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ORIGINAL ARTICLE

A novel 450-nm blue laser system for surgical applications: efficacy of specific laser-tissue interactions in bladder soft tissue

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Abstract

Low-power blue laser allows clean cutting with little bleeding and no undesired coagulations in adjacent tissues; however, studies on high-power blue laser soft tissue ablation properties, including vaporization and coagulation, have not been reported yet. The purpose of this study is to evaluate and analyze the ablation efficacy and coagulation properties of bladder epithelium tissues with a 30-W 450-nm wavelength blue laser. Well-designed ex vivo experiments compared blue laser and 532-nm LBO green laser, both with laser power up to 30 W, for porcine bladder tissue vaporization and coagulation at different experimental parameter settings. At working distance of 1 mm and sweeping speed of 1.5 mm/s, the vaporization efficiency of blue laser and green laser was 5.14mm^3/s and 1.20mm^3/s, while the depth of coagulation layer was 460 ± 70 μm and 470 ± 80 μm, respectively. We found both blue laser and green laser have excellent efficacy of tissue vaporization and similar tissue coagulation properties. Moreover, in a set of in vivo experiments simulated laser transurethral resection (TUR) surgery on dogs, we found both blue laser and green laser exhibited similar and satisfactory vaporization and coagulation outcomes. Taken together, our results demonstrate that a 450-nm wavelength high-power diode blue laser, like 532-nm wavelength green laser, is capable to produce high efficient tissue vaporization, low-laser tissue penetration, good tissue coagulation, and has low thermal damage to adjacent tissues. Therefore, a 30-W blue diode laser could be a new and safe alternative for surgeries of superficial bladder diseases.

Keywords Blue laser · Bladder · Vaporization · Coagulation

Introduction

Laser has been used for soft tissue ablation in the surgery for a long time, and laser energy can be effectively absorbed by soft tissues, converted into thermal energy to precisely vaporize, incise, and coagulate soft tissues for surgical applications.

The blue diode laser obtained more attention since Shuji Nakamura et al. invented high-power and high-efficiency blue light-emitting diode (LED) and won the Nobel Prize of Physics in 2014 [1]. Compared to lasers at other visible or infrared wavelength, blue laser has shorter wavelength and higher absorption in the in soft tissues, including hemoglobin and melanin [2–4], and like green light, blue light penetration depth is much shallower than red light. Consequently, this low penetration depth of blue laser light may result in the low risk of accidental injuries in deeper tissue layers, and the laser light can be guided more precisely. On the other hand, considering that soft tissues contain high percentages of water, hemoglobin, melanin, lipids, and proteins, blue laser energy absorbed by soft tissues may result in ablation and coagulation, and blood vessels inside the coagulation layer could be coagulated and stopped bleeding. By taking these advantages, blue laser allows clean cutting with little bleeding and without major side effects in adjacent tissues due to the special absorption properties in the tissue components [5]. Preliminary clinical observations showed that the 450-nm laser technology could be a promising tool for surgical incision [6].

However, the study on the cutting properties such as tissue vaporization and coagulation of high-power diode blue laser has not been reported yet, and only a few studies have reported

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that low-power blue laser was applied in oral epithelium incision [6]. On the other hand, recently, semiconductor lasers are used in an increasing number of fields in research, industry, medicine, and to no small extent the consumer sector due to their compact structure, high electrical to optical power conversion efficiency, and reliability. Our team developed a novel 450-nm semiconductor blue laser device with laser output power up to 30 W at fiber tip. The purpose of the present study is to evaluate the efficiency of bladder tissue incision with 30-W 450-nm blue laser through systematically analyzing the structural changes in bladder epithelium after diode laser incision, and to test the hypothesis that a 30-W blue light laser device can be efficiently and safely used in the bladder tissue incision without increasing thermal damage.

