Near-Infrared Intraoperative Imaging of Pelvic Autonomic Nerves:Clinical Trial

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Original research

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Abstract

Background: The pelvic autonomic nerves control and regulate anorectal and urogenital function. The dysfunction of pelvic autonomic nerves lead to disorders of anorectum, bladder and male sex organs. Thus the intraoperative identification of pelvic autonomic nerves could be crucial in complications prevention and diseases treatment. Our clinical trial aims at estimating the effectiveness and validity of intraoperative indocyanine green fluorescence imaging in pelvic autonomic nerves identification.

Methods: Intraoperative fluorescence imaging using indocyanine green was performed in 10 patients and the feasibility was determined. From February 2019 to June 2019, the 10 patients undergoing laparoscopic colorectectomy was administrated 4.5 mg/Kg indocyanine green 24 hours before surgery. The near-infrared fluorescence imaging was conducted during surgery. A novel white light and near-infrared dual-channel laparoscopic equipment was applied. For each patient, signal background ratio values for pelvic autonomic nerves were recorded and analyzed.

Results: We confirmed the best dose and timing of indocyanine green administration was 4.5 mg/Kg and 24 hours before surgery. Using the dual laparoscopic equipment, we could observe the splanchnic plexus, inferior mesenteric artery plexus, and sacral plexus successfully with a high signal background ratio value of 3.18 (standard deviation: 0.48).

Conclusion: Pelvic autonomic nerves could be observed using indocyanine green fluorescence imaging during surgery. The novel method may replace the current visual identification method and become the standard clinical practice.

Background

The pelvic autonomic nerves regulate many anorectal and urogenital activities, such as defecation, urinatio, and male erectile function [1, 2]. Laparoscopic surgeries, for instance, total mesorectal excision could result in pelvic autonomic nerves injury. [3] Currently, stimulation of pelvic autonomic nerves is the main treatment method for anal-bladder functional disturbances [4], including underactive bladder [5], bladder-sphincter dyssynergia, and anorectal dysfunction [6]. But the method is not very useful and would cost much [7–9]. Consequently, precise intraoperative identification of pelvic autonomic nerves is crucial for the prevention of related disorders and for the development of novel therapy techniques.

Pelvic autonomic nerves is a slim white-colored pelvic autonomic nerves starting from the inferior hypogastric nerves. Its width and length varies, and so far, no pelvic autonomic nerves could be clearly identified by naked eyes [10]. Even though some anotomical markers could guide surgeons to identify the pelvic autonomic nerves intraoperatively, surgeons generally insist that visualizing pelvic autonomic nerves is difficult [11, 12]. Some nerve-sparing surgery techniques were invented to help surgeons to minimize the injury to pelvic autonomic nerves by separating the deep uterine vein and the splanchnic plexus when dividing the parametrial tissue with the middle rectal artery as a landmark [13]. However, the effect of this method is limited, and a catheter has to be placed to drain the bladders for several postoperative days [14]. Some nerve fibers visualization methods were also put forward. For example, Bulter-Manuel *et al.* tried to visualize paracervix nerve fibers using immunohistochemistry method [15]. Possover *et al.* and Katahira *et al.* applied an intraoperative neuronavigation technology in surgery, visualizing the splanchnic nerve pathways by stimulating the separate splanchnic plexus [16, 17]. Although these techniques could reduce postoperative complication rates, the various small nerve fibers are not be able to be preserved by these methods.

Among the intraoperative angiography techniques, fluorescence imaging (FI) is a novel one. FI technique could help surgeons to detect specific malignant and/or benign tissues [18], and has been applied in the diagnosis and treatment of various diseases, including ovarian cancer [19], head and neck cancer [20], colorectal cancer and its related peritoneal carcinomatosis [21], hepatocellular carcinoma [22], parathyroid [23], etc. However, only a few clinical studies of nerve FI have been reported. He *et al.* identified the thoracic sympathetic nerves with indocyanine green (ICG) FI during video-assisted thoracoscopic surgery [24]. Wagner *et al.* recognized the contralateral phrenic nerve by FI in the procedure of thymectomy [25]. Chen and his workmates visualized facial nerves by FI during mastoidectomy [26]. But no FI identification of pelvic autonomic nerve has been reported.

Our study firstly applied ICG FI in pelvic autonomic nerves identification at Zhuhai People's Hospital (Zhuhai Hospital Affiliated with Jinan University), and analyzed the signal to background ratio (SBR)'s relevance to ICG injection timing and ICG dose. A FI system was applied in detecting the subtle pelvic autonomic nerves. The system is a white light and NIR dual-channel laparoscopic equipment developed by CAS key laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Science. We conducted a clinical trial in Zhuhai People's Hospital (Zhuhai Hospital Affiliated with Jinan University).

Methods

Trial registration

The name of registry of our study: Chinese Clinical Trial Registry (ChiCTR)(www.chictr.org.cn). Registration number : ChiCTR1900025336. Registration time: 2019−8−24.

Fluorescence Laparoscopic System

Chinese Academy of Science's Key Laboratory of Molecular Imaging developed the white-light (400–650 nm) and NIR (800–900 nm) dual-channel laparoscopic system (Fig. 1). Four parts compose the system: the display part, the control part, the detection part (with a 30°viewing angle custom prism), and the light-source part. The system has a minimal detectable ICG concentration of 0.01 μM and a spatial resolution of 35 μm. The prism provides surgeons with a wide visual field and makes it easier to detect the pelvic autonomic nerves. This system has an improved quality of color and images, and improved function of quantitative analysis. We could conducted real-time processing of fluorescence intensity and

SBR. The system’s quantitative analysis technique include distribution analysis of fluorescence intensity, and fluorescence images’ radiometric calculation.

Patients

The trial has 10 eligible patients scheduled for video-assisted laparoscopic surgery in our hospital between February 2019 and May 2019 (Table 1). We included the patients according to the following criteria: age from 18 to 85, colorectal diseases scheduled for laparoscopic colectomy or rectectomy, no allergies to ICG or iodine, a negative ICG skin test result, normal preoperative liver function, volunteering to take part in this trial, and agreement to sign written informed consent. We excluded the patients according to the following criteria: preoperative liver dysfunction, allergies to ICG or iodine, positive ICG skin test result, and other physical conditions deemed unsuitable for enrolment.

Table 1
Characteristics of the 10 patients who participated in this study

Study no.	Age	Sex	BMI	History of allergy	Lesion size (cm)	Lesion location	Pathology
1	69	M	17.5	NO	4.5*4*1.7	R	ADE
2	39	M	19.7	NO	5*3*2	AC	CD
3	77	F	26.3	NO	5*3.5*2.5	R	ADE
4	49	F	18.7	NO	5*3*1.5	SD	ADE
5	53	M	21.0	NO	1.5*0.7*0.2	SD	U
6	78	M	22.0	NO	3*2.5*2	R	ADE
7	69	M	17.5	YES	4.5*4*1.7	R	ADE
8	85	F	24.4	NO	3.5*3*2.5	AC	ADE
9	49	F	21.7	NO	0.7*2*2.5	R	U
10	63	F	23.4	NO	2.5*2.5*2	TC	AIS
ADE: adenocarcinoma; CD: Crohn’s disease; U: ulcer; IN: adenocarcinoma *in situ*.							
SD: sigmoid colon, R: rectum; AC: ascending colon; TC: transverse colon.							

