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DYNAMIC MANUSCRIPTS

Novel technique for identification of ureters using sodium fluorescein

Fernando D. Dip · Mario Nahmod · Francisco Suarez Anzorena · Alejandro Moreira · Luis Sarotto · Carolina Ampudia · Sudhir N. Kalaskar · Pedro Ferraina · Raul J. Rosenthal · Steven D. Wexner

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Abstract
Background The unique property of sodium fluorescein has made it ideal for use in medical applications such as diagnostic ophthalmology and intravenous angiography. It is mainly excreted via the renal system and although extensively used in these diagnostic applications, it has not been widely used to aid in the visualization of the ureters. It is possible to visualize the urinary tract by shining a source of light and studying the fluorescence using a special filter. The goal of our study was to assess the real-time visualization of ureters using intravenous sodium fluorescein under the stimulus of a 530 nm wavelength light.

Materials and methods Nine 250 gm Wister rats were given an intravenous dose of 0.01 ml of sodium fluorescein. A laparotomy was immediately performed following the administration of dye. Anesthesia was performed with an intraperitoneal dose of ketamine–xylazine. The retroperitoneum was exposed and observed under an alternating white xenon and a 530 nm excitation light with an objective to visualize the organs captured within the fluorescence of the compound (sodium fluorescein).
Results Under xenon light, the location of the kidneys and urinary bladder were visualized, but not the ureters. The light was then changed to a 530 nm wavelength mode when the location and orientation of the ureters was visualized along with the peristaltic movements. Fluorescence visualization of the ureters was noted 5–10 min following kidney visualization. In addition, the vascular structures in close proximity to the ureters were also visualized. None of the rats underwent any retroperitoneal dissection, and in one case, partial mobilization of a kidney was undertaken. All rats were euthanized at the completion of the procedure.
Conclusion Intravenous administration of sodium fluorescein enables fluorescence visualization of the ureters in a rat model, after activation with a 530 nm light transmitter.

Keywords Fluorescence · Ureters · Pelvis surgery

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F. D. Dip · M. Nahmod · F. S. Anzorena · A. Moreira · L. Sarotto · P. Ferraina
Training Centre and Experimental Surgery José de San Martín Clinical Hospital, Buenos Aires, Argentina

F. D. Dip · C. Ampudia · R. J. Rosenthal
Department of Minimal Invasive, Metabolic and Bariatric Surgery, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, FL 33331, USA

F. D. Dip (✉)
Department of General Surgery, The Bariatric and Metabolic Institute, Minimally Invasive and Bariatric Surgery, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, FL 33331, USA
e-mail: fernandodip@gmail.com

S. N. Kalaskar · S. D. Wexner
Department of Colorectal Surgery, Cleveland Clinic Florida, Weston, FL, USA
e-mail: wexners@ccf.org

Background

Intraoperative ureteral injury during pelvic procedures is the most common urologic complication, a serious cause for concern due to the gravity of its consequences [1]. In some cases, intraoperative identification of the ureters can be challenging. Ureteral injury reportedly ranges from <1 % to 10 % of all pelvic procedures. Some procedures

are inherently associated with a higher risk for inadvertent ureteral injury, especially colorectal and gynecological surgery. Among the injuries reported, 50 % arose from gynecological procedures [2]. An increase in ureteric injury appears to be more common during the past decade, with the advent and subsequent popularity of the laparoscopic/minimally invasive approach. This increase could be related to the challenging eye-hand coordination that is required with the laparoscopic approach as well as the absence of tactile feedback [3]. Ureteric injury may not be intraoperatively recognized as urine leakage may not be evident due to bladder decompression with a catheter [4]. Delayed recognition of severe ureteral injury may result in a urinary fistula through the surgical wound, drain site, or massive urinary ascites or abscess; the need for a renal transplant has been reported in 40 % of cases [5]. Visualization of the ureters by their peristalsis (Kelly sign) is necessary in relatively common operations such as hysterectomy in which ureteral injury occurs in up to 48 %, followed by bowel operations at 17 %, and oophorectomy at up to 13 % [6].

Materials and methods

All procedures were performed at the Experimental Surgery Centre of the Jose de San Martin Clinical Hospital, approved the institutional ethics committee and following the International Guiding Principles for Biomedical Research Involving Animals.

