Fluorescence colposcope with dye TMTP1-PEG4-ICG is comparable to the conventional colposcope with acetic acid and Lugol's iodine in identifying cervical precancerous lesions - A randomized controlled trial

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Abstract

Objective: To compare the diagnostic efficiency of fluorescence colposcope with dye TMTP1-PEG4-ICG versus conventional colposcope with acetic acid and Lugol's iodine in identifying cervical precancerous lesions. Design and setting: Randomized controlled trial conducted at Colposcopy Center. Population: Women with abnormal cervical cancer screening results including cytology and/or HPV test. Methods: All participants were randomized to fluorescence colposcope group or conventional colposcope group. Patients of fluorescence colposcope group were applied dye TMTP1-PEG4-ICG to the cervix uteri. Patients of conventional colposcope group routinely administrated acetic acid and Lugol's iodine to stain the cervix uteri. Main outcome measures: The colposcopists gave colposcope assessment impressions according to the cervical staining reactions and fluorescence signal-to-background ratio (SBR) calculation results. The diagnostic efficiency of fluorescence colposcope and conventional colposcope was calculated on a per-patient and per-site basis. Results: 195 women were successfully completed the study protocol and were randomized to fluorescence colposcope group (n=97) and conventional colposcope group (n=98). The accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of fluorescence colposcope on a per-patient basis were 61.9%, 66.7%, 61.0%, 23.8%, 90.9%, respectively. The above data corresponded to 73.9%, 69.6%, 74.2%, 15.5%, and 97.3% on a per-site basis in fluorescence colposcope group. In the conventional colposcope group, the above diagnostic indicators corresponded to 59.2%, 54.2%, 60.8%, 31.0%, 80.4%, respectively. Conclusions: The fluorescence colposcope with dye TMTP1-PEG4-ICG was comparable to the conventional colposcope with acetic acid and Lugol's iodine, and exhibited better accuracy, sensitivity and excellent NPV on the basis of per cervical sites.

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Running Title: Fluorescence colposcope identify cervical lesions.

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Population: Women with abnormal cervical cancer screening results including cytology and/or HPV test.

Methods: All participants were randomized to fluorescence colposcope group or conventional colposcope group. Patients of fluorescence colposcope group were applied dye TMTP1-PEG4-ICG to the cervix uteri. Patients of conventional colposcope group routinely administrated acetic acid and Lugol's iodine to stain the cervix uteri.

Main outcome measures: The colposcopists gave colposcope assessment impressions according to the cervical staining reactions and fluorescence signal-to-background ratio (SBR) calculation results. The diagnostic efficiency of fluorescence colposcope and conventional colposcope was calculated on a per-patient and per-site basis.

Results: 195 women were successfully completed the study protocol and were randomized to fluorescence colposcope group (n=97) and conventional colposcope group (n=98). The accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of fluorescence colposcope on a per-patient basis were 61.9%, 66.7%, 61.0%, 23.8%, 90.9%, respectively. The above data corresponded to 73.9%, 69.6%, 74.2%, 15.5%, and 97.3% on a per-site basis in fluorescence colposcope group. In the conventional colposcope group, the above diagnostic indicators corresponded to 59.2%, 54.2%, 60.8%, 31.0%, 80.4%, respectively.

Conclusions: The fluorescence colposcope with dye TMTP1-PEG4-ICG was comparable to the conventional colposcope with acetic acid and Lugol's iodine, and exhibited better accuracy, sensitivity and excellent NPV on the basis of per cervical sites.

Keywords: Fluorescence colposcope; Cervical cancer screening; Cervical intraepithelial neoplasia; Diagnostic imaging; TMTP1-PEG4-ICG

Introduction

Cervical cancer is the third most common female cancer worldwide. With the improvement of screening methods and the application of human papillomavirus (HPV) vaccines, the cervical cancer elimination plan in developed countries is accelerating[1]. More than 85% of cervical cancer deaths currently occur in low- and middle-income countries. Because of large population, significant regional socioeconomic disparities, and insufficient medical resources, cervical cancer continues to be a serious public health problem in the developing world, including China[2]. Improving screening methods for cervical cancer is crucial. Guidelines recommend that women aged 21-29 years should perform cervical cytology test every three years and women

aged 30-65 years should co-test with cytology and HPV every 5 years[3]. When these cervical cancer screening results are abnormal, colposcopy and colposcopy-directed biopsies are then recommended.

