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Research Article
Efficacy and Security of Improved Thumbtack-Type Cervical Cold Knife Conization to Treat Cervical High-Grade Epithelial Lesions

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Abstract

Background and Objective: Women's second-most prevalent malignancy is cervical cancer. After cervical cancer screening became widespread, cervical intraepithelial neoplasia (CIN) increased but cervical carcinoma decreased. This study aimed to evaluate the safety and efficacy of the new thumbtack-type cervical cold knife cone in cervical high-level epithelial neoplasia. **Materials and Methods:** A retrospective analysis was conducted of the clinical data of 114 patients with cervical high-grade epithelial fibrosis at The Affiliated Hospital of Guizhou Medical University Hospital from January, 2019 to December, 2019. The study group consisted of 55 patients with underlying thumbtack-type cervical cold knife taper (TCKC) and 59 patients with traditional cervical cold knife cutting (CKC) in the control group. The results of the two groups were analyzed, comparing surgical time, in-surgery bleeding and pathological results. **Results:** Compared with the control group, the difference in surgical time and bleeding, cone length and cone diameter was statistically significant ($p<0.05$) and the age comparison difference was not statistically significant. The difference between the study and control groups was not statistically significant in comparing the positive margin rate at the bottom of the cone ($p>0.05$). **Conclusion:** The surgical thoroughness and safety of thumbtack-type cervical cold knife conization were consistent with traditional cervical cold knife conization, but thumbtack-type cervical cold knife conization had the advantage of less bleeding tissue damage and a shorter surgery time, therefore being more minimally invasive than CKC. Compared with the traditional operation, the improved push-pin-type cervical conical surgery had the best outcomes.

Key words: Cold knife conization, cervical intraepithelial neoplasia, minimally invasive surgery, malignancy, epithelial fibrosis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cervical cancer is the second most common malignant tumor in women. In 2018, there were 569,847 new cases worldwide and 311,365 women died from the disease[1]. Most cervical cancers are associated with high pathogenicity Human Papillomavirus (HPV) infection, which causes cervical lesions, from chronic inflammation to intraepithelial epithelioma cervical intraepithelial neoplasia (CIN), eventually developing into cervical cancer[2]. The appearance of CIN means that the cervical epidermis has changed cell morphology under the continuous action of HPV and there is a possibility of cervical cancer. Intervention during this period is of great significance in preventing cervical cancer[3].

Nationwide screening programs in developed countries have been reducing the incidence of cervical cancer over the past five decades[4]. Due to the popularity of cervical cancer screening, CIN is gradually increasing, while cervical cancer is slowly decreasing. It is currently recognized that the treatment of CIN can prevent the occurrence of cervical cancer[4]. Every year, around 500,000 women are diagnosed with CIN 2/3[5]. Cervical conization is one of the standard treatments for CIN patients who require retention of reproductive function. It is currently recommended by the World Health Organization (WHO) and National CIN Guidelines[6].

The procedure usually requires removing enough cervical tissue to ensure that the palace has no CIN residue, so a large amount of cervical epithelial and interstitial tissue will be removed. This can result in postoperative bleeding, incomplete cervical function and reduced reproductive function after surgery. Reducing trauma and tissue loss may be one way to reduce postoperative cervical insufficiency and reduce the risk of miscarriage and premature birth in postoperative pregnancy[7]. To reasonably reduce trauma, tissue loss and postoperative cervical insufficiency. The article analyzed the improved traditional CKC and the recent efficacy of enhanced surgery. Tailored treatment may help reduce surgical trauma and ensure negative margins. Tailored treatment is a more precise treatment method that can reduce tissue damage. It has not yet been widely used in the treatment of CIN and The Affiliated Hospital of Guizhou Medical University Hospital has already used it in the treatment of CIN. This study will observe the application of Tailored treatment in CIN and compare its advantages, to provide more evidence for the widespread application of Tailored treatment in CIN.

