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PRODCT: **Indocyanine Green and Near-infrared fluorescence (NIRF) video endoscopic system**

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TITOLE: **INDOCYANINE GREEN AND NEAR-INFRARED VISION FOR DETECTION OF ENDOMETRIOSIS (*GRE-ENDO TRIAL*)**

PROTOCOL NUMBER: **736513. A 287 / C.E./2013**

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SUMMARY

Background

A. **Endometriosis**

Endometriosis is a common gynecologic condition characterized by the presence of endometrial glands and stroma outside the uterine cavity. Its prevalence in the general population among women undergoing tubal ligation is about 4%;[1] however, the disease is much more common in women with pelvic pain and infertility, ranging from 40% to 60% and 20% to 30%, respectively.[2]

Endometriosis is categorized into three different diseases: peritoneal, ovarian and deep endometriosis.[3, 4] Peritoneal disease is defined by the presence of superficial peritoneal implants. Ovarian disease includes ovarian surface implants and ovarian endometriomas. Deep endometriosis, on the other hand, involves infiltrative lesions larger than 5 mm in depth affecting the rectovaginal septum, retro-cervical region, sigmoid, rectum, ureter or bladder.[5] These 3 endometriosis disease types are known to behave and affect women differently - it has been shown that compared to peritoneal and ovarian endometriosis, deep endometriosis is significantly correlated with pelvic pain and infertility.[6]

In 2003, Abrao et al evaluated the histological patterns of endometriosis, observing these histological aspects of the disease: stromal pattern, with the presence of stroma morphologically similar to that of topical endometrium in any phase of the cycle, with no glandular epithelium; well-differentiated glandular pattern, with presence of surface epithelium or epithelium forming glandular or cystic spaces (the morphology of the epithelial cells is indistinguishable from that of topical endometrium during the different phases of the menstrual cycle; undifferentiated glandular pattern, with presence of surface epithelium or epithelium forming glandular or cystic spaces (the epithelium is flattened or low cuboidal, with no correspondence with topical epithelium, resembling the mesothelium lining the peritoneum) and glandular pattern of mixed differentiation with presence of epithelium with a well-differentiated or undifferentiated pattern in the same biopsy. We concluded that the histological classification of endometriosis can predict the prognosis of the disease.

B. Indocyanine Green

In 1958, ICG (Indocyanine Green) was submitted for approval to the FDA for use in indicator-dilution studies in humans. Absorption and fluorescence wave length of IGG lie in the near-infra-red (nIR) spectrum. The fluorescence maximum varies with the solvent and lies around 830nm in plasma and 834nm in whole blood. The absorption maximum for blood and plasma is 805nm.

Over the past several years, there has been an explosion of reports describing successful in vivo NIR fluorescence imaging. Many studies are qualitative; however, quantitative methods are beginning to emerge where dictated by necessity. Among the clinical applications for ICG fluorescence are:

- Ophthalmic Angiography Studies
- Hepatic Function Studies
- Measurement of Cardiac Output
- Sentinel Lymph Node Diagnosis

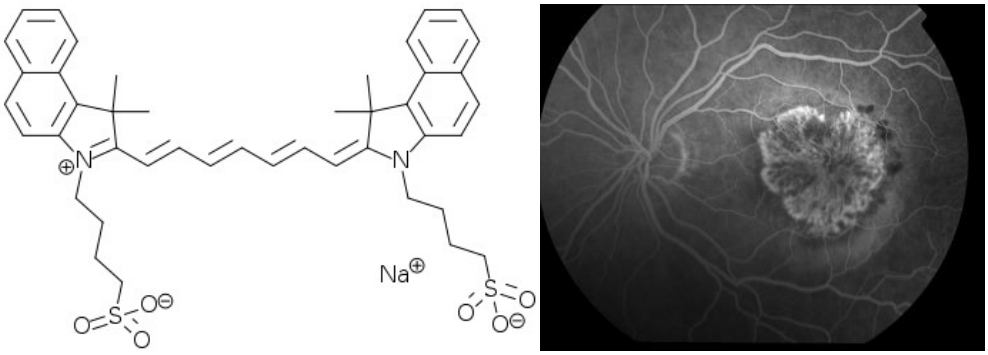

Figure: Chemical structure of IGC (left) and angiogram of the retina (right)

The endoscopy system described in this document should enable the surgeon to visualize ICG fluorescence in laparoscopic surgery to reach the following goals:

- Detection of ectopic endometrial lesions in the abdominal and pelvic space in the sense of deep infiltrating endometriosis
- Detection of Sentinel Lymph Nodes during tumour resection of cervical or endometrial cancer.

