Taiwanese Journal of Obstetrics & Gynecology 62 (2023) 119–122

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Short Communication

Spillage and displacement of indocyanine green-stained tissues from uterine cervix to pelvic peritoneum: A proof of concept study for colpotomy approach in minimally invasive surgery

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ARTICLE INFO

Article history:
Accepted 23 August 2022

Keywords:
Colpotomy
Indocyanine green
Minimally invasive radical hysterectomy
Peritoneal spillage

ABSTRACT

Objective: To analyze peritoneal spillage and displacement of indocyanine green (ICG)-stained tissues from uterine cervix to pelvis during intracorporeal/vaginal colpotomy in laparoscopic-assisted hysterectomy.

Materials and methods: Eleven patients undergoing laparoscopic-assisted hysterectomy were included. One patient with an incidental diagnosis of endometrial cancer was excluded. Of the 10 patients, five underwent intracorporeal colpotomy (IC) and five received vaginal colpotomy (VC) during laparoscopic-assisted hysterectomy. Approximately 5 cm of resected round ligament from each patient was stained with ICG and cut to 1.0 × 1.0 cm in size. Four to five fragments of ICG-stained tissues were placed and sutured on the uterine cervix before colpotomy. During and after colpotomy, serial pictures under white and fluorescence light were taken to document peritoneal spillage and displacement of ICG-stained tissues to the pelvic peritoneum.

Results: Peritoneal spillage of ICG occurred in the entire IC group. Displacement of ICG-stained tissues from uterine cervix to pelvic peritoneum were visualized in three (60%) patients undergoing IC. In the five patients who received VC, peritoneal spillage of ICG and displacement of ICG-stained tissue to pelvic peritoneum did not occur. There were no perioperative complications.

Conclusions: IC in minimally invasive radical hysterectomy should not be performed because peritoneal spillage of ICG and displacement of ICG-stained tissues from uterine cervix to pelvis frequently occurs during IC. Therefore, specific measures to prevent tumor exposure during colpotomy should be implemented in cervical cancer patients.

Introduction

The phase III Laparoscopic Approach to Cervical Cancer (LACC) trial has revealed that women undergoing minimally invasive radical hysterectomy (RH) for early-stage cervical cancer have a significantly decreased disease-free survival with more possibility to develop pelvic and peritoneal carcinomatosis than patients receiving abdominal RH [1,2]. Among risk factors associated with higher recurrence of minimally invasive RH in early-stage cervical cancer patients, the most important factor that surgeons can control might be the colpotomy approach. Several authors have suggested that protective maneuvers at the time of colpotomy including protective vaginal closure and vaginal colpotomy should be implemented to avoid intraperitoneal tumor spread [3,4].

Unlike early-stage endometrial, colonic, or gastric malignancies, cervical cancer tissues exposed to vaginal cavity may migrate into the pelvic peritoneal cavity when laparoscopic intracorporeal colpotomy (IC) is performed under CO_2 pneumoperitoneum. However, the migration of cervical cancer tissues cannot be visually confirmed during surgery. It is estimated by retrospectively analyzing the type of tumor recurrence. In this study, indocyanine green (ICG)-stained round ligaments were cut into small pieces and sutured to the uterine cervix. Laparoscopic-assisted hysterectomy

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https://doi.org/10.1016/j.tjog.2022.08.016

was then performed using a uterine manipulator to create a similar situation that could occur in surgery for cervical cancer patients. The aim of this study was to analyze peritoneal spillage and displacement of ICG-stained tissues from the uterine cervix to the pelvis during IC or vaginal colpotomy (VC) in laparoscopic-assisted hysterectomy.

Methods

Study cohort and surgery

In this prospective observational study, women undergoing laparoscopic-assisted hysterectomy were recruited between March 8, 2021 and September 31, 2021. Surgical indications were uterine fibroids and adenomyosis with menometrorrhagia in 11 patients. One patient with an incidental diagnosis of endometrial cancer was excluded. Laparoscopic-assisted hysterectomy was performed as routinely planned. Of the remaining 10 patients, 5 underwent IC and 5 received VC. Ten patients were alternately assigned based on the date of entry.

Preparation of indocyanine green (ICG)-stained tissue on the uterine cervix

One vial of 25 mg ICG powder (DID Indocyanine Green [Dongindang Inc., Gyeonggi-do, Republic of Korea]) was suspended in 10 ml of sterile water. Approximately 5 cm of resected round ligament from each patient was retrieved, stained with ICG, and cut to 1.0 × 1.0 cm in size. Four to five fragments of ICG-stained tissues were placed and sutured on the uterine cervix in front of the vaginal occlude balloon before colpotomy (Fig. 1).