MATERIALS AND METHODS

Study area: This was a retrospective analysis of 114 cases with cervical high-level epithelial tumor-like lesions admitted to The Affiliated Hospital of Guizhou Medical University from January to December, 2019.

General information: The subjects were divided into two groups. There were 55 cases in the study group. Patients in this group were treated with the thumbtack-type cervical cold knife conization, their ages ranged from 21-66 years and the average age was 43.38±11.69 years. Fourteen cases were CIN 2 (25.45%) and 41 cases were CIN 3 (74.55%). There were 59 cases in the control group. In this group, the patients were treated by the traditional cervical cold knife conization, their ages ranged from 29-53 years old and the average age was 41.10±6.26 years. Twenty-one cases were CIN 2 (35.59%) and 38 were CIN 3 (64.41%). The age difference between the two groups was not statistically significant ($p>0.05$).

Ethical consideration: The study was approved by the Ethics Committee of Guizhou Medical University Affiliated Hospital and was carried out according to the ethical standards (Reg. No.: 20190213T). All subjects signed informed consent and the researchers kept all data strictly confidential.

Inclusion criteria: Preoperative HPV, cervical fluid-based cytology examination, digital colposcopy examination; cervical biopsy pathological examination, pathological examination confirmation of cervical intraepithelial neoplasia (CIN 2/3), operated on within 7 days of the end of menstruation and surgically removed cervical parts are complete cones.

Exclusion criteria: Incomplete clinical data, the patient was unwilling to join the project, the patient was diagnosed with CIN 3 and required the uterus to be removed, the excision specimen is disorder but not standard cones.

Surgical method

Study group: After routine disinfection of the vagina and cervix, the cervical surface was treated with a 5% acetic acid immersion for 1-2 min, waiting for acetic white lesions to appear. At 5 mm to the edge of the lesion, an injection of 3 μ of pituitrin (added to 10 mL 0.9% sodium chloride) was applied, using an injector of 10 mm. The general injection comprised six to eight points, connecting each injection point becomes the external incisional edge of the cervical vagina, using a size 11 tip knife to cut open the cervical mucous membrane and lower the interstitial layer to 5 mm, then, the direction of the scalpel is changed to a horizontal incision parallel to the mucosal surface of the cervix, at about 5 mm away from the mucosa of the cervical tube. The direction of the scalpel is changed to cut towards the uterus when the incision height reached 1.5 cm, the lesion was removed from

the cervix, In this way the cervical lesion is removed in a thumbtack shape (thumbtack-type cold knife cone (TCKC)). If preoperative colposcopy and biopsy prompted cervical tube lesions, the cone length extended to more than 2 cm. After the cervical tissue excision was completed, the wound turned white or yellowish after 30 W high-frequency electrocoagulation was used even if there was no bleeding. The cervical wound was lightly dressed with gauze. The patient can remove the vaginal gauze by himself after 24 hrs. If there is any vaginal bleeding, return to the hospital for an examination.

Control group: After routine disinfection of the vagina, the cervical surface was coated with 3% potassium iodide and the cervix was injected with 6 μ pituitrin (added to 10 mL 0.9% sodium chloride), using the size 11 tip knife to cut open the cervical mucous membrane and under the interstices 5 mm outside the iodine-dyed coloring. The cervix inner orifice direction of a cone was cut to ensure that the cone was removed up to 1.5 cm or more. The surface was stitched with a 2.0 absorbable surgical suture and a high-frequency electric knife 30 W electrode. The cervical wound was lightly dressed with gauze. The patient can remove the vaginal gauze by himself after 24 hrs. If there is any vaginal bleeding, return to the hospital for examination.

Disposal of surgical specimens: The cervical tissue that was surgically removed was immediately sent to the pathology department. The pathology staff examined the cone's shape and measured the cone length, the bottom width and the inner and outer orifice diameter. Conventional methods were used for tissue pathology examination.

The presence of CIN 2/3 on the edge of the surgical specimen (including outside the cervix, intra-cervix and deep matrix) is defined as a positive margin.