Material and methods

Laser systems and experimental platform

Particularly for this study, a homemade novel 30-W blue diode laser system was specially designed and made by Blueray Medical Ltd. (Xi'an, China) and the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China). The laser consists of 36 blue laser diodes in TO56 package, each diode emits up to 1.6-W laser power with wavelength between 440 and 460 nm, centered at about 450 nm. By using beam collimation, beam shaping, fiber coupling, and fiber combining, the laser generates more than 30 W of optical power at center wavelength of 450-nm visible blue light through a 2.5-m long optical fiber with core diameter 760 μm. This output fiber with numeric aperture (NA) of 0.22, one end has a standard SMA905 connector to the laser, the other has a straight cut end producing 25° beam divergence, was used for all experiments in this study. The green laser (Realton Corp, Beijing, China) is a diode-pumped and frequency-doubled Nd:YAG laser system, emitting 532-nm wavelength light at pulse repetition rate of 12 kHz and pulse width about 120 ns, and the pulse energy is 2.5 mJ. This laser output is delivered by the same fiber used for the blue laser.

The in vitro vaporization was operated on a 3-axes custom-made linear stage with *X*–*Y* motorized moving and *Z* manually moving. The two computer-controlled electrical step-motors independently control speed and position of *X* and *Y* axes, and a fiber holder mounted on *Z* axis stage can be manually adjusted the distance from the fiber tip to the bladder tissues.

Porcine bladder model and measurement of in vitro vaporization

Sharing similar physical structure as human bladders, porcine bladders were selected as the in vitro experimental model. All experimental procedures have been approved by the Hospital's Institutional Animal Care and Use Committee. Ten frozen porcine bladders were obtained from a local slaughterhouse, and all of them were kept in temperature of 4 °C saline to minimize dehydration and structural changes for 4 h. Three hundred milliliters of water was then injected into each bladder to monitor the condition of fullness under cystoscopy. Due to the lack of physiological activity, the full bladder could not contract into its original status, which was split then unfolded on the tissue holder infiltrated with 20 °C saline. The laser vaporization process mimicked the transurethral resection (TUR) under cystoscopy ex vivo.

To examine the relationship between vaporization efficiency and laser power density and laser sweeping speed, several parameter settings were selected, including four different stage moving velocities (0.5 mm/s, 1 mm/s, 1.5 mm/s, 2 mm/s) and three working distances from the fiber tip to the bladder tissues (1 mm, 2 mm, 3 mm), resulting to a total of 24 sets of parameters in the experiments. In each vaporization process, the laser fiber stepped forward 10 mm along the *x* axis to vaporize a groove, then another groove was made in a similar way with a 5–6-mm separation. Each set was repeated at least three times to make the results more reliable.

Two methods were used to measure the grooves' depth and width as described previously [7, 8]. Macroscopically, the depth and width were measured by a Vernier caliper and by an imaging scope (Canon G12). Histologically, the specimens were fixed in 4% paraformaldehyde solution for at least 24 h, then embedded in paraffin, sectioned into slices (2 slices per specimen), stained with hematoxylin and eosin, and examined by imaging with optical microscopy.

Vaporized tissue volume was calculated according to the groove depth and width, and length measured above. The cross section of the groove is approximately a triangle, so the volume is the triangle's area (1/2 × width × depth) multiplied by the groove's length.

To measure the coagulation thickness, the slices were stained with hematoxylin and eosin, and the coagulation thickness was measured with Image-Pro 6.3 software under Olympus (BX51) microscope. The gray-tan coagulation zone was characterized microscopically by superficial cellular and stromal disruption and underlying tissue architectural preservation with nuclear chromatin condensation and hypereosinophilic cytoplasm.

Beagle canine bladder model and in vivo vaporization

These experimental procedures were approved by the Hospital's Institutional Animal Care and Use Committee as well. Four adult female Beagle dogs aged 2 years and weighed 10 kg were used. The operation was performed by an experienced anesthetist and a urological surgeon

under sterile operating room conditions. Both blue laser and green laser were used to vaporize the bladder on each dog. All four Beagle dogs were operated by the same procedure but different observation periods. Two treated dogs as chronic subjects were sacrificed after 2 weeks, and the others as acute subjects were sacrificed after 3 h.

