indigo carmine. Indigo carmine had high sensitivity (91.1%) and specificity (99.8%), with a negative predictive value of 99.8%.[2] More recently, a clinical study of 118 patients evaluated ureter jet visualization, comparing indigo carmine with saline.[10] The time to visualization of indigo carmine was a median of 6 minutes. Blinded video recordings of both saline and indigo carmine were evaluated by independent reviewers on a 5-point conspicuity scale, ranging from 1 ("No jet observed") to 5 ("Strong jet flow with striking contrast in color"). Patients were classified as responders if the score for indigo carmine was at least 1 point greater than the score for saline and was at least a score of 3 ("Color contrast or significant jet flow, significance was visual"). Most patients' ureters scored a 4 or higher on the conspicuity scale following the injection of indigo carmine, which was statistically significantly better than it was for saline ($P < .0001$). Overall, 92.3% of patients were rated as responders for either ureter.[10]

Though no adverse events related to indigo carmine were reported for the clinical trial,[10] rare complications from the historical literature include cardiovascular events such as hypotension, cardiac arrest, arrhythmia, asystole, second-degree atrioventricular block, hypertension, and bradycardia as well as immune system reactions such as hypersensitivity

and anaphylactic reaction.[11,12] Indigo carmine may also transiently interfere with pulse oximetry, and there is the potential for a temporary false low-oxygen saturation reading, although indigo carmine has less effect in this regard than methylene blue.[13]

Methylene Blue

Methylene blue was reintroduced as an alternative option for ureteral visualization when indigo carmine went into shortage. It is administered intravenously at a dosage of 1 to 2 mg/kg over several minutes and has a half-life of 24 hours[14,15]; however, the dye remains problematic for several reasons. As discussed by Voelker and colleagues,[4,5] methylene blue's time to visualization and quality of color vary because of its metabolism. When given intravenously, approximately one-third of the dose eliminated by the kidneys is eliminated as leucomethylene blue, and one-third is eliminated as leucomethylene blue, the reduced state of methylene blue, which is colorless. As the conversion to leucomethylene blue is reversible, this may explain some of the variation in time to visualization and color intensity of the ureteral flow.[16] The conversion rate also varies by patient, which may be a factor in its lack of visualization.[17,18]

Methylene blue visualization is also delayed in patients with azotemia and kidney impairment.[17] Lee et al[19] reported a substantial delay in excretion after IV administration. Because of methylene blue's metabolism, the current recommendation is administration up to 45 minutes before cystoscopy.[14] There are few publications in the literature on the use of methylene blue for the evaluation of ureteral patency, which hinders the determination of its specificity or sensitivity, and there are no published data on the mean or range of time to visualization using cystoscopy.

Methylene blue is not FDA approved as a diagnostic dye for visualization of ureteral flow. Its only approved indication is for the treatment of pediatric and adult patients with acquired methemoglobinemia.[15] Beyond its unapproved status, methylene blue is contraindicated in patients with glucose-6-phosphate-dehydrogenase deficiency and may not be an effective tool in patients with kidney impairment because of its delayed visualization and recommendations for a reduced dose.[15] Methylene blue can transiently reduce oxygen saturation readings by pulse oximetry and can artificially lower the bispectral index for monitoring the depth of anesthesia.[13] There have been reports of delayed emergence from anesthesia and other neurologic issues after use of methylene blue. Licker et al[20] evaluated the effect of methylene blue on anesthesia and determined that patients pretreated with methylene blue required a mean 50% lower dose of propofol than patients in the control group, even though their bispectral index values were similar. Methylene blue carries a black-box warning for serious or fatal serotonin syndrome when used in combination with serotonergic drugs or opioids.[15] Additional potential adverse events include anaphylaxis, hemolytic anemia, confusion, dizziness, vision disturbance, hypertension, fever, nausea, and vomiting.[14,15]

Sodium Fluorescein

Sodium fluorescein is red-orange in color and is FDA approved for use in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.[21] It is not approved as a diagnostic dye for the visualization of ureteral flow. Sodium fluorescein is administered intravenously, with primarily kidney excretion that colors the urine bright yellow. After IV administration, the urine remains slightly fluorescent for 24 to 36 hours, and systemic clearance of fluorescein is essentially complete by 48 to 72 hours after administration.[21]