Observation indicators: The duration of surgery was calculated by the anesthesiologist and marked on the anesthetic list. The amount of bleeding during surgery was assessed by the surgeon and recorded in the surgical record. Postoperative pathology results include the specimen cone length, the cone bottom diameter and the positive margin.

Statistical methods: The data was analyzed and processed with SPSS 22.0. Age was randomly distributed and there was no difference between the two groups of incidences of CIN 2/3. The distribution was described using the mean, the standard deviation ($\bar{x}\pm s$) and the data differences were compared using a t-test. The cut-edge positive was qualitative data and was tested using a card square. The remaining variables did not conform to the normal distribution criteria. Their distribution was described using the median and 25,75 percentiles [M (P25, P75)], comparing the differences between the data with rank and test, $p<0.05$ is defined as having statistical significance.

RESULTS

The schematic diagrams of the operations were shown in Fig. 1a-b. The green dotted line represents the incision made using the classic cold knife cone technique. The black line represents the incision made using the TCKC technique. The black dotted line represents the margin of the white lesions caused by acetic acid. Figure 2a displayed a cervical cold knife with a thumbtack-like design used for making intracervical incisions. Figure 2b shows the whole specimen after cervical cold knife-cutting surgery using a thumbtack-type instrument. Figure 2c express the specimens were sliced using a thumbtack-type cervical cold knife, resulting in 12 point-cut samples. A TCKC incision was done to the 5 mm cervical submucosal stroma depth and transversely cut at the external cervical orifice. Cutting was done vertically upward 5 mm from the cervical mucosa and the lesion was detached from the cervix at 15 mm or more. This incision removed enough submucosal stromal tissue to allow pathological evaluation of infiltration depth and completely resected lesions, avoiding needless loss of cervical mucosa and interstitial tissue. In the study group, cone length and diameter differed significantly from the control group ($p<0.05$), however the positive rate of incisal margin did not change from conventional CKC. Pushpin CKC surgery damages cervical tissue less than CIN because the length and diameter of cervical tissue are lower. Discharge follow-up showed no bleeding or infection. Thus, TCKC surgery outperforms CKC surgery in efficacy and safety. Figure 3a shows one month after receiving a cervical cold knife conization procedure employing a biopsy punch, the status of the cervix. Figure 3b shows the condition of the cervix after undergoing a surgical procedure known as cervical cold knife cutting, similar to the use of thumbtacks. This operation was performed two months ago. Figure 3c shows the appearance of the cervix three months after undergoing cervical cold knife-cutting surgery using a thumbtack. After TCKC, the external opening of the cervix was tiny and spherical and the mucosa fully covered the incision, like the non-fertile cervix (Fig. 3a-b). In traditional CKC, the cervix and vagina generally shorten or vanish after surgery owing to the fragile cervix and intraoperative suture technique, which causes poor cervical remodelling (Fig. 3c). These findings revealed that cervix shape and function vary significantly following surgery.

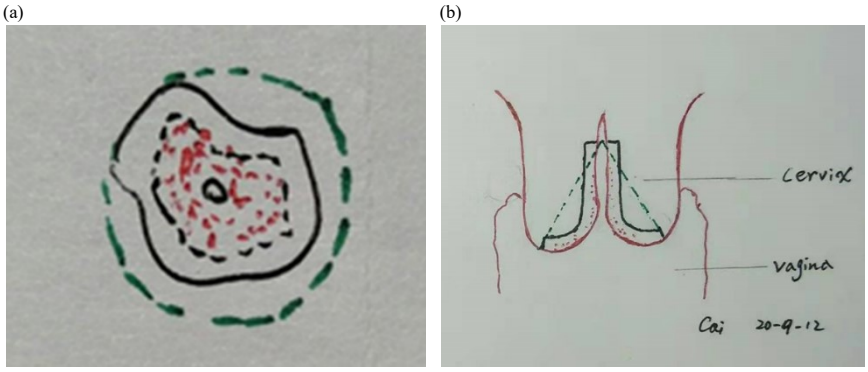

Fig. 1(a-b): Schematic diagrams of the operation diagram of (a) Cold knife cutting incision and (b) Thumbtack-type cervical cold knife cutting cervical mucosa incision
Green dotted line shows the traditional cold knife cutting incision, solid black line shows the thumbtack-type cold knife cutting incision and black dotted line shows the white vinegar lesions edge

