INFORMATION BRIEF (RAPID REVIEW)

[redacted]CERVICAL COLD COAGULATOR FOR TREATMENT OF CERVICAL PRECANCEROUS LESION

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
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TITLE: [redacted] CERVICAL COLD COAGULATOR FOR TREATMENT CERVICAL PRECANCEROUS LESION

PURPOSE

To review the effectiveness, safety and cost-effectiveness of [redacted] Cervical Cold Coagulator for the treatment of cervical precancerous lesion based on request from the Deputy Director, Medical Services Development Section, Ministry Of Health Malaysia following a proposal to introduce the product to Ministry of Health.

BACKGROUND

Cervical cancer is the fourth most common cancer among women globally and the third most common malignancy among women in Malaysia with an age-standardised incidence rate of 6.2/100,000 population in 2012-2016.[1,26] Despite cervical cancer being potentially preventable, it is the third most prevalent cancer among Malaysian women.[28] Chinese women were found to have the highest incidence of cervical cancer followed by Indian and Malay. Unfortunately, the majority of cervical cancer patients (76%) are often detected at stage two and above which affects their prognosis.[27] In November 2020, the World Health Organization (WHO) launched the global strategy to accelerate the elimination of cervical cancer as a public health problem, defining 90-70-90 targets which 90% of girls should be vaccinated by age 15, 70% of women should be screened with a high precision test by 35 and 45 years of age, and 90% of women with precancerous lesions and invasive cervical cancer should receive treatment and care at national level by 2030.[2] The World Health Organization (WHO) Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013–2020 identifies HPV vaccination and cervical cancer screening and treatment as best buys.[5] Screening programmes have dramatically reduced cervical cancer rates in high-income countries. In the United States of America (USA), for example, mortality has been reduced by 80% in 50 years following screening by the Papanicolaou (PAP) smear test and treatment of confirmed precancerous cervical intraepithelial lesions grade 2 or more (CIN2+ (2). The prevalence of having a Pap smear test done once in their lifetime ranges from 55.2% to 55.7% in Malaysia. Given the relatively low rate of Pap smear screening in Malaysia, it is worth considering the implementation of a national program that promotes self-sampling as an alternative approach.[29] Screening using the same cytology-based method and histological confirmation of lesions is a challenge in low- and middle-income countries (LMICs), mainly because of high costs and logistical considerations specific to the PAP smear test, general lack of colposcopy and histology services, and inadequate access to treatment of precancerous lesions in these regions.[17] Cervical cancer is commonly caused by human papillomavirus infection (HPV) with 99% of cases being linked to it.[3,4] Persistent HPV infections can cause precancerous lesions that may lead to cervical cancer if left untreated.[6]

Cervical intraepithelial neoplasia grade 2 (CIN2) and CIN3 are considered precancerous lesions that may develop into cervical cancer.[8] The guidelines of the American College of Obstetricians and Gynecologists recommend that for women with a histological diagnosis of CIN2, CIN3, or CIN2, 3 and adequate colposcopic examination, both excision and ablation

are acceptable treatment modalities, except in special circumtances such as for pregnant women.[9] Currently, cryotherapy is the ablation modality that is most used to treat ectocervical premalignant cervical lesions. For low and middle income countries (LMICs), the World Health Organization (WHO) recommends that cryotherapy should be used to treat women who screened positive for CIN after primary human papillomavirus (HPV) testing or visual inspection with acetic acid, even without colposcopy or histology verified disease. [10] However, one major disadvantage of this technology is the need for a refrigerant gas (N_2O or CO_2). The gas containers are bulky and heavy to transport and some areas of LMICs may have supply issues. In addition, frequent refilling of freezing gas can be costly.[7,16] A more portable technology such as 'cold coagulation' or thermocoagulation or thermal ablation (TA) which have benefits like cryotherapy would have significant advantages for the treatment of cervical precancers.[11,12,13,14,15] The WHO endorsed TA for precancer treatment in 2019.