In brief, anesthesia was induced with pentobarbital sodium (30 mg/kg), and then dogs were subjected to laparotomy and cystoscopy examination. A 10-Fr cystoscope (Olympus) was placed into the bladder after perfusion with 100 ml saline. Bilateral ureteral orifices were recognized as landmarks to make sure the safety of laser vaporization. Within 1–2-mm working distance to the bladder wall, the blue laser and then the LBO green laser were used to vaporize the bladder walls, and bleeding and potential perforation during the surgery were constantly checked. To evaluate laser vaporization effect, sacrificed canine bladders were dissected and fixed in 4% paraformaldehyde solution for 24 h, then embedded in paraffin, sectioned into slices, stained with hematoxylin and eosin (H&E), and then examined by imaging.

Statistical analysis

All statistical analyses were performed with GraphPad Prism software. Quantitative data was presented as mean ± SD. Student's two-tailed t test was used for the determination of statistical relevance between groups, and $P < 0.05$ was considered as statistically significant.

Results

Blue laser has a considerable vaporization and coagulation effect compared with green laser in vitro

As shown in Fig. 1, the vaporization efficiency on porcine bladders by blue laser and green laser was detected at different settings. Under the slowest sweeping speed of 0.5 mm/s, both lasers vaporized deep grooves at working distances from 1 to 3 mm. When the stage speeded up, the grooves at 2-mm and 3-mm working distances became gradually shallower, and finally disappeared at the speed of 2.0 mm/s.

To calculate the vaporization efficiency of blue laser and green laser, the middle parts of vaporized grooves under the 1-mm working distance were sliced and stained with H&E (Fig. 2). We measured the vaporization depth and width and calculated the vaporization volume and efficiency generated by a 30-W blue laser and green laser (Fig. 3), and we found that when the sweeping speed is 0.5 mm/s, the vaporization depth, width, volume, and efficiency of green laser are higher than those of blue laser; however, when the stage moved faster at the sweeping speed 1.0 mm/s and 1.5 mm/s,

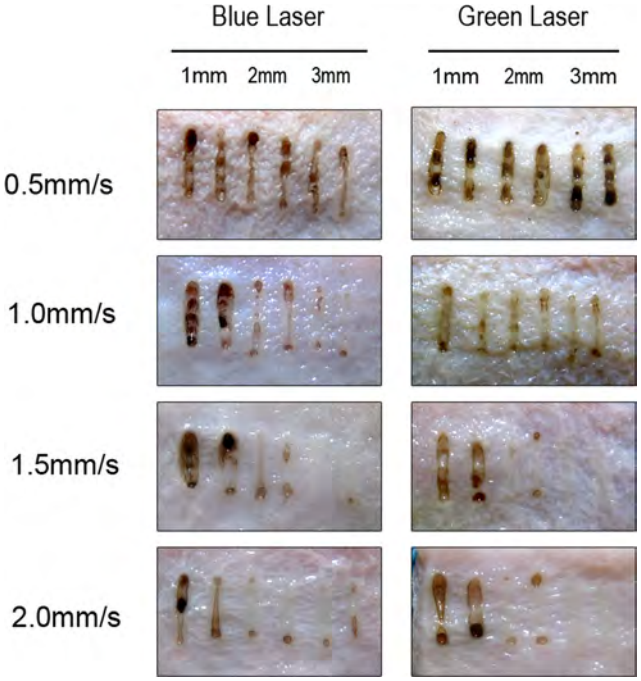

Fig. 1 Images of porcine bladder tissue vaporization grooves at 1 to 3 mm working distance and stage speed of 0.5 mm/s. Both blue laser and green laser were set at 30 W. The length of each groove was 10 mm

the vaporization depth, width, volume, and efficiency of blue laser (1.67 mm, 1.62 mm, 20.80mm^3 and 2.08mm^3/s at 1.0 mm/s; 1.89 mm, 2.37 mm, 34.27mm^3 and 5.14mm^3/s at 1.5 mm/s respectively) are obviously higher than those of green laser (0.74 mm, 0.84 mm, 5.22mm^3 and 0.52mm^3/s at 1.0 mm/s; 0.77 mm, 1.00 mm, 6.02mm^3 and 1.20mm^3/s at 1.5 mm/s, respectively). It is found at a low sweeping speed of 0.5 mm/s that the vaporization depth, width, tissue volume, and efficiency of blue laser are significantly lower than those of green laser, while those parameters of blue laser are significantly higher than those of green laser at high speed of 1.0 mm/s and 1.5 mm/s. The reason behind is not clear and a further study is needed. Except this difference, the vaporization capacity of these two lasers on bladder tissue was comparable in vitro.