Colposcopy plays a pivotal role in reducing the incidence and mortality of cervical cancer. Colposcopy can provide real-time observation and evaluation of the cervix to detect cervical intraepithelial neoplasia (CIN)/squamous intraepithelial lesion (SIL) and invasive cancer. 3% to 5% acetic acid and Lugol's iodine solution are usually applied to identify potential lesions. The colposcopists give colposcopic colposcopy assessment impressions according to visual changes, such as response to acetic acid (acetowhitening), characteristics of lesion borders, sizes and contours, vascular patterns, and degree of iodine uptake[4]. Cervicitis is common in colposcopy, and infected cervical cells may also become acetowhite after application of acetic acid, resulting in false positive results[5]. Professional training and visual acuity are necessary for the screening providers. Because of the subjective nature and inherent inaccuracy of the colposcopic impression, its diagnostic efficiency varies greatly and is limited. Acetic acid and Lugol's iodine co-testing showed a sensitivity ranging 64-100% and a specificity ranging 62-97% in detecting CIN 2+ dysplasia[6, 7]. Therefore, the development of indicators with higher diagnostic efficiency has bright application prospects.

Previously, we developed a dual modal fluorescence colposcope for simultaneous visible reflectance imaging and fluorescence imaging. The fluorescence colposcope combined with tumor-targeting near-infrared (NIR) fluorescent dye TMTP1-PEG4-ICG could help to evaluate cervical lesions in real time[8]. TMTP1-PEG4-ICG possesses advantages of increased tissue penetration and high sensitivity, can specifically bind to cervical cancer or intraepithelial neoplasia cells, making it an ideal molecular diagnostic agent[9]. The preliminary clinical study including 11 involvers showed that the fluorescent colposcope combined with TMTP1-PEG4-ICG could display positive fluorescent signal at the lesions for squamous cell carcinoma, adenocarcinoma and CIN[8].

In order to evaluate the diagnostic efficiency of this fluorescence colposcope combined with the tumor-targeting dye TMTP1-PEG4-ICG, we designed this randomized controlled trial (RCT). Patients with abnormal cervical cancer screening results were randomized to fluorescence colposcope group and conventional colposcope group, then the diagnostic efficiency of the two groups were compared.

Methods

Fluorescence colposcope

The dual modal fluorescence colposcope was developed by integrating a NIR fluorescent imaging system into a conventional clinical colposcope (3ML LED, Leisegang, Berlin, Germany) in our previous research[8]. The wavelength of the excitation light source was consistent with the absorption peak of TMTP1-PEG4-ICG, which was 785nm. The color reflectance imaging and NIR fluorescence imaging of the cervix can be obtained simultaneously with the dual modal fluorescence colposcope by a visible-NIR camera. The magnification of 7.5×/15×/30× was provided, with the corresponding field of view was 35.0mm/16.4mm/8.6mm and the corresponding minimum discernible size was 70.1um/35.0um/24.8um. The working distance was 300mm, which ensured non-invasive operation. Besides, a software integrated with graphical user interface (GUI) was developed to facilitate the acquisition of the cervical images. The fluorescence image was overlapped on the color reflectance image for the convenience of spatial localization of the fluorescence signal. The color reflectance images, fluorescence images and the merge images were displayed simultaneously. The fluorescence colposcope possessed the advantages of real-time imaging, high resolution, high SBR and user-friendly control.

Trial design

This was a prospective non-blinded randomized controlled trial, performed at Colposcopy Center of Department of Obstetrics and Gynecology, Tongji Hospital, Wuhan, China, which was a tertiary university hospital with a particular clinical and research interest in the cervical diseases. The study protocols were reviewed and approved by Ethics Committee of Tongji Hospital on September 14, 2017 (reference No. TJ-IRB20170903). And the trial was prospectively registered at ClinicalTrials.gov (NCT 03321461, Date: October 25, 2017).