All patients were diagnosed with colorectal diseases by electronic enteroscopy and/or computed tomography with a high resolution of 1 mm slice thickness. Informed consents were obtained from all the patients. Zhuhai People’s Hospital Institutional Review Board approved this trial ([2018] IRB-008). The study was registered in Chinese Clinical Trial Registry with a number of ChiCTR1900025336.

Administration of Contrast Agents

We purchased ICG (25 mg vials) from Ruidu Pharmaceutical Co., Ltd. (Dandong, Liaoning Province, China). Before we applied ICG in patients, we refered to previous study about thoracic sympathetic nerves identification [24]. ICG of 4 mg/Kg, 4.5 mg/Kg and 5 mg/Kg was respectively injected to three patients 24 hours before surgery. After that, ICG of 4.5 mg/Kg was respectively injected to three patients 20, 24 and 28 hours before surgery. By observing the fluorescence images, we determined the ICG concentration of 4.5 mg/Kg and injection timing of 24 hours preoperation was the best. Afterwards, 4.5 mg/Kg of ICG was intravenously injected to 10 patients 24 hours before surgery. No allergic or adverse reactions occurred during the trial.

Clinical Imaging Procedure

After injected with ICG, patients were placed in the trendelenburg position underwent general anasthesia with double-catheter trachea insertion. After routine disinfection, the laparoscope was inserted though a navel incision. Operators pulled the rectum to the front and revealed the inferior mesenteric artery, ureter, and lateral ligament of rectum before the colorectectomy operation. After that, operators observed the splanchnic plexus, inferior mesenteric artery plexus, and sacral plexus of pelvic autonomic nerves all the way through. The fluorescence images and positions of the pelvic autonomic nerves were oberserved and recorded. Operators conducted lymphadenectomy after the tumor-bearing colon or rectum was removed. Resected tumors and related tissues were sent to the department of pathology. Operators selected in this trial were a surgeon with 20-year experience, and a surgeon with 10-year experience.

Statistical Analysis

We calculated pelvic autonomic nerves' SBR according to the following methods: First, an image processing software, ImageJ (National Institutes of Health, USA) was applied to describe the pelvic autonomic nerves as a region of interest (ROI), and the mean brightness value of ROI was calculated as value of signal (V_S). At the same time, we highlighted the surrounding region and measured this region's mean brightness value as value of background (V_B). We use V_S to divide V_R and obtained the pelvic autonomic nerves SBR value. The SBR value was calculated six times to reduce errors. We used Kruskai-Wallis test to compare multiple independent samples. We selected the average value of sacral plexus in calculating SBR to maintain the consistency of our calculation. Because of the limitation of the NIR laser's intensity and area, we adopted this approach. We performed data analysis and graphing using SPSS 20.0 (IBM, New York, USA).

Results

The intraoperative ICG fluorescence imaging was applied in our trial to identify the splanchnic plexus along the ureter, inferior mesenteric artery plexus around the inferior artery roots, and sacral plexus along the lateral rectum ligaments (Fig. 2). The average SBR is 3.18 (standard deviation: 0.48). This SBR value is sufficient to help the surgeons to identify the pelvic autonomic nerves intraoperatively. Furthermore, the fluorescence could be observed in more than six hours. For all patients, we calculated the SBR value for splanchnic plexus, inferior mesenteric artery plexus, and sacral plexus of pelvic autonomic nerves (Fig. 3). There was no significant difference between the SBR value for splanchnic plexus, inferior mesenteric artery plexus, and sacral plexus ($p > 0.05$). In data statistical process, the sample number n values are all equal to 15.

Discussion

Main findings

In this study, we researched the effectiveness and safety of ICG fluorescence imaging for pelvic autonomic nerves during surgery in a clinical trial. Using this method, we could observe each patient's splanchnic plexus, inferior mesenteric artery plexus, and sacral plexus on both sides. We obtained the best injection timing and dose of ICG to acquire the highest SBR values. Ideal ICG FI for pelvic autonomic nerves depends on right injection timing, dose of ICG, and imaging equipment efficiency. So we introduced the dual-channel (white light and NIR) laparoscopic equipment from the CAS Key laboratory of molecular imaging, Chinese Acedamy of Sciences for fluorescence images collection and analysis. The intraoperative FI for pelvic autonomic nerves, applied with novel laparoscopic equipment showed promising results in clinical practice.

Strengths of our study

Compared to traditional methods, this novel technique has several advantages. Firstly, the real-time imaging during surgery and high-SBR images could be conductive to intraoperative accurate and precise identification of pelvic autonomic nerves. Secondly, the penetration ability of INR light is much stronger than visible light. Furthermore, In this spectral range, the tissues' autofluorescence is relatively weak. Moreover, the method is noninvasive and does not affect the regular surgical procedure. In addition, this method is safe and there were no allergic reactions and adverse reactions in this trial.

What this study adds with reference to existing international literature?

ICG is a molecular with a weight of 755 Da and water-soluble feature, and has been approved by the FDA in 1956. ICG could bind plasma lipoprotein and has a half-life of 150–180 s [27]. The hepatic system could immediately excreted ICG to the bile. The emission peak of NIR light (810 nm) is close to the absorption peak of ICG (805 nm). ICG would be fluorescent when excited by NIR. The ICG was applied for occult choroidal neovascularization treatment at first. After that, researchers used ICG for the evaluation of hepatic function and cardiac output, and a variety of literature report the use of ICG in tumor borderline identification [28]. Nowadays, ICG was applied in intraoperative identification of tumors [29], lymph node [30], parathyroid [23], and evaluation of tissue perfusion [31]. Our trial was the first to observe pelvic autonomic nerves using ICG FI.

According to the previous literature and ICG properties, we believe that the natural structure of pelvic autonomic nerves determine its high SBR value. In fact, there are lots of nutritional arteries running on and around pelvic autonomic nerves. Some fat cells also exist on the surface of pelvic autonomic nerves. These vessels and fat tissues absorb abundant ICG molecules, enhancing ICG retension and permeability.

So pelvic autonomic nerves show fluorescence when excited by NIR [32]. And the large size of pelvic autonomic nerves contribute to high SBR value. The results show that the SBR value of splanchnic plexus is similar to that for inferior mesenteric artery plexus and sacral plexus. This is mainly because these nerve roots have similar sizes.

The implications for practice.

It has been widely understood that ICG and other protein-bound molecules could accumulate in tumor tissues after injection [33]. It is the best if nerve-specific contrast agents could be applied in FI nerve-sparing surgery. Various research has been done in this field. Nerve sheath-binding fluorescent peptides have been developed as nerve-specific contrast agents using rat models [34]. Clinical trials observing thoracic sympathetic nerves using ICG FI have been reported by He *et al.* [24]. Nevertheless, no clinical trial identifying pelvic autonomic nerves using ICG FI has been reported before.