In addition, we detected the vaporization capacity of these two lasers at 0 scan speed and the laser fiber touched the bladder wall and stay working for 2 s and found that the vaporization of blue laser and green laser only reached the middle muscle tissue of the bladder, and the outer muscle and the serosa layer are intact (data not shown). These data showed the safety and effectiveness of both blue and green lasers on the vaporization and evaporation of bladder tissue. On the other hand, as shown in Fig. 4, the depth of coagulation area on porcine bladder tissue generated by vaporization of blue laser and green laser was about 460 ± 70 μm and 470 ± 80 μm, respectively, showing no significant difference ($p = 0.69$).

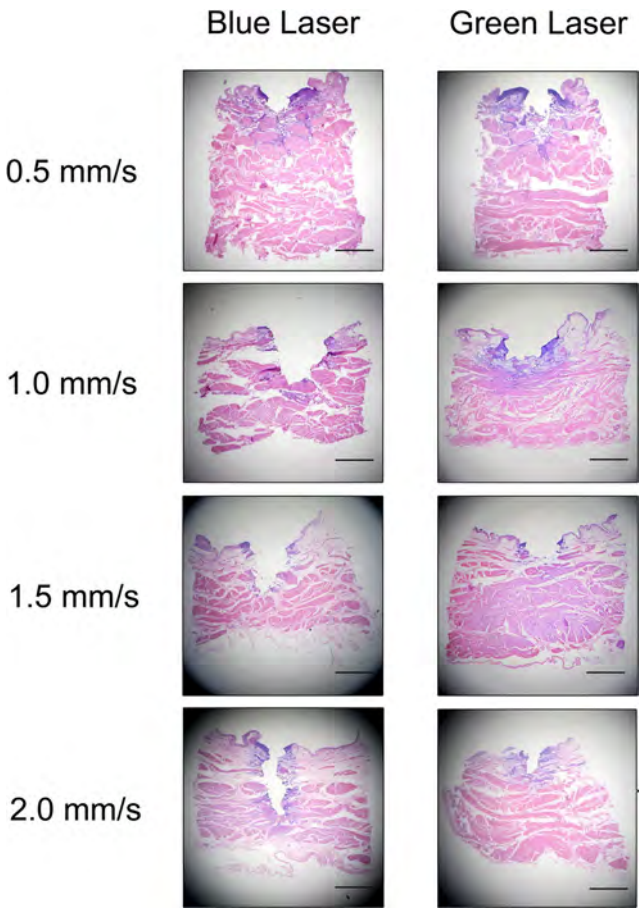

Fig. 2 Histological images of porcine bladder tissue treated with blue laser and green laser at 30 W and at stage speed of 0.5–2 mm/s and 1-mm working distance

In conclusion, our in vitro experiments demonstrate that both blue laser and green laser have excellent effect of tissue vaporization and coagulation on porcine bladder tissues.

Blue laser is efficient in the intravesical dog bladder surgery in vivo

Beagle dogs were selected to test laser tissue vaporization in vivo since its bladders are much smaller and easier to operate than porcine. All operations were video recorded by a cystoscopy image system. As shown in Fig. 5a, blue laser vaporizing bladder tissue for 1 s could produce an apparent hole with white coagulation zone (noted by black arrows). During the operation, there was no perforation, and only minimal bleeding could be seen on the monitor when the laser was shooting the small vessels in the bladder epithelium. However, the bleeding could be stopped by a large area laser illumination to the bleeding spot for coagulation, which is similar with green laser in bladder surgery (Fig. 5b). During the laser operation, the smoke produced by laser vaporization was absorbed by the continuous saline irrigation through the cystoscopy.