Doyle et al[22] evaluated sodium fluorescein in a case series of 12 patients, with doses starting from 0.11 mL of a 10% solution. They found that dosing at 0.25 to 0.5 mL produced a yellow flow, but the lower dose of 0.1 mL had poor visualization and the higher dose of 1.0 mL caused yellowing of the sclera and palms in 1 patient.[22] The time to visualization ranged from 1.8 minutes to 6.1 minutes. Delbos et al[23] followed with a prospective series of 30 patients treated with 0.25 mL of a 10% solution. The primary outcomes were jet color, rated on a 3-point scale ("very colored," "somewhat colored,"

or "not colored"), and surgeon satisfaction, rated on a 3-point scale ("highly satisfied," "satisfied," or "not satisfied"). The surgeons were highly satisfied 90% of the time, with 93% of patients having colored ureteral jets and 83% of patients having bilateral, brightly colored jets. One patient had no color in either jet but was found to have normal ureteral flow. One patient had no ureteral coloration on 1 side, and obstruction was detected and corrected. The average time to visualization was 7 minutes (range, 3-13 minutes). In contrast to Doyle's series of patients, who experienced no adverse events,[22] 10% of the patients in Delbos and colleagues' study[23] had hypotension after injection of sodium fluorescein in the operating room that required epinephrine, and 1 patient had delayed hydronephrosis as a result of an undetected partial ureteral obstruction. Bright yellow urine persisted for 48 hours in 50% of the patients, and 10% of these patients experienced itching.[23] Morgan-Ortiz et al[24] evaluated a series of 54 patients using 1 mL of a 10% sodium fluorescein solution. The mean time to visualization was 7.5 minutes, and no ureteral injuries or adverse events were observed.[24]

Extravasation during IV injection of sodium fluorescein can cause severe local tissue damage, including sloughing of the skin, superficial thrombophlebitis, subcutaneous granuloma, and toxic neuritis. These complications can cause severe pain in the arm for up to several hours. Rare cases of death as a result of anaphylaxis have been reported. At the higher doses used for sodium fluorescein's approved indication, adverse reactions include nausea, vomiting, gastrointestinal distress, headache, syncope, hypotension, and symptoms and signs of hypersensitivity. Cardiac arrest; basilar artery ischemia; severe shock; convulsions; thrombophlebitis at the injection site; hives and itching; bronchospasm; anaphylaxis; and, in rare cases, death have been reported.[21]

Phenazopyridine

Phenazopyridine is an oral tablet indicated for the symptomatic relief of pain, burning, urgency, frequency, and other discomforts arising from irritation of the mucosa of the lower urinary tract caused by infection, trauma, surgery, endoscopic procedures, or the passage of sounds or catheters. The FDA has not found this drug to be safe or effective for any indication, however, and it is marketed as an unapproved over-the-counter product. An orange-red coloration appears in the urine 1 hour after ingestion of a 100-mg to 200-mg dose, and the half-life is reported to be 48 to 75 minutes.[14]

A retrospective chart review conducted by Strom et al[25] evaluated 207 patients who received 100 mg to 200 mg phenazopyridine either the morning of their procedure or the night before. During cystoscopy, if the ureters could not be visualized, sodium fluorescein was injected. Of the 207 patients, phenazopyridine was effective in ureteral visualization in 190 (91.8%).[25]

Phenazopyridine has been associated with headache, rash, pruritus, and hypersensitivity reactions.[26] It is contraindicated in patients with glucose-6-phosphate-dehydrogenase deficiency and may cause hemolytic anemia, methemoglobinemia, and kidney dysfunction.[27]

Vitamin B_2

Vitamin B_2 (riboflavin) has also been used for ureteral patency. Given alone or as part of a vitamin B complex, it is water soluble, has limited absorption, is excreted through the kidneys, and can make urine yellow-orange.[28] It is taken orally 1 to 4 hours before surgery or the night before. Time to visualization is highly variable, as is its consistency in coloring the urine.[14] In a randomized study of 66 patients comparing 400 mg vitamin B_2 with placebo given the night before the patients underwent a procedure, the vitamin B_2 group had a statistically significantly higher score for yellow-colored urine compared with placebo based on a 3-point scale. The surgeon rated the visualization as better with vitamin B_2 (5 vs 4 on a 5-point scale), but the proportion of patients with both ureteral jets visualized was not statistically significantly different.[29] Vitamin B_2 is listed in the FDA's Inactive Ingredients Guide for oral use and has been designated by the FDA as generally recognized as safe. The FDA has not approved it for any diagnostic use.