2. Detail description of clinical testing:

a) Near-infrared fluorescence Imaging (NIRF) imaging as a supportive tool for localisation of deep infiltrating endometriosis (DIE) lesions during laparoscopic surgery

Endometriosis is a disease of the uterus in which tissue from the uterine cavity becomes implanted in the abdominal cavity and, rarely, metastasizes to organs at a distance from the uterus. Endometriosis tissue is biologically the same as basal endometrial tissue.

Foci of endometriosis consist of glands, stromal cells, and smooth muscle; they are supplied by nerves (neurogenesis), lymphatic vessels, and blood vessels (angiogenesis).

The diagnosis of endometrial lesions by simple laparoscopic visualization is difficult and often inaccurate.

b) **Aim of the Study**

Aim of the clinical testing is review the feasibility and potential to establish a new and more accurate method to visualize the peritoneal changes caused by endometriosis by ICG mediated fluorescence imaging. The results and scientific findings obtained within this study shall be used to design a follow-up controlled trial with a higher number of patients.

c) **Investigation Points**

- Question: Appearance of endometrial lesions and differentiation from surrounding tissue observed in the NIRF image in general
- Hypothesis:
    - It is possible to increase the visual detection rate of peritoneal and deep endometriosis by means of ICG mediated fluorescence.
    - The estimation of extent and size of an endometriotic lesions can be aided by means of ICG mediated fluorescence prior to its excision.
    - Endometriosis of undifferentiated pattern may have different appearance by means of ICG mediated fluorescence than well differentiated and stromal disease

d) **Study Design and Study Participants**

- Study Participants:Prospective analysis of 25 patients undergoing laparoscopy for suspected endometriosis under white light illumination and ICG imaging diagnosis.
- Inclusion criteria:
    - Suspected endometriosis with necessity for laparoscopic confirmation and resection
    - Regular menstrual cycles
- Exclusion criteria:
    - Patients younger than 18 years and older than 50 years at time of operation
    - Subject has previous history of adverse reaction or allergy to ICG, iodine, shellfish or iodine dyes
    - Documented allergy to sulfur containing compounds
    - History of allergic reactions attributed to compounds of similar chemical or biologic composition to ICG
    - Subject has significant liver disease, cirrhosis or liver insufficiency with abnormal liver function tests (Total bilirubin increased by factor 1.5 than normal and/or serum glutamic oxaloacetic transaminase increased by factor 2 than normal)
    - Subject has uremia, serum creatinine (> 2.0 mg/dl)
    - Subject has severe coronary heart disease (instable angina pectoris)
    - Pregnant or breast-feeding women

- Subject is actively participating in another drug, biologic and/or device protocol
- The presence of medical conditions contraindicating general anesthesia or standard surgical approaches
- Subject has any medical condition, which in the judgment of the Investigator and/or designee makes the subject a poor candidate for the investigational procedure

e) Procedure:

- Patients are recruited within the clinical routine after indication for laparoscopy under consideration of inclusion and exclusion criteria. After obtaining the patient's consent the patient is included into the study. Withdrawal of the patient from the study is possible at any time without resulting disadvantages or drawbacks in the patient's treatment.
- During the procedure, the sites is initially subjected to visual inspection using direct laparoscope visualization under white light conditions. All areas suspected of peritoneal endometriosis are classified as white, black and red lesions and recorded together with their anatomic location in the surgical record for the purposes of subsequent extirpation. All areas suspected of deep infiltrating endometriosis are recorded together with their anatomic location in the surgical record for the purposes of subsequent extirpation (retrocervical, vaginal, rectosigmoid, bladder lesions)
- After initial visual inspection the patient is administered with 0.05 – 0.25 mg /(kg BW) ICG intravenously. The ICG imaging mode of the Olympus ICG Imaging System is activated and suspect areas in ICG imaging mode are recorded with their corresponding appearance in white light mode.
- Areas that are conspicuous in ICG imaging mode shall be differentiated into white, red, and black lesions and inconspicuous peritoneum.
- If areas suspect in either white light or ICG imaging mode were present, specific sample excisions will be taken from these areas.
- In addition control biopsy specimens from inconspicuous peritoneum will be taken. The control biopsy specimens will be taken at least 2 cm away from any conspicuous structures of the peritoneum.

f) Study Duration and Time Plan

- Study Duration: 6 Month (data acquisition phase)
- Planned Start: T.B.D.

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