To evaluate the immediate vaporization effect of both lasers, two Beagle dogs were sacrificed 3 h after the surgery, whose bladders were exteriorized and split with clear vaporization spots (Fig. 6, white arrows on upper panel). Histological slices show the cross section of bladder wall vaporized by both lasers. There was no perforation at vaporization locations.

To evaluate the bladder recovery effect after the laser vaporization, two Beagle dogs were sacrificed 2 weeks after the operation. During this observing period between the surgery and sacrifice, no significant postoperative complications, including severe hematuria, dysuresia, urinary incontinence, and infection, were observed. When the surgical specimen was split, the vaporization spots 2 weeks ago have been almost disappeared and recovered with slight hemorrhagic spots showed with white arrows (Fig. 6, lower panel). H&E staining also showed the same results that the bladder epithelia regenerated and covered the cavities with minor hemorrhage of vaporization spots for both lasers. Moreover, as shown in Fig. 7, the depth of coagulation areas on bladder tissue generated by vaporization of blue laser and green laser was 550 ± 70 μm and 550 ± 80 μm, respectively, which had no significant difference ($p = 0.94$). These results suggested that blue laser could be effectively and safely applied in bladder tissue surgery in vivo.

Discussion

Although it has been reported that diode blue laser could be used as a tissue cutter, the effect of high-power diode blue laser on tissue vaporization and coagulation has not been reported yet. In the present study, we evaluated the effect of 30-W 450-nm blue diode laser on bladder tissue vaporization and coagulation in vivo and ex vivo, comparing with 30-W 532-nm green laser. The ex vivo experiments demonstrate, with different parameter settings (sweeping speed 0.5–2.0 mm/s; working distance 1–3 mm), both blue laser and green laser have excellent efficacy of tissue vaporization and coagulation on porcine bladder tissues. Moreover, in the in vivo experiments, both blue laser and green laser exhibit high tissue vaporization capacity, and good tissue coagulation ability during TUR on dogs. Our results present, like 532-nm green laser, that the high-power diode 450-nm blue laser has high tissue vaporization capacity, good tissue coagulation ability, and low tissue penetration; can interact with tissues precisely; and has low thermal damage to adjacent tissues. Therefore, 450-nm blue laser could be safely applied in surgeries of superficial diseases, such as CIS, Ta and T1 stage bladder cancers, and on other soft tissues.

Lasers have been widely used in treating multiple urologic disorders such as urinary stones, benign prostatic hyperplasia (BPH), bladder cancer, kidney cancer, urothelial tumors, and