Patient population

Women with abnormal cervical cancer screening results were asked to participate in this study. The inclusion criteria included: 1) women over 21 years of age; 2) infected with high-risk strains of HPV (including type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and/or with abnormal cytological examination (atypical squamous cells of undetermined significance, ASCUS or worse); 3) were willing and able to sign the informed consent. The exclusion criteria included:1) women were breast-feeding or pregnant; 2) allergy to TMTP1-PEG-ICG, acetic acid, Lugol's iodine or alcohol; 3) diagnosis of vaginitis or other sexually transmitted diseases makes it unsuitable for biopsy sampling; 4) with severe heart failure, liver insufficiency or renal insufficiency; 5) participated in another clinical trial with an investigational drug within 3 months. In addition, patients with the vaginal lesions were not included in the final statistical analysis.

Sample size

As a brand-new device, there was no RCTs to assess the diagnostic efficiency of this fluorescence colposcope previously. However, based on the reported sensitivity and specificity of conventional colposcope in detecting cervical lesions, we calculated the sample size of the conventional colposcopy group and set the sample size of the fluorescence colposcope group to be consistent with it. We estimated a sensitivity of 88% and a specificity of 85% in conventional colposcopy group, and set both the sensitivity and specificity error range to be ± 0.1, type 1 error α as 0.05. The number of subjects required for each group was 90. Assuming a dropout rate of 10%, the total number of subjects for recruitment was set as 200.

Colposcopy procedures

The involved patients were randomly divided into fluorescence colposcope group and conventional colposcope group by random number table method. Neither the registrar nor colposcopy operator participated in the random grouping work. For patients of fluorescence colposcope group, 0.1% fluorescent dye TMTP1-PEG4-ICG was apply to the cervix 30 minutes before colposcopy as we described previously[8]. 2-4 cervical sites with obvious fluorescent signal or suspected lesions were sampled for biopsy. For patients of conventional colposcope group, firstly, a cotton ball containing 5% acetic acid were applied to the cervix for one minute. Take out the cotton ball, observe for 2-3 minutes, and acquire acetic acid acetowhitening response pictures. Then wipe the cervix with a dry cotton ball and stain the cervix with 5% Lugol's iodine solution. Observe for 1-2 minutes and collect the cervix images again. 2-4 cervical sites with abnormal visual changes or suspected lesions were taken for biopsy. If no suspicious lesions were observed in both of the groups, the 3, 6, 9, 12 areas of the cervix were sampled.

Image interpretation

For conventional colposcopy, the colposcopists recorded the results of the colposcopy based on the staining of acetic acid and iodine solution and gave the colposcopic impression (normal/benign; low grade; high grade; cancer) before biopsy taking. Colposcopy-directed biopsy was taken as the gold standard to assess visual inspection readings. As for fluorescence colposcope, in addition to the visible fluorescent signal, we added a regions of interest (ROI) tool to the image acquisition software to calculate the SBR of a certain site in real time. Each sampling site got an SBR value. The larger the value, the greater the possibility of cervical intraepithelial neoplasia.

Statistical analysis

After the SBRs of all sampling sites were calculated using the method mentioned in the previous study[8], a receiver operating characteristic (ROC) curve for SBRs of fluorescence colposcopy was drawn by a custom-written Matlab (MathWorks, the United States) code, and the cut-off value was set at the maximum of Euclidean's index. SBR greater than the cut-off value was considered a positive examination result. When analyzing on the per-patient basis, we took the sampling site with the highest SBR value for each patient as the measurement index.

The diagnostic efficiency according to the patient and the sampling point respectively were calculate by comparing the results of the colposcopy with the pathological diagnosis. The indicators of diagnostic efficiency included accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)

and associated 95% confidence intervals (CI). To compare the diagnostic efficiency of fluorescence colposcopy and conventional colposcopy, chi-square test or Fisher's exact test were performed by IBM SPSS statistics 22. Differences were considered to be statistically significant at $P<0.05$.