Dextrose, Mannitol, and Saline

Dextrose, mannitol, and saline are other agents that have been used to aid in ureteral patency visualization. With these agents, the physician relies on the difference in viscosity and the movement of the jet within the fluid in the bladder. Without a difference in color, visualization can be more challenging, particularly if the flow is not robust. The velocity of the jet flow may be difficult to gauge. Diluted urine may also make visualization more difficult without a coloring agent.[14]

Comparison Studies

In trials evaluating multiple visualization tools, Espaillat-Rijo et al[30] performed a multicenter randomized trial comparing sodium fluorescein with phenazopyridine, 10% dextrose, and saline. Each comparison group consisted of 44 patients. The primary evaluation was visualization of the ureteral jet on a 3-point scale ("not visible," "somewhat visible," and "clearly visible"), with a secondary evaluation of surgeon satisfaction measured on a 4-point scale ("very satisfied," "satisfied," "somewhat satisfied," and "unacceptable"). Sodium fluorescein was statistically significantly better than saline for visibility, and its satisfaction rate ("very satisfied" or "satisfied") was 88.7%, while saline's satisfaction rate was 60%. It was statistically better for visibility and physician satisfaction than phenazopyridine but was not statistically different from 10% dextrose for either visibility or physician satisfaction. For visualization and physician satisfaction, phenazopyridine was not statistically significantly better than the saline control group. In contrast, 10% dextrose was statistically significantly better than the saline control group and phenazopyridine for visibility and physician satisfaction. There was no statistical difference in the rate of urinary tract infections or acute urinary retention; however, the study was not powered to detect a difference in adverse event rates.

In a randomized, blinded study of 84 patients comparing phenazopyridine with vitamin B_2 or placebo, phenazopyridine had statistically significantly more intense yellow staining than vitamin B_2 or placebo.[31] Vitamin B_2 was classified as moderate or intense in coloration in only 57% of patients, which was not statistically significantly different than placebo.

Grimes et al[32] designed a single-center, randomized trial of 130 patients comparing sodium fluorescein with phenazopyridine, mannitol, and saline for visualization of ureteral flow. Assessment was performed by a visual analog scale of 1 to 100, with 0 being complete agreement and 100 being complete disagreement. The surgeon evaluated satisfaction with method, ease of use, visualization of ureteral jets, and global satisfaction. The anesthesiologist and circulator evaluated ease of administration. Mannitol was the superior agent for determining ureteral patency, ease of use, visualization of the ureter flow, and for global satisfaction by the surgeon. There was no statistically significant difference in ease of administration by the anesthesiologists or circulators. Pairwise comparisons were not included in the analysis, so it is unclear how the other agents compared with each other.

Duncan-Lothamer et al[33] randomly assigned 276 patients to receive sodium fluorescein or no dye with either saline or water as the bladder distension medium. The outcome measure was jet strength, measured on a 5-point scale by the surgeon and an assisting surgical resident or fellow. A score of 2 or less indicated poor jet strength and initiated further evaluation. Though the distension medium had no statistical impact on jet strength, there was a statistical advantage to the use of sodium fluorescein for the right ureteral jet ($P = .046$), and the left ureteral jet approached statistical significance ($P = .05$). The no-dye group required more stent placements for poor visualization, but this outcome did not reach statistical significance. Time to visualization was not statistically different; however, 38.5% of the data were missing from the no-dye group, and the collection of data by category may have also lessened the surgeon's ability to detect a difference between the dye and no-dye groups.