Pelvic autonomic nerves are functional in transmitting sympathetic signals to the organs and tissues of the pelvic cavity, including anorectum, bladder, and reproductive organs. Intraoperative FI could contribute to the preservation of pelvic autonomic nerves in various surgeries, including colorectal cancer surgery, which is of great significance in preserving male sexual function. Moreover, FI could be crucial in pelvic autonomic nerves stimulation in the diagnosis and treatment of related diseases. In addition, this technique is promising in developing novel therapy methods. In our work, we attempt to optimize the dose and timing of ICG and use this method to critically prevent postoperative complications. In the future, we would recruit more participants to further verify the use of ICG angiography in intraoperative pelvic autonomic nerves identification. Moreover, in vitro and animal experiment would be conducted to understand the mechanism of pelvic autonomic nerve angiography.

Conclusions

The pelvic autonomic nerves were completely and clearly observed in our clinical trial with the guidance of ICG fluorescence imaging. In addition, the ideal dose and timing of ICG has been verified, and the white light and NIR dual-channel laparoscopic equipment has been tested to be effective. This technique may bring new method for surgeons to identify pelvic autonomic nerves intraoperatively and is promising to be the standard practice for pelvic autonomic nerves identification.

Abbreviations

FDA
Food and Drug Administration; ICG:indocyanine green; NIR:near-infrared; ROI:region of interest; SBR:signal to background ratio.

Declarations

Ethics approval and consent to participate:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review boards of Zhuhai People's Hospital (Zhuhai, China) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the individual participant included in the study. The participants gave consent for his personal and clinical details along with any identifying images to be published in this study.

Consent for publication:

Not applicable.

Availability of data and materials:

All the data are within this manuscript and there is no other data.

Competing interests:

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Authors' contributions:

CM and **LLG** proposed the study. **LLG, CM** and **JH** performed the research and wrote the first draft. Both authors contributed to the design and interpretation of the study and to further drafts. **LLG is** the guarantor.

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References

1. Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. Lancet. 2007;369:512–25.
2. Banerjee AK. Sexual dysfunction after surgery for rectal cancer. Lancet. 1999;353:1900–2.
3. Fang JF, Zheng ZH, Wei HB. Reconsideration of the Anterior Surgical Plane of Total Mesorectal Excision for Rectal Cancer. Dis Colon Rectum. 2019;62:639–41.
4. Moszkowski T, Kauff DW, Wegner C, Ruff R, Somerlik-Fuchs KH, Krueger TB, Augustyniak P, Hoffmann KP, Kneist W. Extracorporeal Stimulation of Sacral Nerve Roots for Observation of Pelvic

Autonomic Nerve Integrity: Description of a Novel Methodological Setup. Ieee T Bio-Med Eng. 2018;65:550–5.

5. Lee S, Wang H, Peh WYX, He T, Yen SC, Thakor NV, Lee C. Mechano-neuromodulation of autonomic pelvic nerve for underactive bladder: A triboelectric neurostimulator integrated with flexible neural clip interface. Nano Energy. 2019;60:449–56.
6. Peh WYX, Mogan R, Thow XY. Novel Neurostimulation of Autonomic Pelvic Nerves Overcomes Bladder-Sphincter Dyssynergia. Front Neurosci. 2018;12:1–18.
7. Langdale CL, Hokanson JA, Sridhar A, Grill WM. Stimulation of the Pelvic Nerve Increases Bladder Capacity in the Prostaglandin E2 Rat Model of Overactive Bladder. Am J Physiol-Renal. 2017;313:F657–65.
8. Kashif M, Goebel A, Srbljak V, Chawla R, Draper M, Cox A, Sharma M. Classical Predictors Do Not Predict Success with Sacral Nerve Stimulation for Chronic Pelvic Pain; A Retrospective Review in a Single Center. Pain Med. 2019;20:1059–62.
9. Mitchell B, Verrills P, Vivian D, Barnard A. Sacral nerve stimulation for the treatment of chronic low back, pelvic girdle and leg pain - A prospective study. J Sci Med Sport. 2017;20:e14.
10. Manganaro L, Porpora MG, Vinci V, Bernardo S, Lodise P, Sollazzo P, Sergi ME, Saldari M, Pace G, Vittori G, Catalano C, Pantano P. Diffusion tensor imaging and tractography to evaluate sacral nerve root abnormalities in endometriosis-related pain: A pilot study. Eur Radiol. 2013;24:95–101.
11. Leonard D, Penninckx F, Fieuws S, Jouret-Mourin A, Sempoux C, Jehaes C. Factors predicting the quality of total mesorectal excision for rectal cancer. Ann Surg. 2010;252:982–8., Van Eycken E.
12. Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol. 2010;11:292–301.
13. Querleu D, Morrow CP. Classifi cation of radical hysterectomy. Lancet Oncol. 2008;9:297–303.
14. Fujii S, Takakura K, Matsumura N. et al. Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. Gynecol Oncol. 2007;107:4–13.
15. Butler-Manuel SA, Buttery LD, A'Hern RP, Polak JM, Barton DP. Pelvic nerve plexus trauma at radical hysterectomy and simple hysterectomy. Cancer. 2000;89:834 – 41.
16. Possover M, Quakernack J, Chiantera V. The LANN technique to reduce postoperative functional morbidity in laparoscopic radical pelvic surgery. J Am Coll Surg. 2005;201:913 – 17.
17. Katahira A, Niikura H, Kaiho Y. et al. Intraoperative electrical stimulation of the pelvic splanchnic nerves during nerve-sparing radical hysterectomy. Gynecol Oncol. 2005;98:462 – 66.
18. Nguyen QT, Tsien RY. Fluorescence-guided surgery with live molecular navigation - a new cutting edge. Nat Rev Cancer. 2013;13:653–62.
19. Van Dam GM, Themelis G, Crane LMA, Harlaar NJ, Pleijhuis RG, Kelder W, Sarantopoulos A. De Jong JS, Arts HJG, Van Der Zee AGJ, Bart J, Low PS, Ntziachristos V. Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-α targeting: First in-human results. Nat Med 2011;17:1315–9.