Results

Patient characteristics

Between 4 December 2018 and 13 August 2020, a total of 218 women were enrolled and 195 women were finally analyzed in this study (Figure 1). The trial ended when the sample size requirement was reached. 18 women withdrew from the study based on their own willingness, and 5 women with vaginal lesions were not included in the final statistical analysis. 97 women underwent fluorescence colposcope guided biopsy with NIR fluorescent dye TMTP1-PEG4-ICG, and another 98 underwent conventional colposcope directed biopsies with acetic acid and Lugol's iodine solution. As shown in Table 1, the average age of the fluorescence group and the conventional group was 41.7 and 39.9, respectively. In the fluorescence group, 35 patients had an abnormal Thinprep cytologic test (TCT) and 91 had a positive HPV test. For the conventional group, there were 27 and 94 patients with abnormal TCT and HPV positive, respectively.

Comparison of imaging characteristics betweenfluorescencecolposcope and conventional colposcopy

Typical images captured with the colposcope were shown in Figure 2. Fluorescence colposcope could show specific fluorescence signals at cervical lesions in patients with CIN 3 (from patient of No.15), and the patient with normal pathological result (from patient of No.68) had no obvious fluorescence signal at the cervix. Representative visible light pictures, fluorescent pictures and combined pictures were displayed in Figure 2A. As for conventional colposcopy, acetic acid stained the cervical lesions of CIN 2-3 patient (from patient of No.16) white, while Lugol's iodine didn't stain the lesion. And patient with benign cervix (from patient of No.38) had no acetic acid white reaction and normal iodine intake. The representative original pictures, acetic acid staining pictures and iodine staining pictures of the conventional colposcopy group were displayed in Figure 2B. Both groups of patients had no obvious local irritation during cervical staining and colposcopy.

Comparison of diagnostic efficiency between fluorescence colposcope and conventional colposcopy

The comparison results of colposcopy and pathological examination were illustrated in Table 2. We analyzed the diagnostic efficiency of fluorescence colposcopy on a per-patient basis and per-site basis separately. On the per-patient basis, the ROC curve of each patient's SBRs was shown in Figure 3A. The set cut-off value was 2.34, correspondingly, there were 10, 32, 50, and 5 patients with true positive (TP), false positive (FP), true negative (TN), and false negative (FN) respectively (Figure 3B, Table 2). A total of 360 cervical sites were sampled in the 97 patients of fluorescence colposcope group. The ROC curve of SBRs on the per cervical site basis was displayed in Figure 3C and the cut-off value was 1.63. The cervical sites of TP, FP, TN, and FN were 16, 87, 250, 7 respectively (Figure 3D, Table 2). For conventional colposcope, comparing the colposcopic impressions with the pathological results, the number of TP, FP, TN, and FN cases were 13, 29, 45, 11 respectively (Table 2).

The diagnostic efficiency including accuracy, sensitivity, specificity, PPV, NPV and associated 95% CI were calculated and shown in Table 3. The diagnostic efficiency of fluorescence colposcope on a per-patient basis (accuracy=61.9%, sensitivity=66.7%, specificity=61.0%, PPV=23.8%, NPV=90.9%) was similar to the conventional colposcope group (accuracy=59.2%, sensitivity=54.2%, specificity=60.8%, PPV=31.0%, NPV=80.4%). However, when performing statistical analysis on a per-site basis, the accuracy, specificity, and NPV of the fluorescence colposcopy group (73.9%, 74.2%, 97.3% respectively) were better than those of the conventional colposcopy group (p=0.005, 0.021, 0.000 respectively), but the PPV (15.5%) was lower (p=0.035). These results indicated that fluorescence colposcope had a comparable effect in diagnosing cervical precancerous lesions compared with conventional colposcope. Surprisingly, this fluorescence colposcope also demonstrated an excellent negative predictive effect, which was valuable for cervical cancer screening.

Discussion

Main findings

In the present RCT, we found that fluorescence colposcope with dye TMTP1-PEG4-ICG was comparable to the conventional colposcope with acetic acid and Lugol's iodine in identifying cervical precancerous lesions. When performing more detailed statistics on the basis of per cervical sites, the fluorescence colposcope exhibited better accuracy and sensitivity as well as excellent NPV.