Fluorophore

Fluorescein sodium is a water-soluble organic dying substance used when examining the blood vessels of the eyes. It was discovered by the chemist and Chemistry Nobel Prize winner (1905) Professor Johann Friedrich Wilhelm Adolf Baeyer (1835–1917). Fluorescein is a yellow, water-soluble, organic, dying substance that belongs to the xanthine group and produces an intense green fluorescent color in alkaline solutions at a pH higher than 7. When exposed to light, fluorescein sodium reacts to electromagnetic radiation and light between the wavelengths of 465–490 nm and fluoresces; that is, it emits light at wavelengths of 520–530 nm.

Consequently, the hydrocarbon is excited by blue or infrared lights, emitting light that appears yellowish green. After intravenous injection of fluorescein sodium in an aqueous solution, the unbound fraction of the fluorescein can be excited with infrared light and observed with the aid of a camera source equipped with a light filter. Fluorescein and its metabolites are mainly eliminated via renal excretion; however, the urine remains slightly fluorescent for 24–36 h. A renal clearance of 1.75 ml/min/kg and a hepatic clearance (due to conjugation) of 1.50 ml/min/kg have been estimated. Systemic clearance is essentially complete within 48–72 h after administration of 500 mg fluorescein [14].

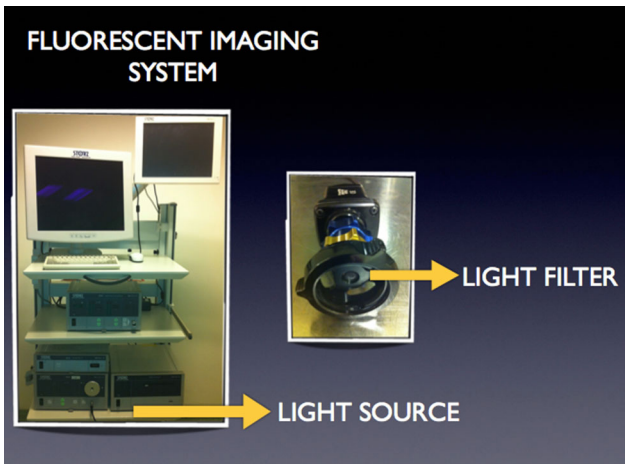

Fig. 1 Storz® xenon light source and laparoscope, charge-coupled device (Xenon Short Arc lamp, KARL STORZ Endoskope, Tuttlingen, Germany)

Materials and methods

A Storz® xenon light source and laparoscope (Fig. 1), with a charge-coupled device (filtered Xenon Short Arc lamp, KARL STORZ Endoskope, Tuttlingen, Germany), that filters out light wavelengths of 830 nm using a specific infrared light source with a 780 nm image was used in each case. During the procedure, the exposure was altered from xenon to infrared light to identify the ureters and other structures in the urinary tract. Fluorescein is cleared by glomerular filtration and can be found inside the lumen of the ureters. When excited with infrared light, fluorescein emits a light with a longer wavelength that cannot be visualized with the naked eye. The visualization system uses a filter within its camera that is capable of detecting this fluorescence from the illuminated structures.

A digital recording device (AIDA Compact II System, Karl Storz, Tuttlingen, Germany) was implemented during each procedure.

Ureteral visualization

A total of 9,250 gm Wister rats were included in the study. All subjects received an intravenous dose of 7 mg/kg of sodium fluorescein (Fig. 2). After administration of the dye, the rats immediately underwent surgery. The rats were anesthetized using ketamine 90 mg/kg and xylazine

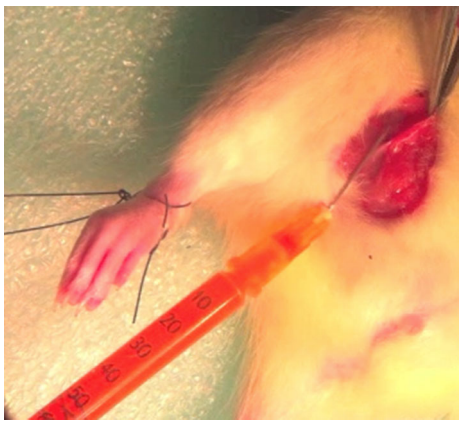

Fig. 2 Intravenous administration of ICG after venous disection

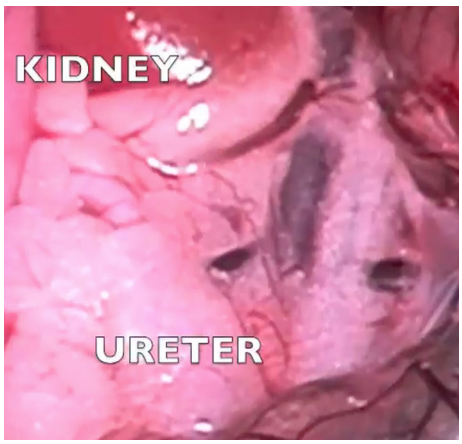

Fig. 3 Xenon light visualization of retroperitoneum

10 mg/kg intraperitoneally, and then a mid-line laparotomy was performed to obtain adequate exposure of the abdominal viscera. The contrast was administered orally, and the rats were operated on 24 h later to generate an acceptable drug washout window, thereby reducing the fluorescence of adjacent tissues.