According to the WHO Guidelines for the Use of Thermal Ablation for Cervical Pre-cancer Lesions (2019), thermal ablation, also called 'cold coagulation' or thermocoagulation, is an ablative treatment for CIN. Eligibility for treatment should be assessed by colposcopy (if available) or by naked eye examination of cervix after applying 3% to 5% acetic acid for one minute. The equipment is simple, lightweight (devices can weigh much less than 2 kg), and is easily portable to LMICs field clinics. Treatment is based on a 20 to 40 second application (multiple if needed) of a reusable metallic probe that is electrically heated to approximately 100 °C, leading to epithelial and stromal destruction. Like cryotherapy, thermal ablation is provided by a variety of health care personnel, including primary healthcare workers, and typically performed without anaesthesia.[7] A thermal ablation device is a self-contained, electrically powered medical instrument designed to destroy tissue of the uterine cervix with low-grade heat. It may also be referred to as thermal coagulation or Semm cold coagulation, after the inventor of the device. The term "cold" has been used due to the treatment temperature of 60-120°C, which is lower than that used for standard clinical electrocautery (usually between 400-600°C).[23,24]

From the documents provided by the [redacted], [redacted] thermo coagulator (Figure 1) is handheld, mobile and claimed as easy to be used, independent of power grid and clinical infrastructure and optimised for use in low-resource settings. The simple handling device features a single optimally designed thermo-probe, together with a fixed temperature setting and a timer function to eliminate any possible source for human error. According to Boles T et al (2022), the thermal probe provides heat at 100°C for 60 seconds; the distal end of the probe is teflon-coated to prevent the adherence of any tissue to the probe. The included slider can be placed over the thermal probe to provide heat protection for the vaginal walls when the probe is removed. A white light LED is integrated into the handle to aid visibility when placing the probe in contact with the cervix. The heating button allows the operator to activate and deactivate probe heating. A green LED blinks as the probe heats to 100°C, and stays constantly green once the treatment temperature is reached. The operator can activate the timer by pressing the timer button on the handle, and audible beeps can be heard after 30 seconds, 45 seconds, and 60 seconds of treatment. Probe options include flat probes that are 17 mm and 20mm in diameter, as well as a 20mm endocervical probe with a nipple. According to the manufacturer, the probe able withstand 500 use-disinfection cycles before it has to be replaced. The estimated price for this device is approximately [redacted] including two probes and two sliders while the cost for additional probes or tips is approximately [redacted] each. [20] The device is manufactured by [redacted]

and indicated to be used as a treatment for C2+ (CIN 2, CIN 3, Adenocarcinoma In Situ, or cancer)[9] lesions for the outpatient setting. [21]

Figure 1: Cervical Cold Coagulator/ [redacted]

EVIDENCE SUMMARY

A total of 14 titles were retrieved from the scientific databases such as Medline, Pubmed and from the general search engines [Google Scholar and US Food and Drug Administration (USFDA)] study on cervical cold coagulator. The search was limited to English language and human only. A total of two randomised controlled trials and one guideline were found to be relevant and included in this review.

EFFICACY/ EFFECTIVENESS

Soler M et al. (2022) conducted a noninferiority randomised trial comparing the effectiveness and safety of three ablation treatments for women older than 18 years, with biopsy- confirmed cervical intraepithelial neoplasia (CIN) grade two or higher. This trial was conducted at the Hospital 1° de Mayo of the Instituto del Seguro Social in San Salvador, El Salvador; Hospital Universitario San Ignacio in Bogota, Colombia, the Shanxi Bethune Hospital in Taiyuan and Shanxi Province and three women's health hospitals in Xinxiang, a semirural area in Henan Province, China and involving a total of 1024 women. Data presented in this study were collected from June 19, 2017 to November 30, 2021. Women with positive pregnancy test were excluded from the study. Others underwent a speculum examination by a trained gynecologist to visually assess contraindications to ablation treatment. Ineligibility for ablation included lesions that covered more than 75% of the cervix, extended into the endocervical canal, or extended further than the surface of the smallest probe tip of the three devices, a disfigured or hard-to-reach cervix, a not fully visible squamocolumnar junction, and suspicion of invasive cancer. Eligible patients were assigned to one of the three following treatments using site-stratified random assignment:

i. CO2 gas-based cryotherapy (CO2): double-freeze (freeze for 3 minutes, thaw for 5 minutes, and freeze for 3 minutes) using a Medgyn Cryotherapy System MGC-200 (Medgyn Products, Inc, Addison, IL)
ii. Non-gas cryotherapy: single-freeze (5-minute freeze) with CryoPen, or
iii. TA with a portable device: 40-second application at 100°C followed by additional 20-second applications as necessary to cover the entire squamocolumnar junction using a WiSAP C3 thermocoagulator.

All randomly assigned patients were asked to return for a 6-week follow-up for an evaluation of clinical side effects and a final visit at 12-18 months to obtain samples to ascertain cure rates. Over 90% (934/1024) had attended the 6-week visit and 69% (706/1024) had returned to the 12-month visit. At the treatment visit, self-reported pain levels were obtained. Pain was evaluated at four points: before speculum introduction, after speculum introduction but before treatment, during treatment, and within five minutes after speculum removal. After treatment, a provider explained post-treatment recommendations (ie, avoidance of immersion baths, vaginal douches, inserting tampons into the vagina, and sexual relations). At the six-week visit, patients underwent a speculum examination and were administered a questionnaire to assess the duration (in days) and intensity (mild, moderate, or severe as a multiple-choice item) of side effects. Patients also evaluated their adherence to post-treatment recommendations and responded to a brief acceptability assessment which was repeated at the 12-month follow-up visit. They found no significant differences in sociodemographic variables across treatment arms. In terms of effectiveness, study outcome reported were pain during treatment and patients acceptability. Table 1 presented all median pain measurements by treatment and site. Women reported a higher level of pain with TA than with either form of cryotherapy, but there were differences across sites. (Refer Figure 2). The proportion of patients with moderate and severe pain (≥ 6) was also higher with TA (n=27 [7.9%]) compared with CO_2 (n=10[2.9%]) and CryoPen (n=17 [5%] (P= .01).

Table 1: Median Pain at Different Stages of Treatment by Treatment and by Site. [22]

		Treatment			
Median (IQR) [Min, Max]	**Overall (N= 1024)**	**CO_2 (n = 342)**	**CryoPen (n = 342)**	**TA (n = 340)**	**P** [a]
Baseline	0 (0) [0, 8]	0 (0) [0, 2]	0 (0) [0, 4]	0 (0) [0, 8]	0.17
Before treatment (after insertion of speculum)	0 (0) [0, 8]	0 (0) [0, 8]	0 (0) [0, 8]	0 (0) [0, 8]	0.22
During treatment [b]	2 (3.3) [0, 10]	2 (4) [0, 10]	2 (4) [0, 10]	4 (4) [0, 10]	< 0.01
After treatment [c]	0 (0) [0, 10]	0 (0) [0, 4]	0 (0) [0, 10]	0 (0) [0, 10]	0.01
		Country			
		El Salvador (n = 251)	**Colombia (n = 78)**	**China (n = 695)**	
Baseline		0 (0) [0, 2]	0 (0) [0, 8]	0 (0) [0, 3]	< 0.01
Before treatment (after insertion of speculum)		1 (2) [0, 8]	0 (2) [0, 8]	0 (0) [0, 6]	< 0.01
During treatment [b]		4 (4) [0, 10]	4 (4) [0, 10]	2 (4) [0, 8]	< 0.01
After treatment [c]		0 (1) [0, 10]	0 (2) [0, 10]	0 (0) [0, 6]	< 0.01

NOTE. Missing values at different measures: baseline (1), speculum insertion (12), during treatment (4), and after treatment (249). The after-treatment pain assessment was added to data collection after study start- up.
Abbreviation: TA, thermal ablation.
[a] Kruskal-Wallis.
[b] Measured at 3 of 4 applications.
[c] Measured within 5 minutes after removing the speculum.