Strengths and limitations

Randomization was one of the strengths of this study. In this way, the fluorescence colposcope group and the conventional colposcopy group could be more objectively compared in the same population. In addition, we sampled the cervix at multiple sites, regardless of the result of fluorescent dye or acetic acid and iodine staining. Previous research had shown that the strength of correlations between colposcopic impression and biopsy histology was poor, with an agreement rate of only 37%[10]. A recent study in China indicated the consistency between colposcopy and biopsy pathology was 59.35% with the moderate strength of kappa coefficient of 0.464 in detecting high-grade squamous intraepithelial lesion and cervical cancer[11]. Multiple biopsies increased the detection of histologic HSIL, regardless of patient characteristics[12]. Therefore, multi-site sampling was recommended as a standard practice of colposcopic biopsy and applied in several researches[13-15]. And multi-site sampling also increases the sample size, which was helpful for statistical analysis. In addition to these, we quantitatively calculated the SBRs at the lesions when evaluating the results of fluorescence colposcopy, so that the results would be more objective and convenient.

This study also had some limitations or implementation challenges. Firstly, all the findings were based on our single-center data, which may cause a certain degree of bias. Secondly, neither patients nor colposcopists were blinded to the colposcopy. The colposcopy operation process of the fluorescence colposcope group was different from that of the conventional group, so the double-blind design cannot be achieved at present. Thirdly, this was a preliminary study of a new device with a relatively small sample size. Fourthly, the sampled tissue was too small to additional histological examination, and there were not enough samples for immunohistochemistry to detect the expression level of TMTP1's potential receptor XPNPEP2. As a result, we could not evaluate the consistency of the levels of SBR and XPNPEP2 expression in the fluorescence colposcope group. In the future, the large sample multi-center clinical research should be further performed to evaluate the application potential of this fluorescence colposcope in the secondary screening of cervical cancer.

Interpretation

In this study, the sensitivity and specificity of the conventional colposcopy were 54.2% and 60.8%, which was at a relatively low level compared with previous research[6, 7]. Most of the statistics in previous studies referred to the detection efficiency of CIN 2+ by colposcopy[11, 16, 17], and our study included CIN 1 as a positive pathological result. The sensitivity of the conventional colposcopy to detect CIN 1 was only 16.7% (1/6) in our research. CIN 1 lesions were too mild to show the staining reactions of acetic acid and iodine. When CIN 1 was included in the statistics, the efficiency of colposcopy would generally be reduced. In addition, the diagnostic efficiency may also be related to the population we included. Previous studies had shown that HPV 16+ was related to clearer visual acetowhite changes in the epithelium, therefore reaching a better diagnostic efficiency for colposcopy[18]. Patients infected with any of the 16 high-risk types of HPV could be included in our study. The colposcopic impression also varied between different observers[19, 20]. The application of dynamic spectral imaging colposcopy and related intelligent algorithms would significantly improve the diagnostic efficiency of colposcopy in the future[21, 22].

The main outcome measure for fluorescence colposcope was the level of SBR at the lesions. We set a cut-off value and defined the positive result as the SBR of the cervical sampling site was greater than the cut-off value. For the conventional colposcope, the positive results included the colposcope assessment impression of low grade, high grade and cancer. The two types of colposcope displayed similar efficiencies in identifying

cervical precancerous lesions on per-patient basis. However, the fluorescence colposcope possessed higher sensitivity and better NPV on per-site basis. One of the major advantages of the fluorescence colposcope was its high sensitivity, and the minimum detectable concentration of the fluorescent dye was approximately 2.7 μg/mL[8]. Because it was too sensitive, some inflammatory lesions could also be recognized after being stained with fluorescent dyes, which leads to the prevalence of false positives. In addition, the cut-off value we set was different on the per-patient basis and the per-site basis. At present, this fluorescence colposcope is in the preliminary research stage, and the exact SBR reference value cannot be determined yet. And more detailed and standardized procedures also need continuous improvement.