20. Moore LS, Rosenthal EL, Chung TK. de Boer E, Patel N, Prince AC, Korb ML, Walsh EM, Young ES, Stevens TM, Withrow KP, Morlandt AB, Richman J, Carroll WR, Zinn KR, Warram JM. Characterizing the utilities and limitations of repurposing an open-field optical imaging device for fluorescence-guided surgery in head and neck cancer patients. J Nucl Med 2017;58:246–51.
21. Liberale G, Vankerckhove S, Caldon MG, Ahmed B, Moreau M, Nakadi IE, Larsimont D, Donckier V, Bourgeois P. Fluorescence Imaging After Indocyanine Green Injection for Detection of Peritoneal Metastases in Patients Undergoing Cytoreductive Surgery for Peritoneal Carcinomatosis From Colorectal Cancer. Ann Surg. 2016;264:1110–5.
22. Kawaguchi Y, Nomura Y, Nagai M, Koike D, Sakuraoka Y, Ishida T, Ishizawa T. Kokudo N,Tanaka N. Liver transection using indocyanine green fluorescence imaging and hepatic vein clamping. Brit J Surg. 2017;104:898–906.
23. Jin H, Dong Q, He Z, Fan J, Liao K, Cui M. Research on indocyanine green angiography for predicting postoperative hypoparathyroidism. Clin Endocrinol. 2019;90:487–93.
24. He K, Zhou J, Yang F, Chi C, Li H, Mao Y, Hui B, Wang K, Tian J, Wang J. Near-infrared intraoperative imaging of thoracic sympathetic nerves: From preclinical study to clinical trial. Theranostics. 2018;8:304–13.
25. Wagner OJ, Louie BE, Vallières E, Aye RW, Farivar AS. Near-Infrared Fluorescence Imaging Can Help Identify the Contralateral Phrenic Nerve During Robotic Thymectomy. Ann Thorac Surg. 2012;94:622–5.
26. Chen SC, Wang MC, Wang WH, Lee CC, Yang TF, Lin CF, Wang JT, Liao CH, Chang CC, Chen MH, Shih YH, Hsu SPC. Fluorescence-assisted visualization of facial nerve during mastoidectomy: A novel technique for preventing iatrogenic facial paralysis. Auris Nasus Larynx. 2014;42:113–8.
27. Yoneya S, Saito T, Komatsu Y, Koyama I, Takahashi K, DuvollYoung J. Binding properties of indocyanine green in human blood. Invest Ophth Vis Sci. 1998;39:1286–90.
28. Ishizawa T, Fukushima N, Shibahara J, Masuda Km, Tamura S, Aoki T, Hasegawa K, Beck Y, Fukayama M, Kokudo N. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer. 2009;115:2491–504.
29. Imboden S, Papadia A, Nauwerk M, McKinnon B, Kollmann Z, Mohr S, Lanz S, Mueller MD. A comparison of radiocolloid and indocyanine green fluorescence imaging, sentinel lymph node mapping in patients with cervical cancer undergoing laparoscopic surgery. Ann Surg Oncol. 2015;22:4198–203.
30. Nguyen DP, Huber PM, Metzger TA, Genitsch V, Schudel HH, Thalmann GN. A Specific Mapping Study Using Fluorescence Sentinel Lymph Node Detection in Patients with Intermediate- and High-risk Prostate Cancer Undergoing Extended Pelvic Lymph Node Dissection. Eur Urol. 2016;70:734–7.
31. Figueroa R, Golse N, Alvarez FA, Ciacio O, Pittau G, Sa Cunha A, Cherqui D, Adam R, Vibert E. Indocyanine green fluorescence imaging to evaluate graft perfusion during liver transplantation. HPB. 2019;21:387–92.

32. Keating J, Newton A, Venegas O, Nims S, Zeh R, Predina J, Deshpande C, Kucharczuk J, Nie S, Delikatny EJ, Singhal S. Near-Infrared Intraoperative Molecular Imaging Can Locate Metastases to the Lung. Ann Thorac Surg. 2017;103:390–8.
33. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986;46:6387–92.
34. Whitney MA, Crisp JL, Nguyen LT, Friedman B, Gross LA, Steinbach P, Tsien RY, Nguyen QT. Fluorescent peptides highlight peripheral nerves during surgery in mice. Nat Biotech. 2011;29:352–6.