The retroperitoneum was observed with alternating white xenon light and 530 nm excitation light. The images were acquired from a digital recording device. All rats were euthanized at the end of the procedures.

Results

After exposing the retroperitoneum to xenon light, it was possible to visualize the location of the kidneys and the gallbladder, but not the path or location of the ureters (Fig. 3). However, after changing the xenon light to a 530 nm wavelength light, it was possible to directly

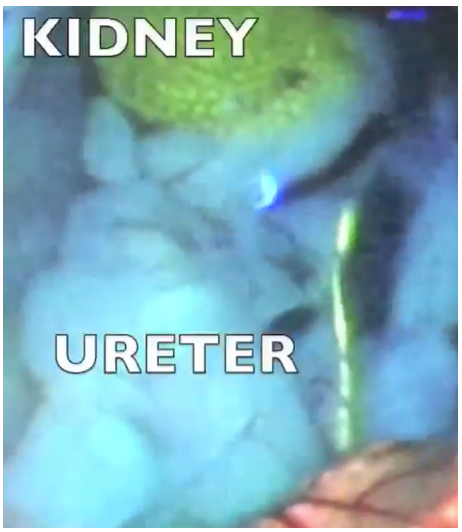

Fig. 4 Fluorescent identification of the ureter

visualize the distribution and location of the ureters and surrounding immediate area on all animals (Video 1). In addition, the vascular structures were clearly distinguishable; their orientation was especially useful for providing anatomic orientation, as was visualization of real-time ureteral peristalsis. The acceptable intensity was observed under excitation inside the ureters only and not in the kidney parenchyma, as shown in Fig. 4.

Discussion

Several methods have been used to identify the intraoperative anatomic location of the ureters, including ureteric catheters (stents) during complicated pelvic surgeries. However, stents are invasive, expensive, and sometimes difficult to insert [7]. Stent complications such as irritative symptoms, hematuria, suprapubic pain, migration, ureteral erosion, or perforation have all been well described [8, 9]. Furthermore, the utility of ureteral stents is sometimes limited during laparoscopic surgery due the lack of tactile sensation [10]. Lighted stents have been used, but they still have the associated invasive disadvantages [11]. Moreover, they may suspend the flow of urine. In the last few years, there have been developments in the identification of the ureters with new study methods using fluorescent techniques. Fluorescence is a natural phenomenon that has been known by humans for thousands of years. This fascinating element has been employed in many areas of research, chemistry, and organic photochemistry [12].

Ishizawa et al. [11] experienced fluorescent visualization of the biliary ducts after intravenous injection of indocyanine green when illuminated with near-infrared light.

Matsui et al. [12] reported visualization of the ureters in a mouse model based on a source of light with a specific wavelength and intravenous injection of fluorophore IR-Dye^{TM}800-CW carboxylic acid (CW800-CA) and methylene blue (MB) capable of generating light under excitation. More recently, Verbeek et al. [13] demonstrated the feasibility of visualizating the ureters 10 min after administration of MB using the Mini-FLARETM imaging system. Fluorescent-guided surgery provides a promising method for identification of these structures. New Food and Drug Administration-approved dyes need to be tested [14]. We present our initial experience in a rat model using fluorescent ureterography.

In addition to providing excellent visibility and identification of the ureters, this contrast is easy to administer, inexpensive, and has minimal side effects at 0.6 %; side effects are mainly limited to urticaria although much rarer, post-injection anaphylactic shock has been anecdotally reported following rapid bolus intravenous injection.

This system can be used during minimally invasive or open surgery.

To our knowledge, there is no description in the literature related to the penetration of fluorescence using fluorescein in the ureters.

Conclusion

We have shown the feasibility of the direct visualization of ureters with fluorescence using sodium fluorescein and a 530 nm light transmitter system and a specific filter. Although our results are encouraging, controlled randomized trials are required to establish the superiority of this newer technique, compared to the use of stents.

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