In addition to the fluorescence signal at the lesions, we could sometimes see the arc-shaped non-specific fluorescence signals at the vaginal vault of the fluorescence colposcopy group, as shown by patient No. 68 in Figure 2A. Before fluorescence colposcopy, unbound fluorescent dyes need to be scrubbed off, and the vaginal vault area was prone to residual fluorescent dyes and resulted in non-specific fluorescent signals. Therefore, this fluorescence colposcope was not suitable for detecting vaginal intraepithelial neoplasia (VIN). Conventional colposcopy-guided biopsy with acetic acid and Lugol's iodine was crucial in detecting VIN[23, 24]. In order to avoid missed diagnosis of VIN or vaginal cancer in this study, suspicious vaginal lesions were also sampled for biopsy. However, the SBRs of the vaginal lesions in the fluorescence colposcope group could not be accurately calculated, so the vaginal lesions in both groups were not included in the statistical analysis.

A variety of fluorescent probes targeting tumors at the molecular and cellular levels have been developed for image-guided surgery[25-27]. However, there are few relevant studies in colposcopy-guided biopsy. The fluorescence colposcope combined with tumor-specific dye TMTP1-PEG4-ICG provides a new idea for the identification of cervical cancer and precancerous lesions.

Conclusion

The fluorescence colposcope with dye TMTP1-PEG4-ICG was comparable to the conventional colposcope with acetic acid and Lugol's iodine in identifying cervical precancerous lesions, and exhibited better accuracy and sensitivity and excellent NPV on the basis of per cervical sites. This new type of fluorescence colposcopy could be a potential candidate for secondary screening of cervical cancer.

Disclosure of interests

The authors declared no conflicts of interest.

Contribution to authorship

Juncheng Wei and Jinling Lu designed the study; Ying Zhou, Chen Wang and Wei Li enrolled volunteers, prepared the data and drafted the manuscript; Wei Li and Ying Zhou performed the colposcopy operations; Chen Wang, Pengcheng Li and Ling Xi analyzed the data; Wanrong Lu performed the statistical analysis. Xiaohu Liu designed the image acquisition software. All authors reviewed and approved the final manuscript before submission.

Details of ethics approval

The study protocols were reviewed and approved by Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology on September 14, 2017 (TJ-IRB20170903). The trial was registered at ClinicalTrials.org (NCT03321461).

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Table 1 Demographic characteristics

	Fluorescence colposcope (n=97)	**Conventional colposcope (n=98)**
Age (years, mean±SD)	41.7±10.7	39.9±9.7
TCT		
Abnormal[a]	35 (36.08%)	27 (27.55%)
Normal	58 (59.79%)	69 (70.41%)
Not available	4 (4.12%)	2 (2.04%)
HPV		
Positive[b]	91 (93.81%)	94 (95.92%)
Negative	2 (2.06%)	1 (1.02%)
Not available	4 (4.12%)	3 (3.06%)

[a] Abnormal TCT results include ASC, LSIL, HSIL, AGC.

[b] HPV positive refers to a positive test for any high-risk strains of HPV, including type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.

Table 2 Comparison of colposcopy results with pathological examination results

Colposcopy results	**Final pathology diagnosis**	**Final pathology diagnosis**	**Final pat**
	Normal/benign	**CIN 1**	**CIN 2/3**
Patients by fluorescence colposcope	**82**	**2**	**13**
Positive[a]	32 (39.02%)	1 (50%)	9 (69.23%)
Negative	50 (60.98%)	1 (50%)	4 (30.77%)
Cervical sites by fluorescence colposcope	**337**	**2**	**21**
Positive[a]	87 (25.82%)	2 (100%)	14 (66.67%
Negative	250 (74.18%)	0 (0%)	7 (33.33%)
Patients by conventional colposcope	**74**	**6**	**18**
Positive[b]	29 (39.19%)	1 (16.67%)	12 (66.67%
Negative	45 (60.81%)	5 (83.33%)	6 (33.33%)