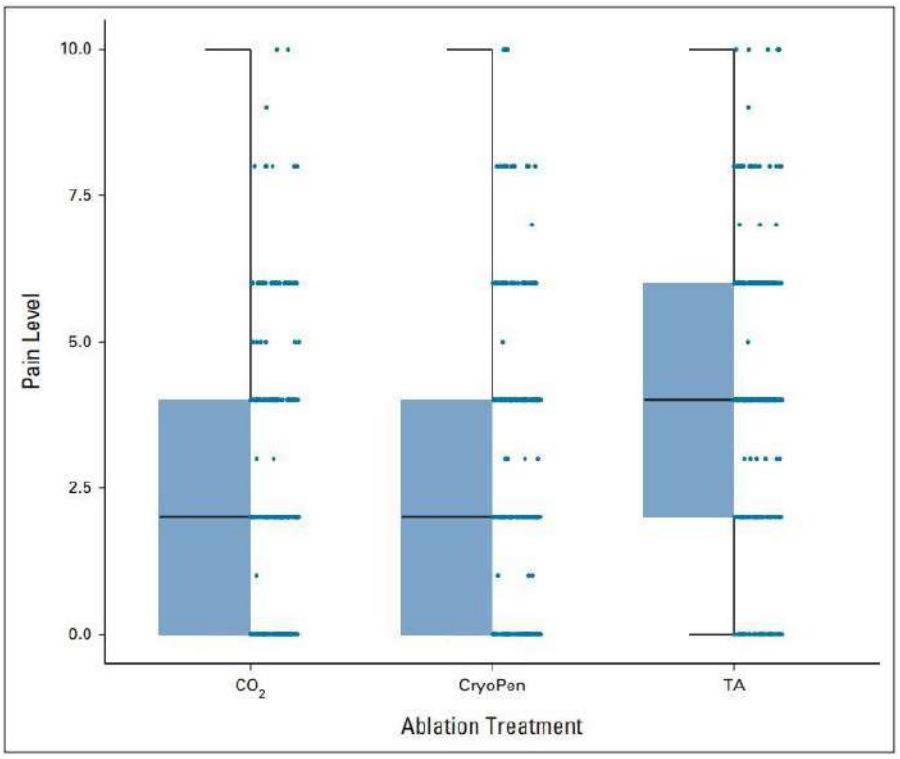

Figure 2: Median pain levels during and after three ablation treatments (range = 0-10). TA, thermal ablation. [22]

In terms of acceptability, at the 6-week and 12-month follow-up visits, 91% (n = 649/713) and 97% (648/668) of women, respectively, reported feeling very satisfied with the treatment they received (other options were somewhat satisfied, neutral, somewhat dissatisfied, and very dissatisfied). There were no differences across treatments. Women were also asked if they would recommend the treatment they received to a friend. At the 6-week visit, 94% (879/934) replied definitely yes and 4% (42/934) replied probably yes; these responses were 97% (648/668) and 1% (9/668), respectively, at the 12-month visit.[22]

In another study conducted by Banerjee D et al. (2020), they compared the safety, acceptability and efficacy of TA to that of cryotherapy to treat women positive on VIA and/or HPV detection tests. Thermal ablation was performed using the cold-coagulator (WISAP® Medical Technology GmbH) after delineating the TZ with Lugol's iodine. The 20 mm flat probe was heated to 100°C and was applied to the cervix for 40 seconds. Based on the criteria mentioned, the cold-coagulator used was C3 Cervical Cold Coagulator. The prospective randomised study was conducted at Chittaranjan National Cancer Institute (CNCI), India and the participants were recruited between February 2016 and July 2017. Participants involved were non-pregnant and previously unscreened women aged between 30 and 60 years. They were screened in rural community-based clinics with HPV test and VIA. The women positive on VIA were immediately assessed by the health workers to determine their eligibility for ablative treatment based on the following criteria:

i. Type I transformation zone (TZ)
ii. Lesion does not cover more than 75% of the cervix
iii. Lesion does not extend to the cervical canal or vagina
iv. Lesion can be covered with 25 mm cryo-tip
v. There is no suspicion of cancer