Colpotomy

A Rowden uterine manipulator injector with a Koh colpotomizer and a pneumo-occluder (Cooper Surgical, Lake Forest, CA) was used to lateralize the uterus and increase the distance between the cervix and the ureter. In the IC group, vaginal cuff was resected intracorporeally in the laparoscopic environment after the cervix was freed from its vascular and suspensory attachments (Supplementary Figure 1-a). In the VC group, two techniques were used to prevent intraoperative tumor spillage: closing fallopian tubes prior to insertion of a uterine manipulator and reverse Trendelenburg position during VC. VC was performed using a single-toothed tenaculum via the vaginal route after the laparoscopic procedure was temporarily terminated (Supplementary Figure 1-b). During and after colpotomy, serial pictures were taken under white and fluorescence light to document peritoneal spillage and displacement of ICG-stained tissues to the pelvic peritoneum (KARL STORZ GmbH & Co. KG, Tuttlingen, Germany). All fragments of ICG-stained tissues were retrieved.

Results

Table 1 shows clinicopathologic characteristics of the study cohort. The median age was 41.0 years in the IC group and 48.0 years in the VC group. The median body mass index was 23.2 kg/m^2 in the IC group and 23.9 kg/m^2 in the VC group. Preoperative diagnosis and pathological results were the same for the two groups (2 patients with uterine fibroids and 3 patients with adenomyosis in each group). The median weight of the uterus was 249.0 g in the IC group and 405.0 g in the VC group. Peritoneal spillage of ICG occurred in the entire IC group (100%). Displacement of ICG-stained tissues from the uterine cervix to the pelvic peritoneum was visualized in three (60%) patients undergoing IC. In the five patients undergoing VC, peritoneal spillage of ICG and displacement of ICG-stained tissues to the pelvic peritoneum did not occur. There were no perioperative complications.

Fig. 2 shows spillage of ICG (arrow) and displacement of ICG-stained tissues (arrowhead) into the pelvic peritoneum during laparoscopic intracorporeal colpotomy under white light mode (a) and near infra-red fluorescence mode using ICG (b).

Fig. 3 shows no intraperitoneal contamination of ICG or ICG-stained tissues after vaginal colpotomy under white light mode (a) or near infra-red fluorescence mode using ICG (b).

Discussion

Spillage (100%) and displacement (60%) of ICG-stained tissues from the uterine cervix to the pelvic peritoneum occurred in the IC group when IC was performed using a uterine manipulator. Although whether cancer tissues not visible to naked eyes could migrate during surgery is unknown, this study using ICG sufficiently reminds us of the risk of IC during minimally invasive RH in early-stage cervical cancer patients.

Although our first study regarding the risk of IC during minimally invasive RH in early-stage cervical cancer patients was reported, findings of that study have not received much attention [5]. However, our study results were cited for the first time in the LACC trial and the risk of IC and the importance of a transvaginal approach were highlighted [1]. In addition, several authors have suggested the following three strategies to prevent tumor exposure during colpotomy in minimally invasive RH [3,4,6–9]. First, specific measures before IC should be taken to prevent the spillage of tumor cells. Prior

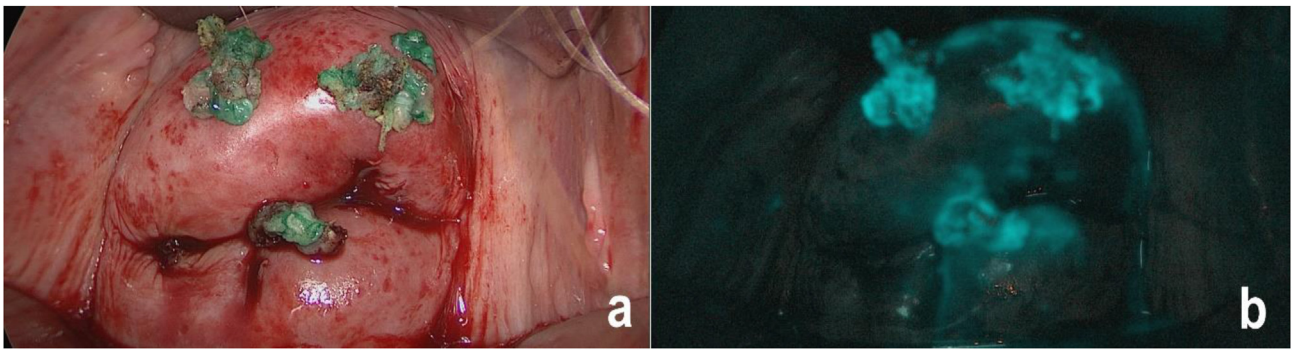

Fig. 1. Indocyanine green-stained tissue on the uterine cervix before colpotomy under white light mode (a) and near infra-red fluorescence mode using indocyanine green (b).