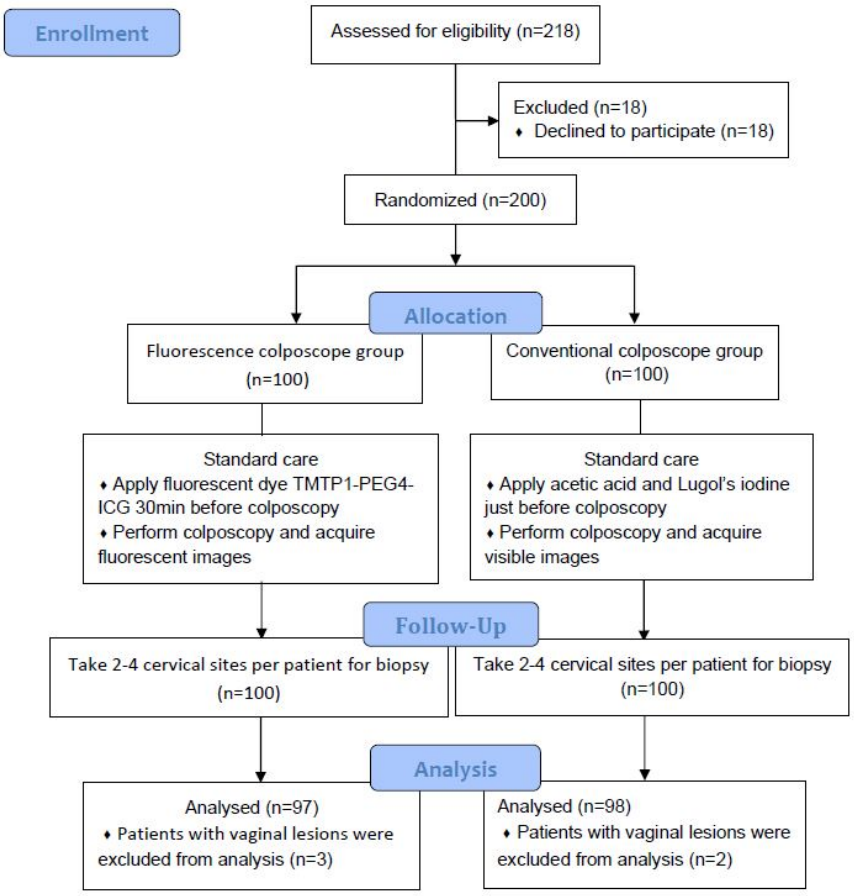
[a] Positive result of fluorescent colposcope means that the SBR of the cervical sampling point is greater than the cut-off value.

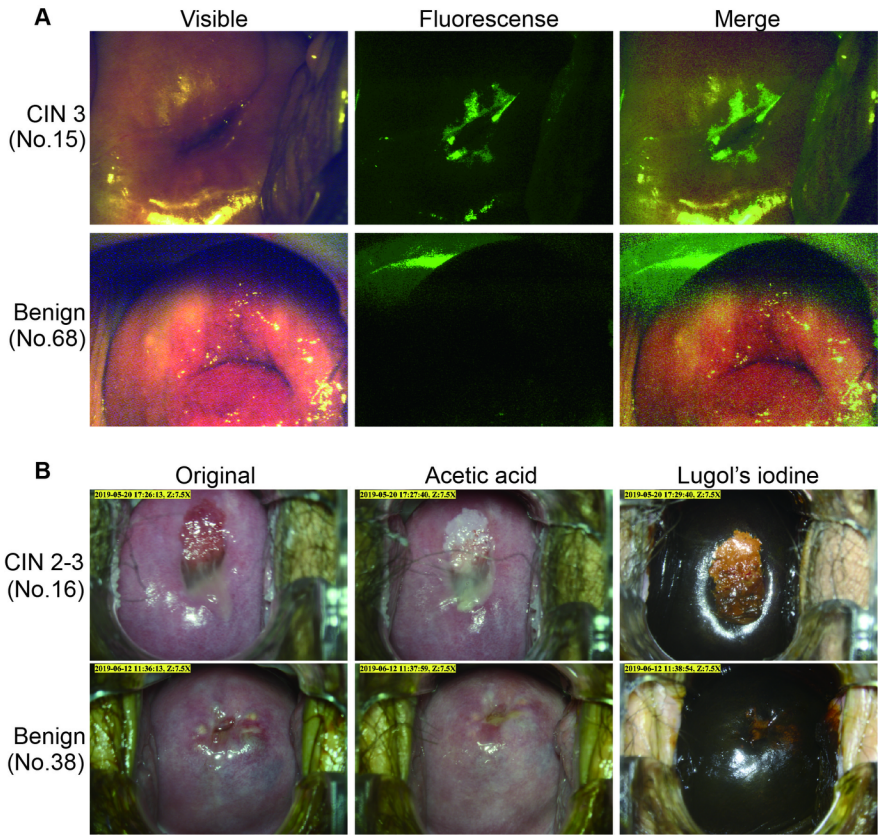
[b] Positive result of conventional colposcope includes the colposcope assessment impression of low grade, high grade and cancer.