The cervical specimens were tested for 13 high-risk HPV types by the Hybrid Capture II technology. The women positive on HCII but negative on VIA were recalled at the community clinics (within four weeks of initial visit). The health workers reassessed their eligibility for ablative treatment using the same criteria mentioned earlier and were counselled by a social worker and were invited to participate in the study. Screen-positive women ineligible for ablation were referred to colposcopy and further management based on the colposcopy and biopsy reports. The randomisation to either cryotherapy or TA treatment was done using a computer-generated randomisation schedule in batches of 100 to maintain 1:1 distribution between two groups. Every participant had colposcopy by a trained gynaecologist immediately after randomisation. The colposcopist obtained a punch biopsy from any visible lesion. In absence of any visible lesion, the gynecologist took a punch biopsy from the anterior lip of cervix closest to the squamo-columnar junction. Thermal ablation was performed using the cold-coagulator (WISAP® Medical Technology GmbH) after delineating the TZ with Lugol's iodine. The 20 mm flat probe was heated to 100°C and was applied to the cervix for 40 seconds. A total of 286 from 6198 eligible women were randomised to receive either cryotherapy (N=150) or TA (N=136). The mean age was 36.1 (SD: 5.6) years in cryotherapy and 36.7 (SD: 7.3) years in TA arm. The randomised arms were well matched for age, various reproductive and socio-demographic factors at enrolment.

They found the outcomes of the screening tests, colposcopy and histopathology at baseline. In the cryotherapy arm 78.7% (118/150) were VIA-positive at baseline. Additional 32 women (21.3%) were recruited in the cryotherapy arm as they were positive on HCII test (though VIA was negative) at baseline. The corresponding figures for the TA arm were 72.8% (99/136) and 27.2% (37/136), which were not significantly different. Overall 33.6% (40/119) of the women recruited to cryotherapy arm and 43.4% (49/113) of those recruited to the TA arm were positive for high risk HPV. In both study arms, nearly half of the VIA-positive women had the acetowhite area occupying <25% of the cervix and the rest half had lesions occupying 25-50% . There was no statistically significant difference in histopathology distribution between the two arms.

In the TA arm majority of participants (61.8%) were treated with a single application of the probe. Two, three and four applications were required in 33.1%, 4.4% and 0.7% women respectively. Pain or cramp in the lower abdomen during or immediately after the procedure was the most frequent side-effect and was reported by significantly higher proportion of women in the cryotherapy arm (75.3%) compared to the TA arm (61.0%). (Refer Table 2). According to the follow up assessment done in this study, only 53.3% (80/150) of participants in the cryotherapy arm and 55.1% (75/136) in the TA arm had done the assessment. Only the women showing CIN 1+ lesions on baseline histopathology were included in the assessment of cure. The cure rates of CIN 1+ lesions for women with no evidence of disease at follow-up were 74.1% (20/27) and 81.0% (17/21) in the cryotherapy and TA arms respectively (p=0.57). The cure rates of CIN 1+ among the women positive for HPV at baseline were 100.0% (6/6) and 81.8% (9/11) in the cryotherapy and TA arms respectively. Only two women with CIN 2/3 at baseline and treated by cryotherapy underwent follow up; one had CIN 1 and the other was normal while for TA, both women with CIN 2/3 at baseline undergoing follow up after TA were free of any CIN. From this study, the author demonstrated that TA is as acceptable to the women as cryotherapy and the women have high level of satisfaction after treatment by either of the procedures. This study reveals the high rate of over-treatment in a screen and treat approach, particularly in settings with low to moderate prevalence of disease. Overall 67.1% of the women treated did not have any CIN lesion.