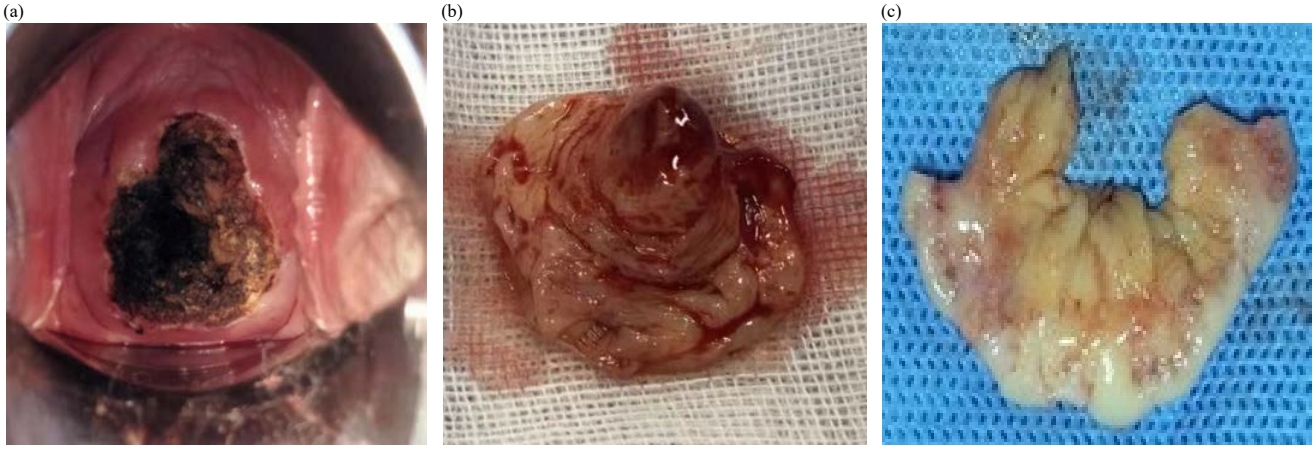

Fig. 2(a-c): (a) Thumbtack-type cervical cold knife cutting intracervical incision, (b) Complete specimen and (c) 12 point-cut specimens after thumbtack-type cervical cold knife-cutting surgery