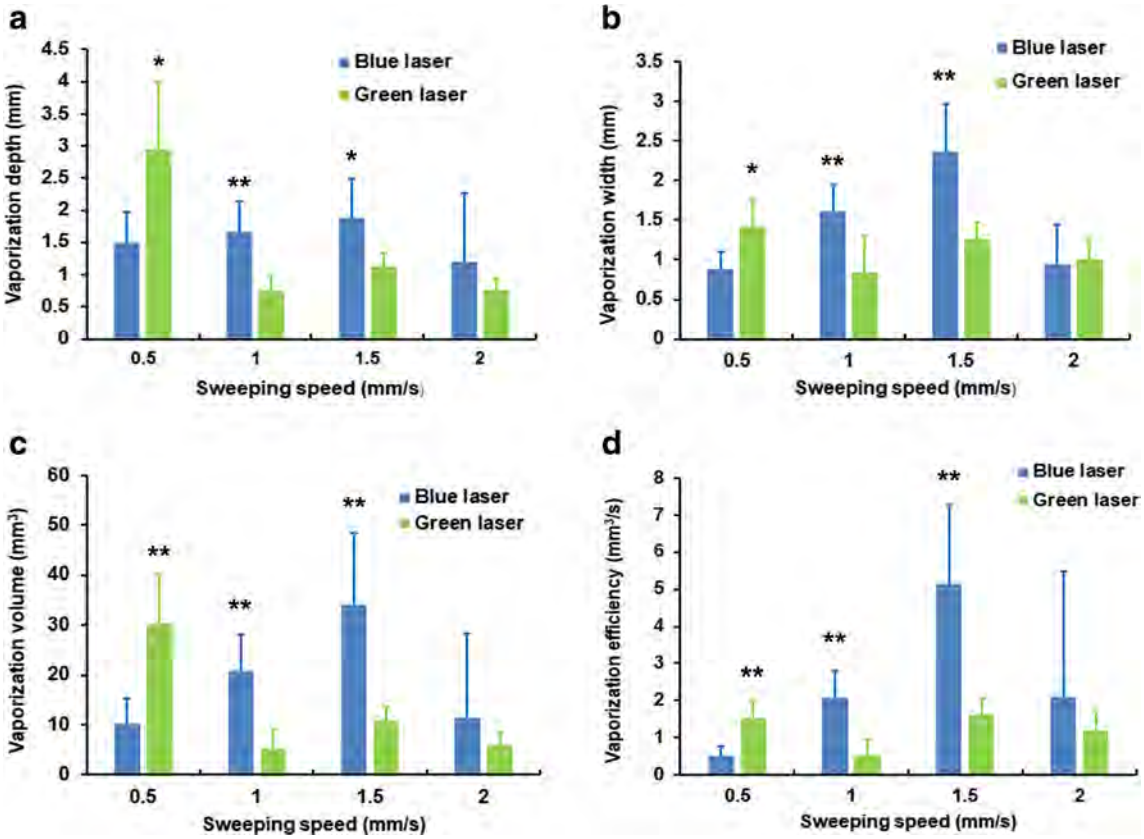

Fig. 3 Vaporization depth, width, volume and efficiency of both blue laser and green laser on porcine bladder tissue in vitro at 1-mm working distance and different sweeping speeds. The power of blue laser and green laser was set at 30 W. An asterisk (*) represents that a p value of 0.01 to 0.05 ($p > 0.01$ and $p < 0.05$) for the comparison between blue laser and green laser groups, while double asterisk (**) represents that a p value of 0.01 or smaller for the comparison between blue laser and green laser groups

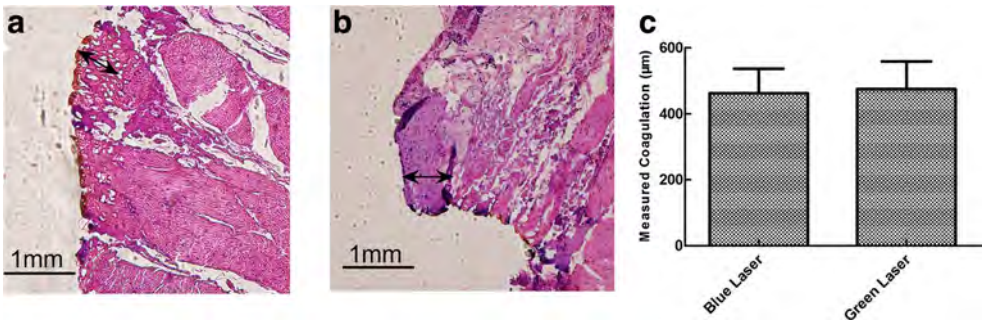

Fig. 4 Coagulation of porcine bladder tissues cut with blue laser and green laser. **a**, **b** Images of tissue coagulation cut with blue laser (**a**) and green laser (**b**), stained with hematoxylin-eosin; **c** Coagulation thickness of tissues. The power of blue laser and green laser were set at 30 W. The black bar indicates 1 mm

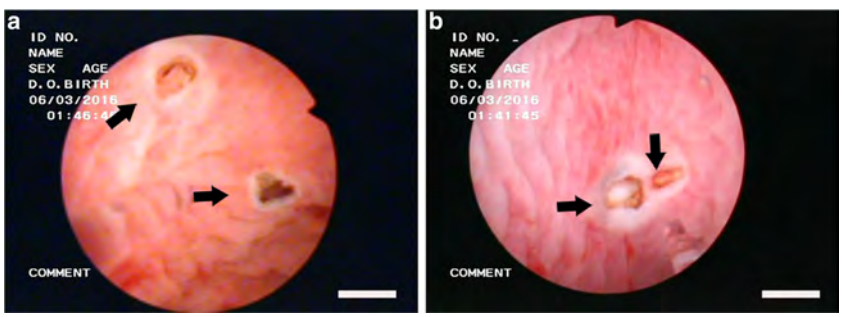

Fig. 5 Intravesical images of bladder tissues of Beagle dog cut with blue laser and green laser at 30 W under cystoscopy. **a** Blue laser and **b** green laser. The white bar indicates 1 mm