Table 2. Number of Applications, Side-Effects, Pain or Discomfort Levels During Treatment, Satisfaction Levels after Treatment and Screening Recommendation to Others. [25]

	Randomization group		Chi²
	Cryotherapy n (%)	Thermal ablation n (%)	*p*-value
Women assessed	150	136	
Number of applications			
One	0	84 (61.8)	
Two	150 (100.0)	45 (33.1)	
Three	0	6 (4.4)	
Four	0	1 (0.7)	
Side-effects during procedure (acceptability)			
None	35 (23.3)	53 (39.0)	0.022
Pain/cramps	113 (75.3)	83 (61.0)	
Bleeding	1 (0.7)	0 (0.0)	
Vasovagal reaction	1 (0.7)	0 (0.0)	
Intensity of pain or discomfort during/immediately after the procedure			
1-3	134 (89.3)	131 (96.3)	0.039
4-6	14 (9.3)	3 (2.2)	
7-9	2 (1.3)	2 (1.5)	
Level of satisfaction with services			
1-3	0 (0.0)	1 (0.7)	0.147
4-6	3 9 (2.0)	0 (0.0)	
7-9	147 (98.0)	135 (99.3)	
Woman to recommend the screening procedure to others			
Yes	149 (99.3)	136 (100.0)	0.34
No	1 (0.7)	0	

SAFETY

There was no retrievable evidence on the approval of the [redacted] cervical cold coagulator by the U.S. Food and Drug Administration (FDA). It is claimed that this technology obtained CE certification (Class IIa) and MDA approved (registration number: [redacted]. [19,21]

According to a study conducted by Soler M et al. (2022), during or after treatment, 282 of 1,024 women (27.5%) experienced symptoms of vasovagal syncope, including dizziness, nausea, headache, and flushing which TA only contributed the lowest rate of side effects, TA (n = 24, 2.3%) compared to CO_2 (n = 138 [13.5%]) or CryoPen (n = 120 [11.7%]). Symptoms resolved in a few minutes with minimal intervention. At the six-week follow-up visit, data were collected on intensity (mild, moderate and severe) and duration (in days) of common side effects. Watery discharge was the most common post-treatment symptom and was more severe and longer-lasting in the gas-based cryotherapy and TA group with incidence rate of 98%. Mild intensity of bleeding was observed during treatments, with a higher incidence rate being reported with TA (30%). Approximately 22% of women treated with TA experienced

malodorous discharge, a potential sign of vaginal infection. However, severe discharge was reported only by 2.4% (22) of women. Six of them were from the TA treatment group. Overall, only 4% (n=41) of women sought medical attention post-treatment, and with one exception, no serious complications were reported. (Refer to Table 3).

Table 3. Side Effects Reported at the 6-Week Follow-Up Visit.[22]

	Overall	By Treatment			
Side Effects	**All Treatments (N = 934)**	**CO_2 (n = 310)**	**CryoPen (n = 309)**	**TA (n = 315)**	***P***
Cramps					
Reported the symptom, No. (%)	302 (32.3)	105 (33.9)	100 (32.4)	97 (30.8)	0.72[a]
Intensity, No. (%)[b]					
Mild	237 (78.5)	78 (74.3)	80 (80.0)	79 (81.4)	0.37[c]
Moderate	51 (16.9)	20 (19.1)	15 (15.0)	16 (16.5)	
Severe	14 (4.6)	7 (6.7)	5 (5.0)	2 (2.1)	
Duration in days, median (IQR)	3 (6)	3 (6)	3 (6)	3 (6)	0.17[c]
Watery discharge					
Reported the symptom, No. (%)	915 (97.9)	304 (98.1)	302 (97.7)	309 (98.1)	0.73[a]
Intensity, No. (%)[b]					
Mild	457 (50.0)	136 (44.7)	156 (51.7)	165 (53.4)	<0 .01[c]
Moderate	302 (33.0)	98 (32.2)	94 (31.1)	110 (35.6)	
Severe	156 (17.1)	70 (23.0)	52 (17.2)	34 (11.0)	
Duration in days, median (IQR)	15 (12)	20 (20)	15 (10)	18 (15)	< 0.01[c]
Malodorous discharge					
Reported the symptom, No. (%)	253 (27.1)	97 (31.3)	84 (27.2)	72 (22.9)	0.06[a]
Intensity, No. (%)[b]					
Mild	181 (71.5)	66 (68)	65 (77.4)	50 (69.4)	0.45[c]
Moderate	50 (19.8)	23 (23.7)	11 (13.1)	16 (22.2)	
Severe	22 (8.7)	8 (8.2)	8 (9.5)	6 (8.3)	
Duration in days, median (IQR)	7 (8)	7 (11)	7 (7)	7 (5)	0.58[c]
Bleeding					
Reported the symptom, No. (%)	218 (23.3)	60 (19.4)	64 (20.1)	94 (29.8)	< 0.01[a]
Intensity, No. (%)[b]					
Mild	192 (88.1)	54 (90)	58 (90.6)	80 (85.1)	0.58[c]
Moderate	17 (7.8)	2 (3.3)	3 (4.7)	12 (12.8)	
Severe	9 (4.1)	4 (6.7)	3 (4.7)	2 (2.1)	
Duration in days, median (IQR)	3 (5)	2 (6)	3 (5)	5 (4)	< 0.01[c]