Table 1
Clinicopathologic characteristics of the study cohort (N = 10).

Variables	Intracorporeal colpotomy (N = 5)	Vaginal colpotomy (N = 5)
Age (years)	41.0 (39.0–53.0)	48.0 (48.0–54.0)
BMI (kg/m^2)	23.2 (19.1–32.0)	23.9 (21.4–36.0)
Surgical indication	Leiomyoma[a] (N = 2) Adenomyosis[a] (N = 3)	Leiomyoma[a] (N = 2) Adenomyosis[a] (N = 3)
Surgery	Laparoscopic hysterectomy with bilateral salpingectomy	Laparoscopic hysterectomy with bilateral salpingectomy
Operating time (minutes)	80.0 (65.0–200.0)	105.0 (65.0–125.0)
Use of Rowden uterine manipulator injector with the Koh colpotomizer and pneumo-occluder	Yes	Yes
Closing of fallopian tubes via cautery or clipping prior to the insertion of a uterine manipulator	Yes	Yes
Reverse Trendelenburg position prior to colpotomy	No[b]	Yes
Pathologic findings	Leiomyoma (N = 2) Adenomyosis (N = 3)	Leiomyoma (N = 2) Adenomyosis (N = 3)
Weight of uterus (gram)	249.0 (136.0–283.0)	405.0 (249.0–720.0)
Spillage of ICG	Yes (N = 5)	No (N = 5)
Displacement of ICG-stained tissue	Yes (N = 3)	No (N = 5)
Transfusion	No	No
Perioperative complications	No	No
Hospital stays (days)	4.0	3.0 (3.0–5.0)

Abbreviation: BMI, body mass index; ICG, indocyanine green.
[a] With menometrorrhagia.
[b] Trendelenburg position during intracorporeal colpotomy.

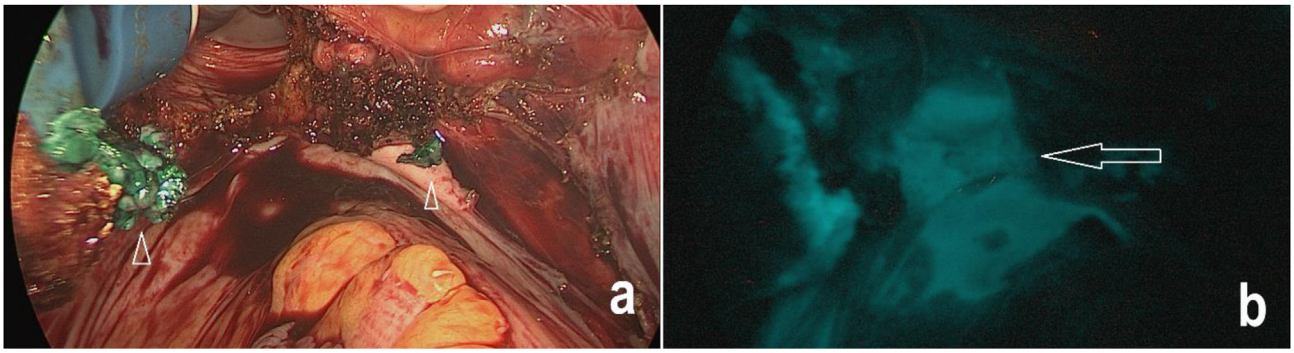

Fig. 2. Spillage of indocyanine green (arrow) and displacement of indocyanine green-stained tissue (arrowhead) into the pelvic peritoneum during laparoscopic intracorporeal colpotomy. Intra-operative views taken under white light mode (a) and near infra-red fluorescence mode using indocyanine green (b).

to resecting the upper third of vagina, either suture or endoscopic stapler could be used in advance to ligate the upper vagina pre-emptively [6,7,9]. Second, creation and continuous suturing of tumor-adapted vaginal cuff can be performed to avoid tumor spillage during colpotomy [3,4]. Third, vaginal colpotomy can be performed to delineate an adequate vagina cuff margin and prevent tumor spillage once the cervical and vagina are freed from their vascular and suspensory attachments through laparoscopic procedures [8]. Although two of these studies were retrospective, surgical techniques including transvaginal closure of tumor-adapted vaginal cuff and vaginal colpotomy did not show any difference in survival rate from open surgery. However, the study using an enclosed colpotomy and an endoscopic stapler was only a report on the surgical technique. We are waiting for the result of survival rate.