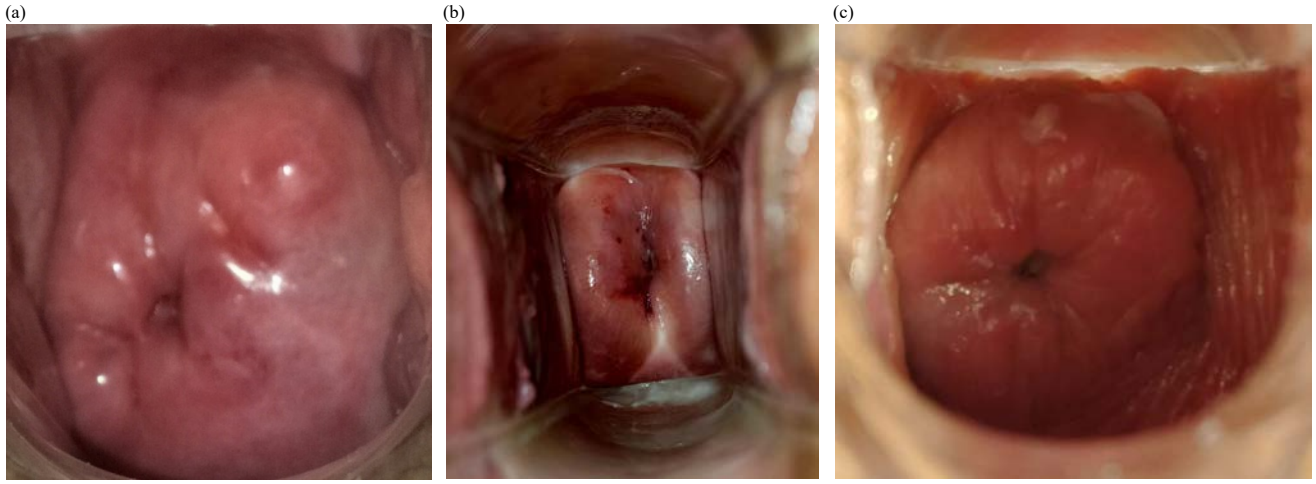

Fig. 3(a-c): Cervix after thumbtack-type cervical cold knife-cutting surgery after (a) One month, (b) Two months and (c) Three months

Table 1: Characteristics of study participants according to postoperative medication

Characteristics	TCKC (n = 55)	CKC (n = 59)	F/Z/χ^2	p-value
*Age (year)	43.38±11.69	41.10±6.26	18.578	0.19
**Surgical time (min)	30.85±15.24	40.34±15.42	3.171	<0.01
**Bleeding (mL)	13.31±14.37	25.90±25.98	3.758	<0.01
Cervical biopsy diagnoses are before cone				
***CIN2	21(38.18%)	20 (33.90%)		
CIN3	34 (61.82%)	39 (66.10%)	0.277	0.634
**Cone length (cm)	1.89±0.75	2.11±0.83	1.58	0.11
**Cone diameter (cm)	1.49±0.65	1.56±0.72	0.536	0.59
***Positive cone margins (n)	4	2		0.427

Data are present with average±SD (x±s) or number/percent for variables. *T-test, **Rank sum test, ***χ^2 test and CIN: Cervical intraepithelial neoplasia, could be divided into grades 1, 2 and 3

Table 1 presents the characteristics of the individuals included in the research based on the medicine they received after surgery. Compared with the control group, the difference in surgical time and bleeding, cone length, cone diameter was statistically significant ($p<0.05$) and the age comparison difference was not statistically significant. The difference between the study group and the control group was not statistically significant in comparing the positive margin rate of the bottom of the cone ($p>0.05$).

DISCUSSION

Cervical epithelial tumor (cervical intraepithelial neoplasia (CIN)) levels 2 and 3 are precancerous cervical cancer lesions. With HPV infection gradually increasing in young women and the promotion of cervical cancer screening, cervical cancer is controlled and the incidence of CIN has increased significantly[8]. Due to the progression of the disease, most CIN 2/3 will progress into cervical cancer and CIN can coexist with cervical cancer in the early stages[9]. Cervical cone slicing is one of the standard techniques for treating cervical epithelial endothelioma (levels 2/3). It has been around for more than 200 years since Lisfranc evaluation in 1815 when it was first used to treat cervical infections and cervical cancer[10]. At present, there are two main ways of making a cervical cone incision: Circular cervical electrocution (Loop Electrosurgical Excision Procedure (LEEP)) and cold knife cone (cold knife cutting (CKC)), which both completely remove cervical lesions. If the postoperative pathology results are lesions or immersion cancer, further surgery may be required. The LEEP has been a widely used clinical treatment for the past 20 years[11]. It is a quick and reliable hemostatic, with fewer postoperative complications.

However, the high-frequency electric knife causing tissue heat damage led to the specimen's pathological interpretation difficulties, causing trouble with the follow-up treatment[12]. Therefore, to understand whether the surgery completely removed the lesion tissue, the surgical specimen should not be destroyed when it is cut. The use of a cold knife can avoid the electrothermal damage of the surgical specimen edge, so the accuracy of the pathology will be better. This makes the clinical use of CKC even more important[13].