Table 1. Overview of Visualization Agents Used to Assess Ureteral Patency

Characteristics	Indigo carmine	Methylene blue	Sodium Fluorescein	Phenazopyridine	Vitamin B_2 (riboflavin)
FDA-approved indication	A diagnostic dye indicated for use as a visualization aid in the cystoscopic assessment of the integrity of the ureters in adults following urological and gynecological open, robotic, or endoscopic surgical procedures[35]	Not FDA approved for any diagnostic use. An oxidation-reduction agent indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia[15]	For diagnostic imaging. Primarily indicated in diagnostic fluorescein angiography or angioscopy of the fundus and of the iris vasculature[21]	This drug has not been found by the FDA to be safe or effective. Not FDA approved for any diagnostic use	Not FDA approved for any diagnostic use
Urine color	Deep blue or bluish-purple[4]	Light blue, pure blue, sea green, or colorless[4]	Fluorescent yellow[24]	Reddish-orange[14]	Yellow-orange[28]
Administration	IV, 5 mL of a 0.8% solution; inject over 1 min[35]	IV, 50 mg or 1-2 mg/kg of a 5-mg/mL solution; administer over 5-30 min[14]	IV, 0.25-0.5 mL of a 10% solution; inject rapidly after taking precautions to avoid extravasation[21,24]	Oral, 100-200 mg at least 30 min before surgery[14]	Oral, 45 mg, 1-4 h before surgery[14]
Time to visualization in urine	4-9 min[35]	Not well documented[14] Methylene blue has been associated with a long delay to excretion after administration[19] Urine jets become only lightly or inconsistently dyed[14]	Approximately 7.5 min[24]	60 min after ingestion[14]	Variable, not well documented[14]
Half-life	12 min[35]	24 h[15]	23.5 min (sodium fluorescein)[21]; 264 min (fluorescein monoglucuronide, fluorescent metabolite)[21]	48-75 min[14]	66-84 min[36]
Black-box warning	No[35]	Yes[15]; may cause serious or fatal serotonin syndrome when used in combination with serotonergic drugs or opioids (avoid concomitant use[15])	No[21]	No	No
Contraindicated in patients with glucose-6-phosphate-dehydrogenase deficiency	No[35]	Yes[15]	No[21]	Yes[27]	No[36]
Kidney impairment	Dose adjustment is not needed in patients with mild to moderate kidney impairment (estimated glomerular filtration rate, 30-89 mL/min/1.73 m^2)[35] Not studied in patients with estimated glomerular filtration rate <30 mL/min/m^2 and is not recommended for use in these patients[35]	Adjust dosage in patients with moderate to severe kidney impairment (estimated glomerular filtration rate, 15-59 mL/min/1.73 m^2)[15]	No dose adjustment reported[21]	Contraindicated in patients with kidney insufficiency[27]	No dose adjustment reported

Abbreviations: FDA, US Food and Drug Administration; IV, intravenous.

Conclusions

An unrecognized or mismanaged ureteral injury resulting in delayed recognition can lead to postoperative complications, including the development of urinoma, abscess, ureteral stricture, and potential loss of ipsilateral kidney or death, and represents not only a patient safety issue but a litigation risk for the surgeon.[34] For IV agents, indigo carmine has rapid visualization rates and a long-established record of efficacy and safety, with more than 30 published studies reporting on more than 7000 patients[2]; it is now an approved and available product for cystoscopic ureteral visualization. Because indigo carmine was unavailable in 2015, methylene blue use became more common, but its issues with reliability for cystoscopic evaluation and safety concerns—including a black-box warning for serious or fatal serotonin syndrome when used with serotonergic drugs or opioids—need to be considered. There are minimal data in the literature and no randomized studies available to evaluate methylene blue's efficacy.[2] Sodium fluorescein has improved visualization compared with phenazopyridine but mixed results compared with mannitol, dextrose, and saline.[30,32,33] Oral agents such as vitamin B_2 and phenazopyridine are readily available, but timing to visualization in urine can be a factor, and the quality of visualization can vary.[14] Physicians should consider these factors when selecting a visualization aid to help determine ureteral patency. From a risk management perspective, physicians and institutions should evaluate how best to incorporate cystoscopy and visualization aids into the surgical workflow to increase early recognition of iatrogenic ureteral injuries. See Table 1 for a comparison of the agents discussed in this article.

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