Figures

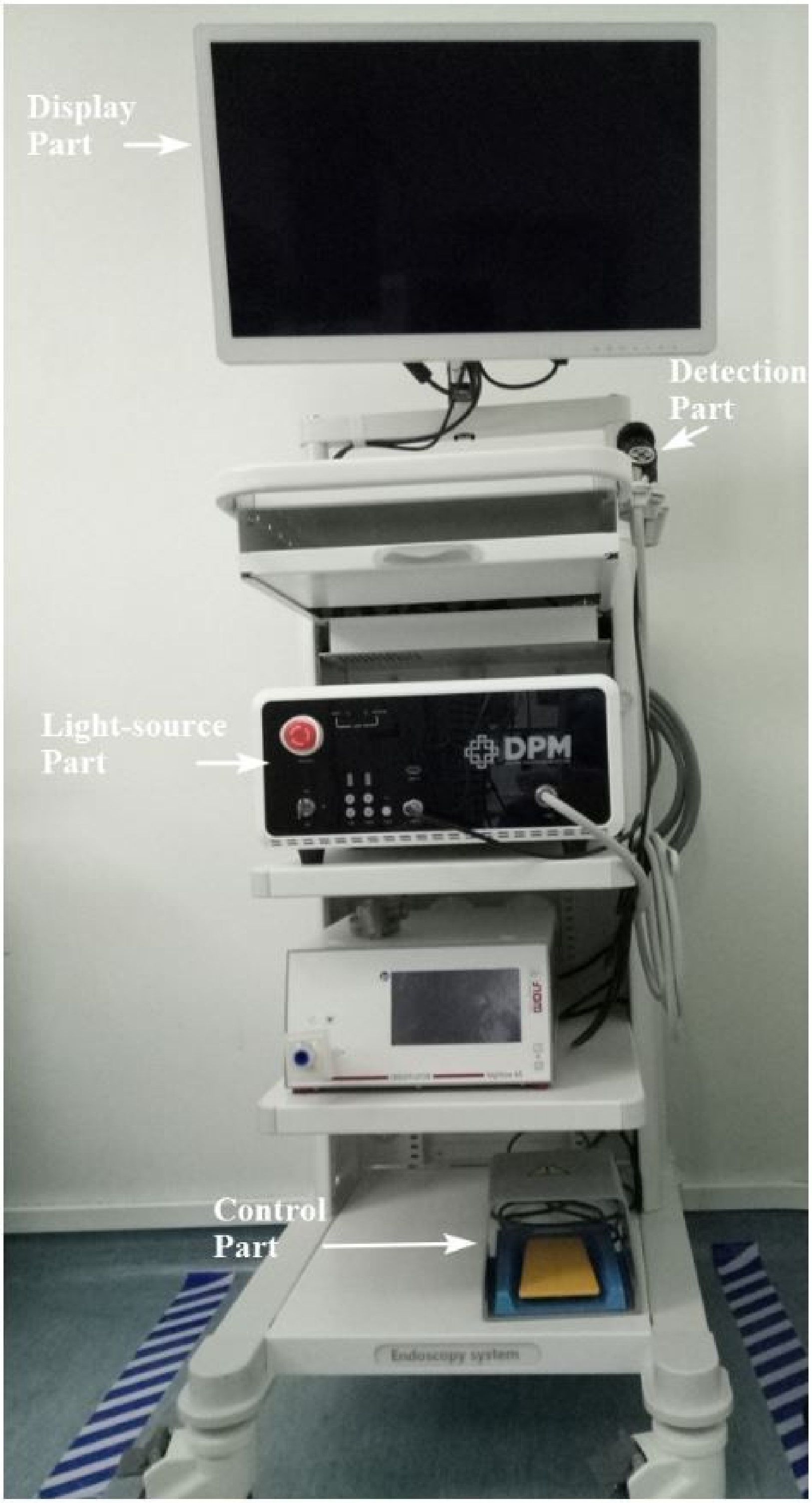
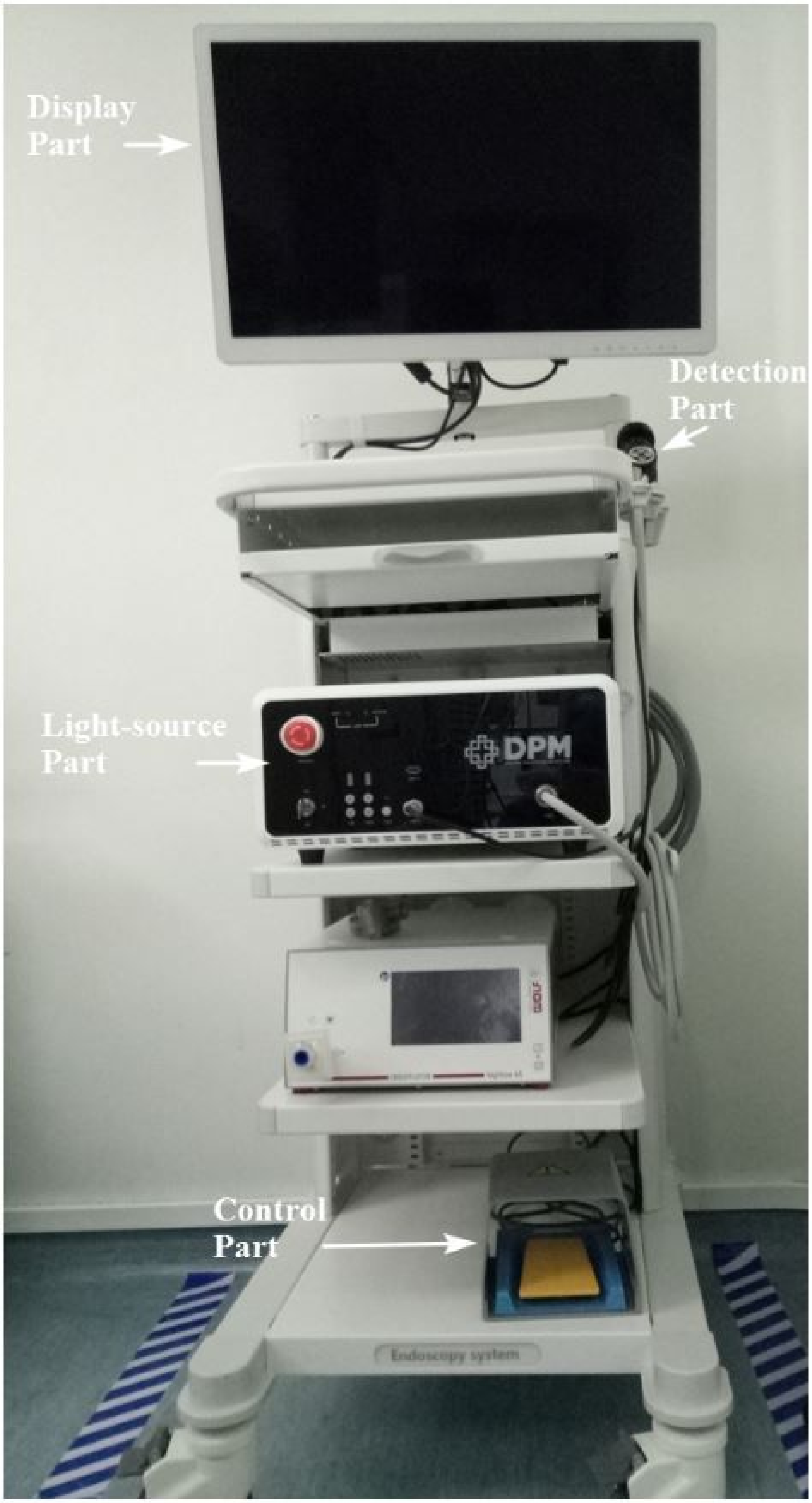


Figure 1

The dual-channel laparoscopic equipment



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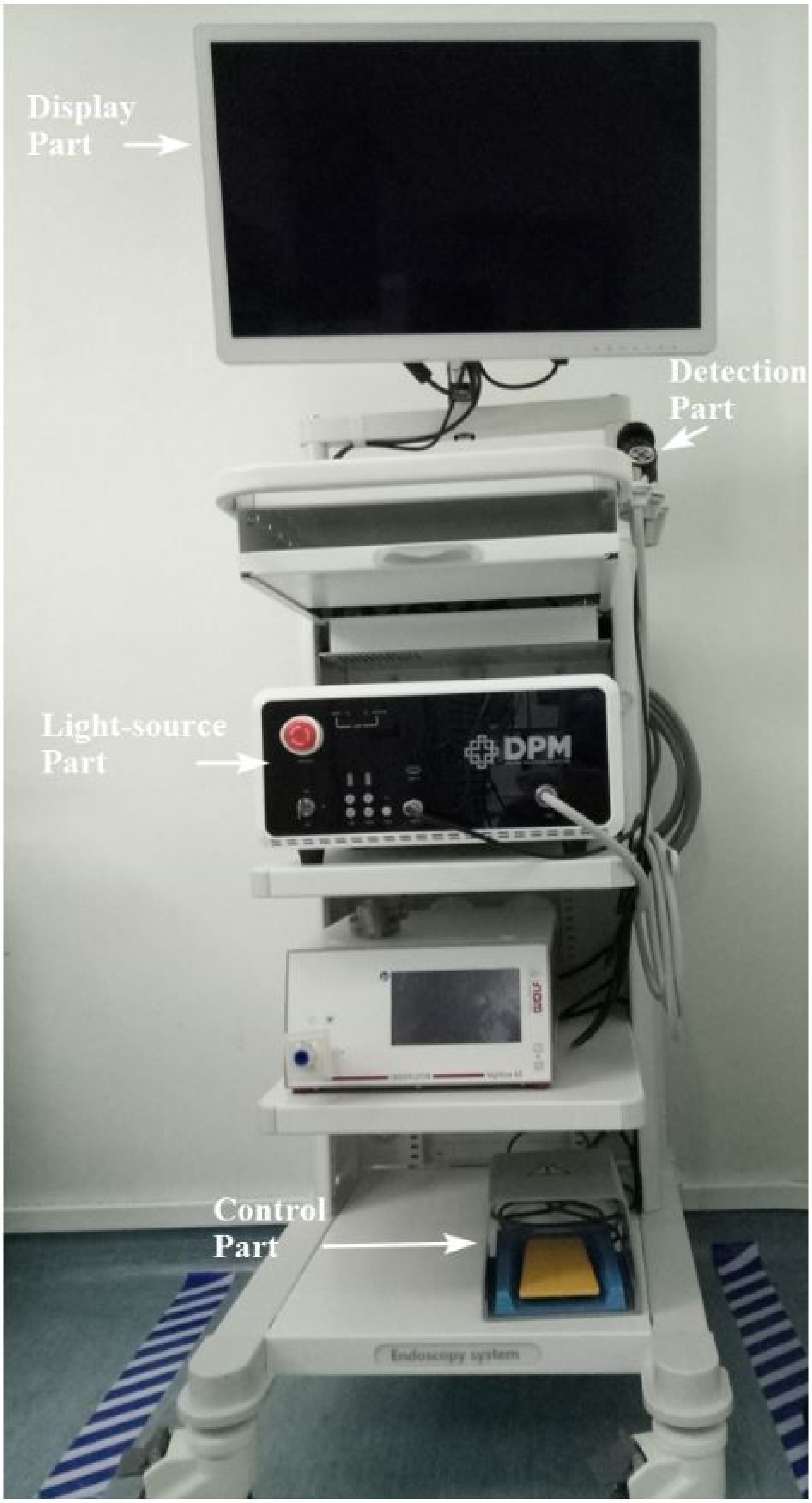