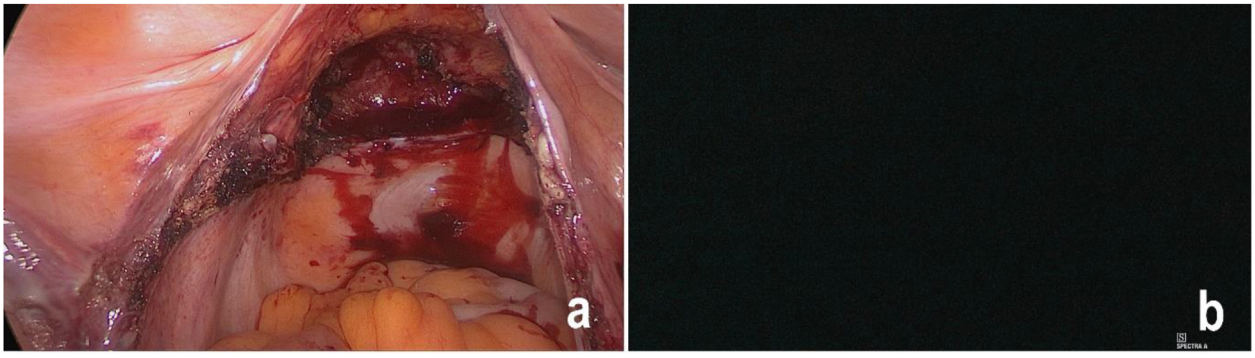

Fig. 3. No intraperitoneal contamination of indocyanine green and indocyanine green-stained tissue. Post-operative view taken under white light mode (a) and near infra-red fluorescence mode using indocyanine green (b).

Two studies have reported that cervical conization prior to minimally invasive RH has a lower risk of disease recurrence in early-stage cervical cancer [10,11]. As the colpotomy approach was not analyzed in these studies, IC might have been performed in a significant number of patients. Therefore, the low recurrence rate in early-stage cervical cancer patients undergoing cervical conization proves that the probability of tumor cells migrating into the pelvic cavity during IC is lower if there are few or no residual tumors in the uterine cervix due to cervical conization.

Several authors have raised concerns that cancer tissues are fragmented and that fragmented cancer tissues can be artificially migrated through the fallopian tube and metastasized into the pelvic peritoneal cavity when the cup and balloon occluder of the uterine manipulator squeeze cervical cancer tissues [12,13]. In addition, women who underwent minimally invasive RH using a uterine manipulator had a 2.76-times higher hazard of disease recurrence [14]. Since the colpotomy approach was not analyzed in early-stage cervical cancer patients in which the uterine manipulator was used, it would be premature to conclude that simply using the uterine manipulator was an independent risk factor related to the recurrence of early-stage cervical cancer patients who underwent minimally invasive RH in this European multicenter study. Since the use of a uterine manipulator during minimally invasive RH has several advantages, intraoperative tumor spillage through the fallopian tube can be sufficiently prevented by ligating the fallopian tube before inserting the uterine manipulator into the uterine cavity [8]. In other words, further study is needed to determine whether the use of a uterine manipulator itself is an independent risk factor for disease recurrence in early-stage cervical cancer patients who undergo minimally invasive RH, or whether IC itself is a risk factor for disease recurrence in patients who undergo minimally invasive RH.

ICG is an FDA-approved product to identify sentinel lymph nodes in patients with gynecological cancer and adverse events related to the use of ICG were not observed in this study. There was a similar study that showed peritoneal contamination of ICG during IC, and indirectly looking at tumor cell spillage using ICG-stained tissues is not the same as an actual surgery [15]. However, this study further demonstrated that the tissue sutured on the uterine cervix can migrate into the pelvic cavity during IC. Considering the cost problem of animal experiments and experiments using flow cytometry or cytology, this study can be said to be the most similar to an actual surgery.

In conclusion, IC in minimally invasive radical hysterectomy should not be performed because peritoneal spillage of ICG and displacement of ICG-stained tissues from uterine cervix to pelvis frequently occurs during IC. Therefore, specific measures to prevent tumor exposure during colpotomy should be implemented in cervical cancer patients.

Declaration of competing interest

The authors declare that they have no conflicts of interest and nothing to disclose.

Statement of ethics

The study protocol was approved by our Institutional Review Board (AJIRB-MED-INT-20-562). All patients provided informed consent.

Data availability statement

The data that support the findings of this study are not publicly available due to sensitive nature of patient health data but are available for S.J.C. upon reasonable request.

Acknowledgments

We are grateful to the patients who consent to the use of their data for research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2022.08.016.

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