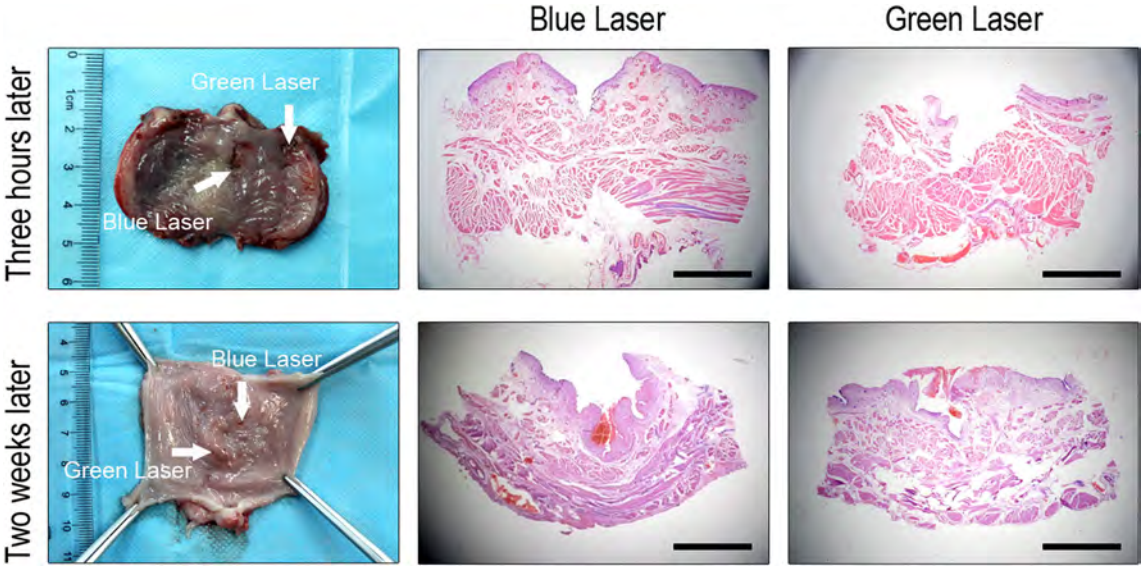

Fig. 6 Macroscopic and histological images of Beagle dogs' bladder tissue vaporization with blue laser and green laser under cystoscopy. The Beagle dogs were sacrificed 3 h (upper panel) or 2 weeks (lower panel) after the operation. The black bar indicates 1 mm. The power of blue laser and green laser was set at 30 W

strictures [9]. Recently, lasers have been applied in laser-assisted partial nephrectomy, laparoscopic nerve-sparing radical prostatectomy, renal tumor interstitial laser ablation, transurethral laser urethrotomy, and in upper urinary tract tumors [10–12]. Various lasers with different wavelengths and optical power have been developed in the market for surgical treatment of different diseases. To our knowledge, this is the first study about blue diode laser with 450-nm wavelength applied in urological tissues, especially in intravesical bladder surgery both in vitro and in vivo.