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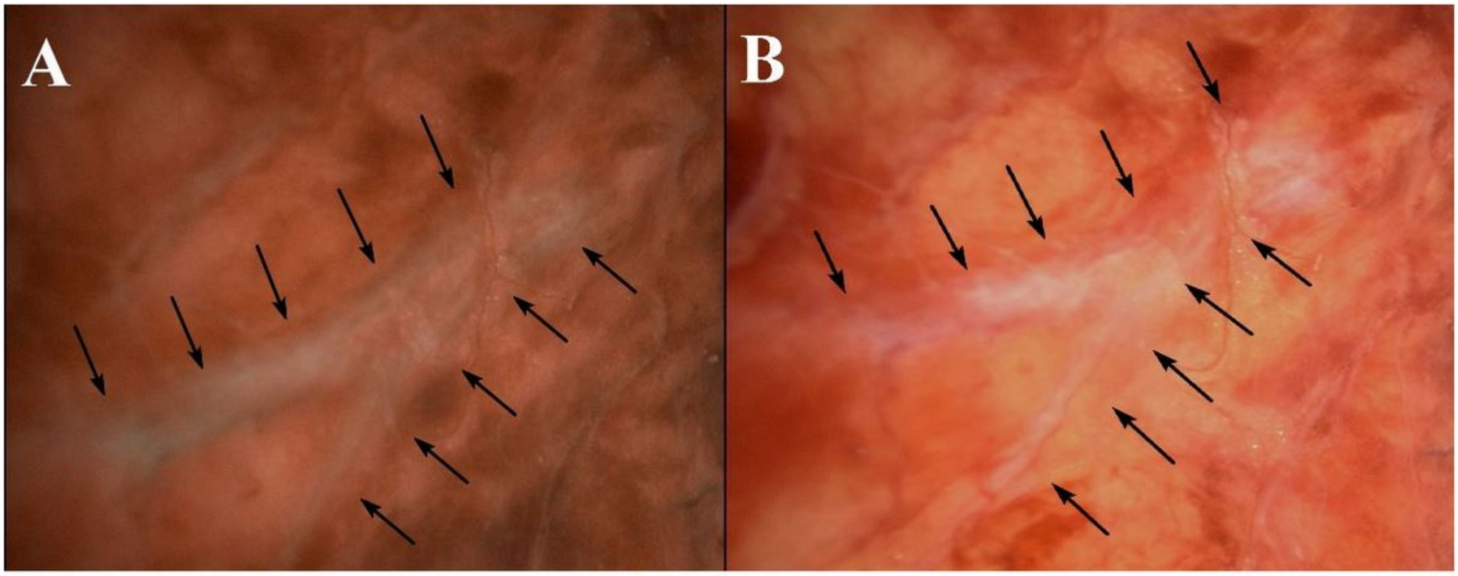
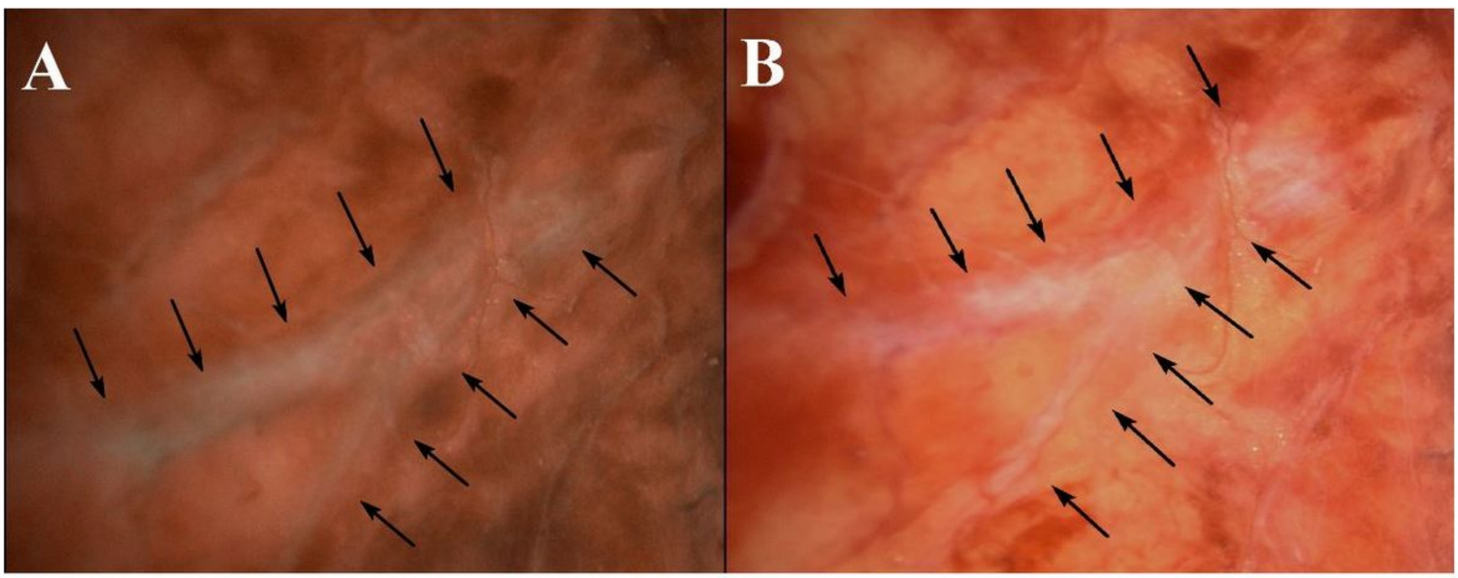


Figure 2

The sacral plexus of pelvic autonomic nerves under the fluorescence (A) and under the white light (B)