In traditional CKC operations, the adverse obstetric outcomes for intraoperative or postoperative hemorrhage and cervical dysfunction concerns both doctors and patients[14]. Improvement of the operation is based on exploring a more minimally invasive and more effective treatment method.

The cervix is mainly composed of connective tissue and contains a small number of elastic fibers[15]. The CIN is a lesion located in the cervical epithelium, which has not penetrated the basal layer. When the tumor tissue penetrates the basal layer, invasive cervical carcinoma will occur. Traditional cervical conization excises the cervical mucosa of the lesion and part of the submucosal cervical parenchyma. The conization of excessive cervical interstitial tissue may attenuate the cervix, making it challenging to perform intraoperative hemostasis. The suture hemostasis method may further shorten the cervix, which is the main reason for subsequent cervical dysfunction[16]. Surgery should be considered to protect cervical function. Current team has been trying to achieve these goals since 2014 and in the process evolved the current thumbtack type of cervical cold knife coning (thumbtack type CKC, Fig. 1a) and different from the standard cone base with a radius of 5-10 mm from the cervical orifice to the farthest lesion in traditional operations. A TCKC incision was cut to the 5 mm depth of the cervical submucosal stroma, where a transverse cutting was performed at the external cervical orifice level. When 5 mm away from the cervical mucosa, the cutting was performed vertically upward and the lesion was separated from the cervix when 15 mm or more was cut. Such an incision ensured the removal of sufficient submucosal stromal tissue (to facilitate pathological determination of the depth of infiltration) and complete resection of lesions, thus avoiding unnecessary removal of cervical mucosa and cervical interstitial tissue. Compared with the control group, the difference in cone length cone diameter

was statistically significant ($p<0.05$), but the positive rate of incisal margin in the study group showed no statistical difference compared with conventional CKC. The length and diameter of cervical tissue during pushpin CKC surgery are smaller, indicating that pushpin CKC causes less damage to cervical tissue compared to CIN. Follow-up after discharge found no bleeding or infection. So, the TCKC surgery is superior to or equal to traditional CKC surgery in terms of surgical effectiveness and safety.

The reason for less intraoperative bleeding in pushpin CKC may be related to less cervical interstitial loss. Regardless of whether there is bleeding throughout the wound, high-frequency coagulation should be used to turn the tissue white or yellowish without black eschar. This method is very effective in preventing postoperative bleeding. There was no postoperative hemorrhage in the TCKC group. Areas with obvious bleeding in traditional CKC can be treated with electric coagulation or absorbable sutures for hemostasis. If there is much bleeding, a lot of time will be needed for the suture. Deep vaginal suturing requires the skill of the surgeon. If the surgeon is not skilled enough, the blood vessels are exposed for a long time and more bleeding occurs. In the TCKC group, high-frequency electrotomy for hemostasis without wound sutures will shorten the operation time, reduce bleeding or secondary infection caused by foreign body reaction and facilitate the growth of cervical mucosa after surgery to cover the wound and reshape the cervix. More clinical data are needed to support these possible advantages. However, this treatment did not increase intraoperative and postoperative bleeding and did not ensure the safety of the procedure in the short term[17].

Most scholars believe that the positive rate of conization incisal margin is associated with the recurrence and persistence of postoperative disease[18]. Alonso *et al.*[19] pointed out that postoperative residue or recurrence was as high as 36.4% in patients with a positive margin after conization, while it was only 11.9% in patients with a negative margin. It can be argued that the positive rate of conization incisal margin is one of the indicators to evaluate the effectiveness of the operation. The pathological findings of the two groups are compared: Four cases had a positive margin (7.27%) in the study group and two cases had a positive margin (3.39%) in the control group and there was no statistical difference between them. Among the four cases with a positive margin in TCKC, two cases had a positive endocervical margin and two cases had a positive ectocervical margin. In the case of a positive endocervical margin, the length of the resected cervical tissue was 2.3 cm. In contrast, the cone length in another case of the positive cervical canal was 1 cm, which shows that the length of the conical margin protect against margin residue. Another two cases had a positive ectocervical and one case was older (52 years old) and another had multiple involved quadrants (three quadrants). Two cases with a positive external cervical incision and one case with a positive cervical incisal margin chose hysterectomy and postoperative pathology did not indicate high-grade pathological changes. Possible factors associated with a positive incisal margin may include age, menopause and other advanced quadrants. It has been reported in the literature that three or four high-grade quadrants are the most important factors affecting the residual lesion after the cone[20]. Given the limited number of samples, it is not possible to conduct a precise analysis of the parameters associated with a positive incisal margin.