Abbreviation: TA, thermal ablation.
[a] Fisher's exact test.
[b] Percentages out of number of women who reported the symptom, not total number of patients.
[c] Kruskal-Wallis

Besides, the study also reported on problems with this equipment or treatment application. For TA (n = 5), the probe tip did not heat up and electrical outlets malfunctioned. Seven patients were referred to excisional treatment due to malfunctions; in the remaining cases,

the issue was resolved or a replacement unit or part was used to complete treatment. In addition, 10 women were referred to excision after incorrect placement of the treatment probe or a clinical determination that the lesion had not been properly treated (eg, the cervix did not appear frozen or the lesion was too large. Five unanticipated or serious adverse events were reported. This included a vaginal infection at the initial visit, an infection post-treatment that resulted in a three-day hospitalization (described above), a diagnosis of adenomatous carcinoma 10 months after treatment, a patient with a worsening lesion at 6 months post-treatment, and a case where the treatment probe caused a minor injury to the vaginal wall. The patients with invasive cancers had returned for non-protocol visits when they were diagnosed. The protocol and informed consent were amended to further inform patients of the risk of infection (October 22, 2018) and incorrect probe placement (July 12, 2019). However, the author did not describe in details which treatments contribute to these adverse events episode. The author concluded that all treatments were safe to patients. [22]

COST-EFFECTIVENESS

There was no evidence retrieved on cost effectiveness of [redacted] cervical cold coagulator for the treatment of cervical precancerous lesion. The WHO document on portable thermal ablation device global agreement (2022) stated that through an innovative grant from Unitaid to prevent deaths from cervical cancer by catalyzing the use of optimal screening and treatment devices, the Clinton Health Access Initiative (CHAI) and the United Nations Children's Fund (UNICEF), have engaged with manufacturers and concluded global price agreements to scale up the use of portable TA devices in low- and middle-income countries. It was also stated that there were two options applicable to public sector buyers in LMICs to procure TA devices at the access prices:

i. Place an order via Unicef Supply Division (SD)
ii. Place an order directly to supplier(s)

Estimated price of the device given was between Euro [redacted] /unit to Euro [redacted] /unit

CONCLUSION

Based on the above review, [redacted] cervical cold coagulator was shown to be effective in treatment of cervical precancerous lesion when compared to cryotherapy. It is feasible to be used within screen-and-treat programmes where patients can be screen and treat in a single visit and may contribute in achieving the Action Plan Towards The Elimination of Cervical Cancer in Malaysia 2021-2030's goals. The technology was acceptable and satisfactory to the study population with minimal side effects. There was no evidence retrieved on the cost-effectiveness of [redacted] cervical cold coagulator. The price has been negotiated at global level. Nevertheless, financial implication should be considered for its implementation.

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