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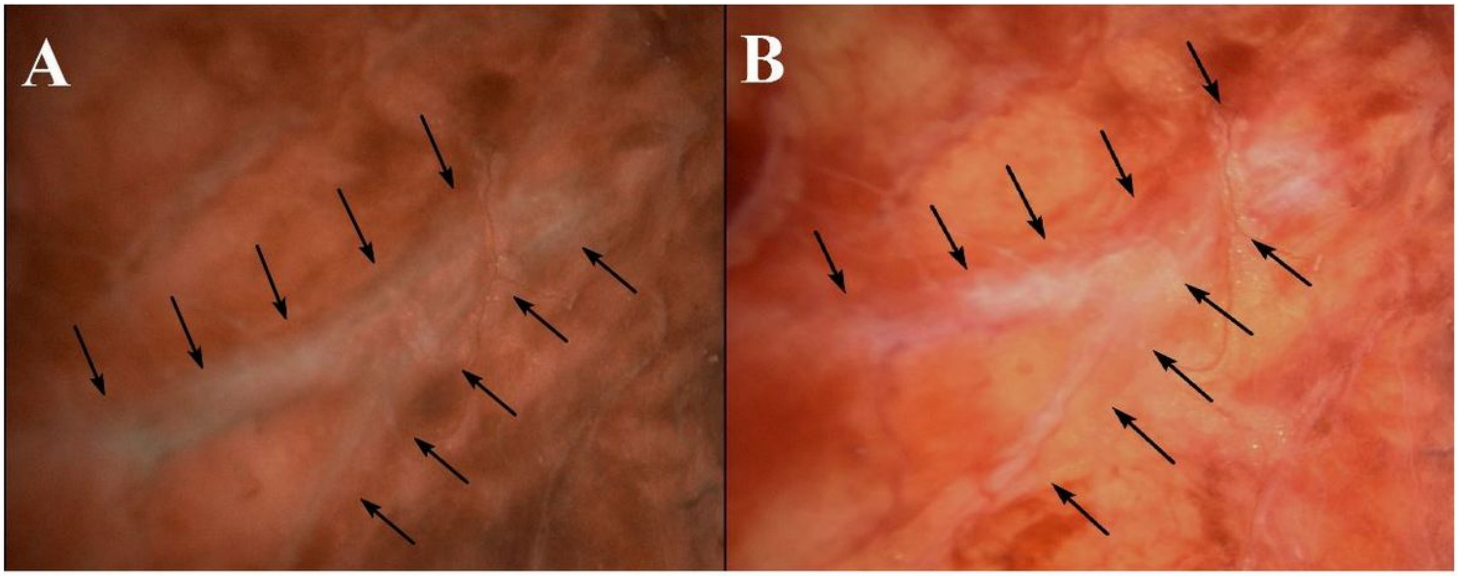

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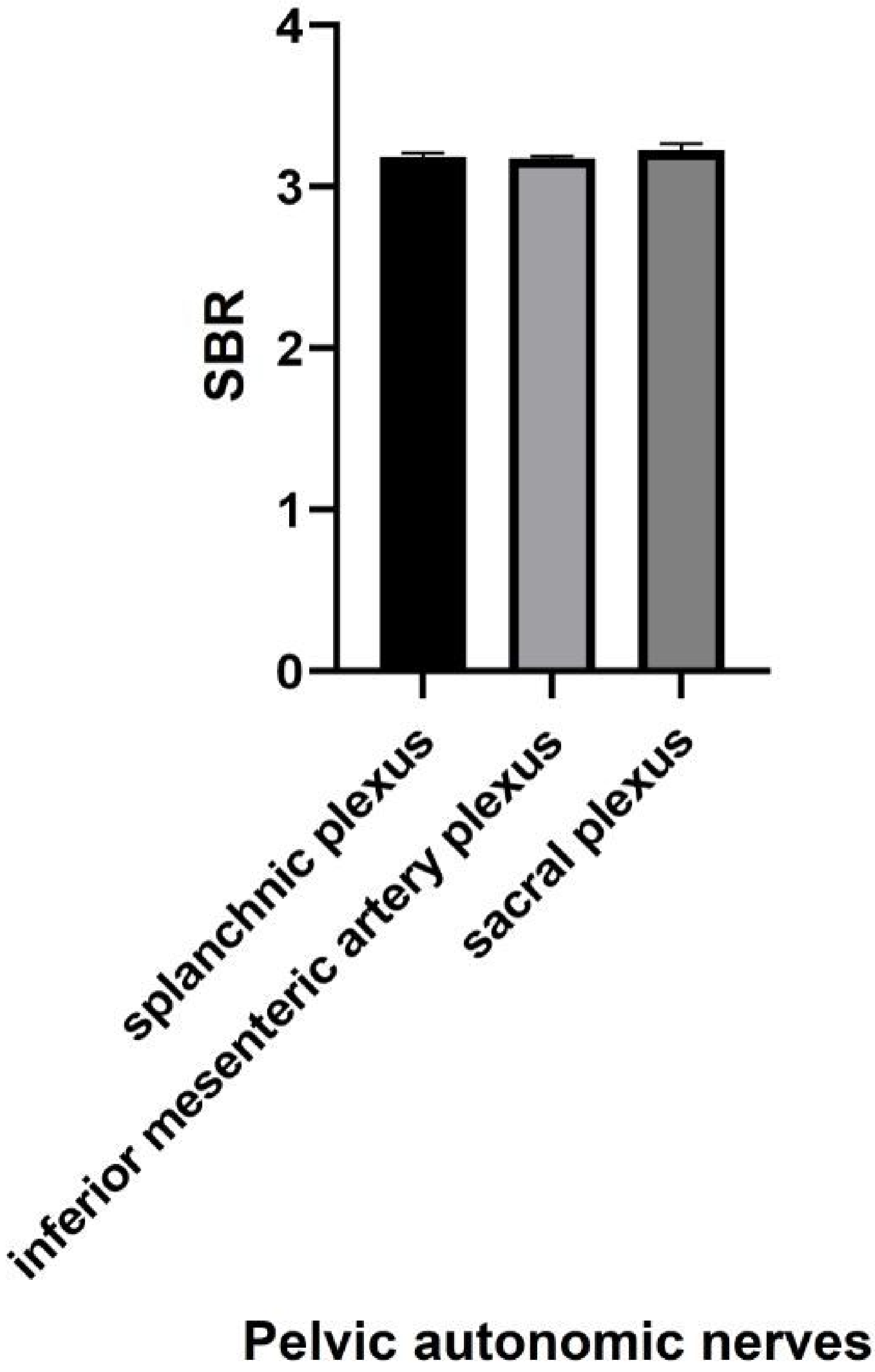
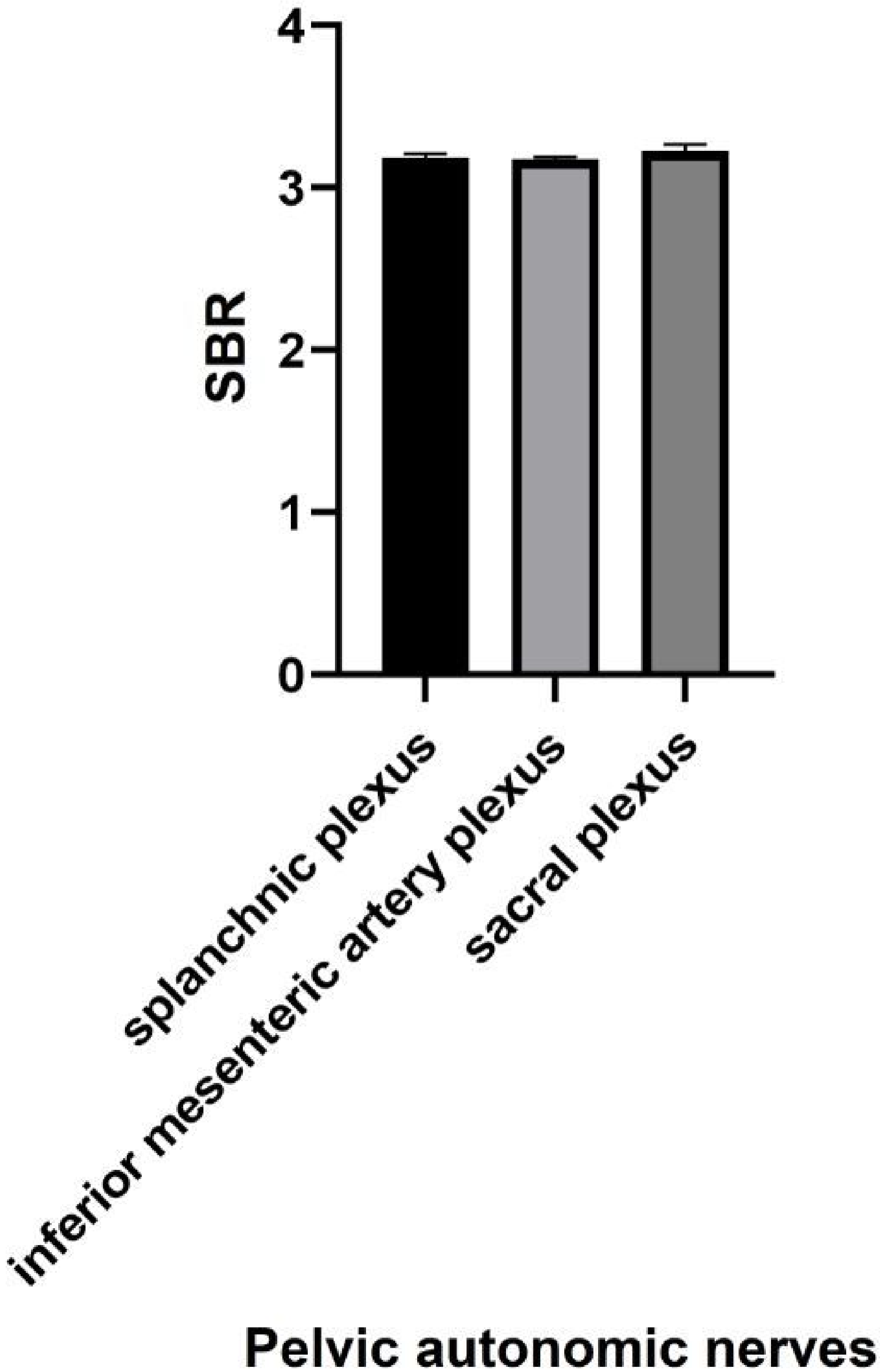