According to the existing data, if the patients wish to retain the uterine fertility function, close follow-up can be conducted for patients with positive incisal margins. However, this treatment did not increase intraoperative and postoperative bleeding and did ensure the safety of the procedure in the short term.

The CKC can cause long-term bleeding, postoperative cervical disorders, cervical tube adhesion, miscarriage due to cervical insufficiency, etc. The TCKC group had a case of uterine cavity hemorrhage during her period caused by cervical tube adhesion. The patient's period was back to normal after one cervical dilation operation. The patient's age was 46 and she had a bacterial vaginal disease before surgery. The surgery was conducted after appropriate treatment, with the conization of the uterine cervix 2.6 cm high and the bottom diameter 2.2 cm. The post-operation follow-up observed the bacterial vaginal disease again. Multiple factors may cause postoperative cervical adhesion and secondary infection during the postoperative wound healing may be one reason. Baldauf *et al.*[20] found that the incidence rate of cervical stenosis was higher when patients were over 50 years old and the length of cervical conization was $\geq$20 mm or the lesions completely occurred inside the cervical canal.

Most scholars believe that the occurrence of cervical stenosis is related to the contracture of cervical scar tissue after cervical conization, primarily associated with long-term postoperative bleeding and co-infection[21]. Traditional CKC surgery uses sutures for hemostasis, although such an approach can stop the bleeding efficiently. However, it can also affect the blood supply of cervical stumps and the appearance of the cervix, its postoperative cervical shape is not ideal[22]. It was clinically observed that the external opening of the cervix after TCKC was small and round and the mucosa completely covered the wound, similar to the non-fertile

cervix (Fig. 3a-b). However, in the postoperative morphology of conventional CKC, the cervix and vagina usually become shorter or disappear, which may be due to the weak cervix and the intraoperative suture method leading to poor postoperative cervical remodeling (Fig. 3c). These results showed that there are significant differences in the structure and function of the cervix after different surgical procedures.

CONCLUSION

One goal of modern minimally invasive surgery is to reduce intraoperative bleeding and tissue damage or loss to reduce postoperative complications. There is no doubt that precision is one way to achieve minimally invasive surgery. The main features of this modified procedure are the personalized design of the cervical and vaginal mucosa incisions and the removal of the cervical lesion in the shape of a thumbtack cone. The TCKC was superior to conventional CKC in terms of surgical safety and the thoroughness of the operation is consistent. It can not only shorten the operation time but also reduce the amount of intraoperative blood and tissue loss. The appearance of the reconstructed cervix after surgery is relatively close to normal, but the changes in cervical anatomy and function require a long period of observational study.

SIGNIFICANCE STATEMENT

Cervical cancer ranks second in women's cancers. Screening for cervical cancer increased CIN but decreased carcinoma. The innovative thumbtack-type cervical cold knife cone was tested for safety and efficacy in cervical high-level epithelial neoplasia. Customised cervical and vaginal mucosa incisions and thumbtack cone cervical lesion removal are key to this better therapy. The TCKC is safer and more comprehensive than CKC. Surgery is shorter and blood and tissue loss are reduced. Surgery leaves the cervix looking normal, but long-term monitoring is needed for cervical structural and function changes.

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All authors contributed to the study and agreed to be listed as authors.

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