Both laser parameters (wavelengths, output power, continuous wave, or pulsed) and laser delivery/illumination parameters (fiber core diameter, numeric aperture NA, fiber tip shape front-firing/side-firing, distance from fiber tip to target tissues, power density, etc.) play important roles in laser urological surgeries [13]. Holmium laser (Ho:YAG) has a wavelength of 2140 nm, and can be effectively absorbed by water with optical absorption coefficient close to 37 cm^{-1}, presenting effective cutting effect on soft tissues but leaving a thin coagulation layer [14]. Continuous wave Thulium laser with wavelength of about 2 μm, similar to Ho:YAG laser also has strong water absorption, but low peak laser power density compared with holmium laser [15]. Five hundred thirty-two KTP or LBO green laser, highly absorbed by hemoglobin but not water [16], has been widely used in surgical treatment of BPH and bladder tumor. Although green laser can effectively ablate soft tissues, this kind of laser inherently relies on a complicate system, consisting of high-power lamps or diode lasers pumping, Q-switches, sophisticated-temperature controlling frequency-up conversion device, like KTP or LBO crystals, and other complicate subsystems, resulting in high manufacture cost, low reliabilities, high noise level, and bulky physical dimensions. In this study, our new desk-top blue diode laser device is much more compact, whose volume is 2.34×10^{-2} m^3 and the weight is < 20 kg, while conventional green laser device weighs 180 kg with volume of 4.88×10^{-1} m^3.

Laser-tissue interaction and distribution of laser energy in tissue depend on laser characteristics and tissue properties [2]. Laser characteristics include laser power, laser wavelength, method of laser delivery, power or energy density profile of the beam, local beam angle of incidence on the tissue, continuous wave or pulse modulation, pulse repetition rate, and pulse width. Tissue properties include contents of

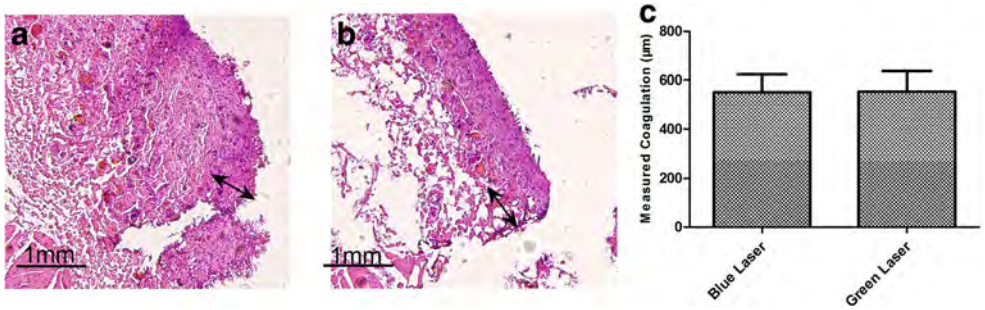

Fig. 7 Coagulation of canine tissues cut with blue laser and green laser. **a**, **b** Images of tissue coagulation cut with blue laser (**a**) and green laser (**b**), stained with hematoxylin-eosin; **c** Coagulation thickness of tissues. The power of blue laser and green laser was set at 30 W. The black bar indicates 1 mm

chromophores, optical absorption coefficient and scattering coefficient for each chromophores, the scattering anisotropy factor, and the refractive index. Even for same type of tissue, its optical absorption and scattering coefficients may also depend on tissue blood concentration, water concentration, tissue temperature, tissue coagulation status, and other factors [17]. For simplicity, most of studies are focused on laser hemoglobin absorption and water absorption. Blood has a significant optical absorption in the blue and green spectrum. Hemoglobin optical absorption coefficients at 532-nm green spectrum and at 450-nm blue spectrum are similar, in a range about 200 cm^{-1} [2], indicating blue diode laser could be a cost-effective alternative for green laser in soft tissue ablation and coagulation. In this study, we have confirmed the capability of tissue vaporization with blue laser on bladder tissues, indicating that blue laser, like green laser, could be applied in bladder surgery and safe for both subjects and operators.

In conclusion, a novel blue diode laser system was developed and presented positive results in bladder tissue vaporization in vitro and in vivo. In addition to its portable and cost-effective advantages, our results demonstrate, like 532-nm green laser, that the high-power diode 450-nm blue laser has a high tissue vaporization capacity, a good tissue coagulation ability, and a low tissue penetration; can interact with tissues precisely; and has a low thermal damage to adjacent tissues. Therefore, 30-W 450-nm blue laser could be a safe alternative approach used in the surgery of superficial diseases on bladder soft tissues.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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