Figure 3

The SBR value for splanchnic plexus, inferior mesenteric artery plexus, and sacral plexus.



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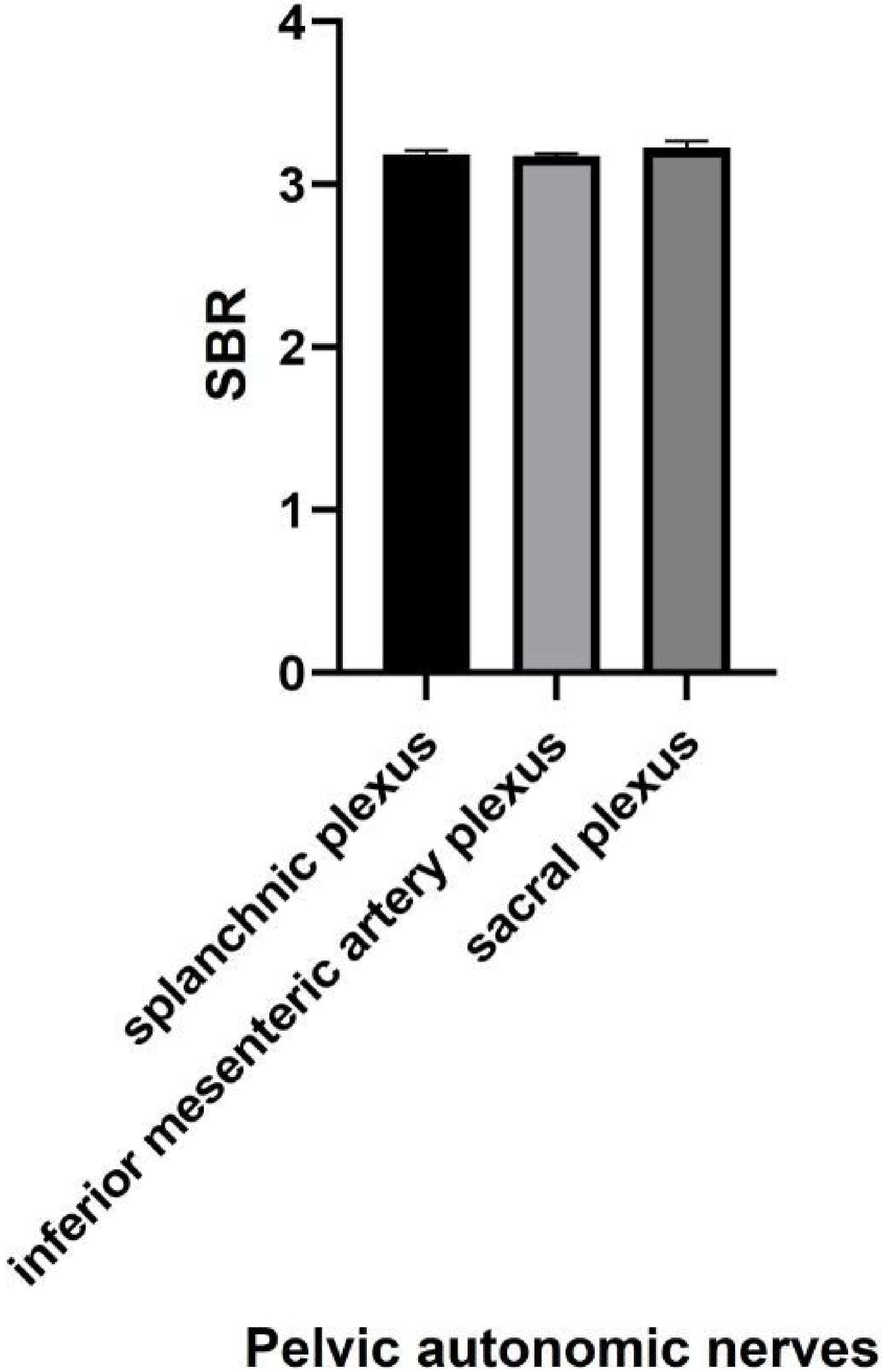

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