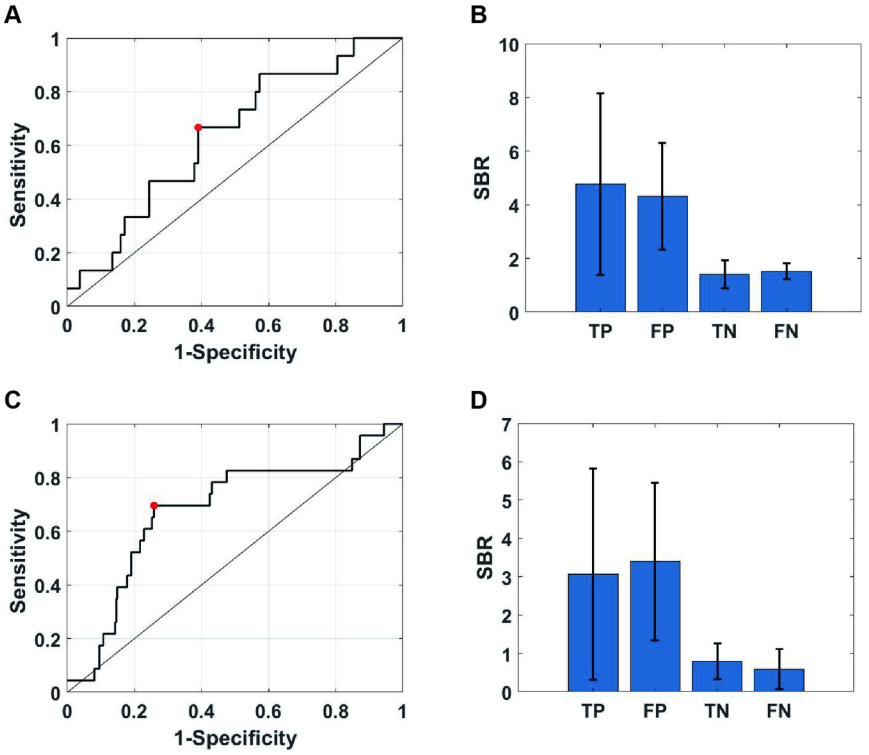
Table 3 Comparison of diagnostic efficiency between fluorescent colposcope and conventional colposcope

Diagnostic efficiency	Accuracy	Sensitivity	Specificity	PPV	NPV
Patients by fluorescence colposcope	61.9%	66.7%	61.0%	23.8%	90.9%
95% CI	52.0%-71.7%	39.6%-93.7%	50.1%-71.8%	10.4%-37.2%	83.1-98.8%
Cervical sites by fluorescence colposcope	73.9%	69.6%	74.2%	15.5%	97.3%
95% CI	69.3%-78.4%	49.2%-89.9%	69.5%-78.9%	8.4%-22.6%	95.3%-99.3%
Patients by conventional colposcope	59.2%	54.2%	60.8%	31.0%	80.4%
95% CI	49.3%-69.1%	32.7%-75.7%	49.4%-72.2%	16.4%-45.5%	69.6%-91.1%

CI: confidence intervals; PPV: Positive predictive value; NPV: Negative predictive value.







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`Figure Legend.pdf` available at https://authorea.com/users/414452/articles/522494-fluorescence-colposcope-with-dye-tmtp1-peg4-icg-is-comparable-to-the-conventional-colposcope-with-acetic-acid-and-lugol-s-iodine-in-identifying-cervical-precancerous-lesions-a-randomized-controlled-trial