REVIEW ARTICLE

Potential of trichloroacetic acid (TCA) for cervical precancerous lesions treatment in Indonesia

I Gde Sastra Winata,* Musa Taufiq
Department of Obstetrics and Gynaecology, Faculty of Medicine, Udayana University/Sanglah Hospital, Bali, Indonesia

ABSTRACT

Cervical cancer becomes one of the most prevalent disease in female worldwide. Human papillomavirus (HPV) is main etiology of cervical cancer, thus this disease is preventable. Before progressed into invasive cervical cancer, cervical precancerous lesions developed and classified into 3 stages: CIN1 (LSIL), CIN2, and CIN3 (CIN2+ also referred as HSIL). World Health Organization (WHO) arranged 'screen-and-treat' programme to treat cervical precancerous lesions immediately before it progressed to cancer. However, a simple and safe modality with high efficacy is necessary to accommodate this strategy. Trichloroacetic acid (TCA) has those advantages and some research suggested high efficacy to treat cervical precancerous lesions with simple, safe, and cost-effective. TCA has potential to become effective treatment for cervical precancerous lesions in the future.

Keywords: Cervical cancer; cervical precancerous lesions; trichloroacetic acid

ABSTRAK

Kanker serviks merupakan salah satu penyakit dengan prevalensi tinggi pada wanita di seluruh dunia. Human papillomavirus (HPV) adalah penyebab utama kanker serviks. Oleh karena itu sebenarnya penyakit ini dapat dicegah. Sebelum menjadi kanker serviks invasif, terjadi perkembangan lesi prakanker serviks yang diklasifikasikan menjadi 3 stadium: CIN1 (LSIL), CIN2, dan CIN3 (CIN2+ juga disebut sebagai HSIL). Organisasi Kesehatan Dunia (WHO) mengatur program 'screen-and-treat' untuk mengobati lesi prakanker serviks segera sebelum berkembang menjadi kanker. Diperlukan modalitas sederhana dan aman dengan kemanjuran tinggi untuk mengakomodasi strategi ini. Asam trikloroasetat (TCA) memiliki keunggulan tersebut dan beberapa penelitian mengungkap efikasi tinggi pengobatan lesi prakanker serviks dengan sederhana, aman, dan hemat biaya. TCA berpotensi menjadi pengobatan yang efektif untuk lesi prakanker serviks di masa depan.

Kata kunci: Kanker serviks; lesi prekanker serviks; asam trikloroasetat

***Correspondence:** I Gde Sastra Winata, Department of Obstetrics and Gynaecology, Faculty of Medicine, Udayana University/Sanglah Hospital, Bali, Indonesia. E-mail: dr.sastrawinata@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I12022.48-51
● Maj Obs Gin. 2022;30:48-51 ● Received 8 Sep 2021 ● Revised 28 Dec 2021 ● Accepted 14 Jan 2022 ● Published 1 Apr 2022
● Open access under CC-BY-NC-SA license ● Available at https://e-journal.unair.ac.id/MOG/

INTRODUCTION

Cervical cancer is one of the most common cancer in women worldwide, yet preventable. The incidence of cervical cancer worldwide is more than 528 000 cases with estimated mortality rate of 266 000 death. In Indonesia, prevalence of cervical cancer is 98 692 cases with incidence rate of 90-100 cases in 100 000 population each year.[1] Those numbers are estimated to rise in the next 10 years by 25% and become a significant health problem if appropriate preventive and treatment programs are not taken.[2]

Human papillomavirus (HPV) contributes to 99.7% of all cervical cancer.[3] HPV16 and 18 are the most virulent high-risk types which contribute to 70% among invasive cervical cancer and only 10% of cervical precancerous lesions may develop to invasive cervical cancer.[4,5] Cervical intraepithelial neoplasia (CIN) is precancerous lesions which classified into 3 stages: CIN1, CIN2, and CIN 3. There is higher risk of CIN2+ (CIN2 or above) to develop into cervical cancer if the treatment is unadequate.[6]

World Health Organization (WHO) recommends 'screen-and-treat' strategy to cope with cervical precancerous lesions, especially in developing countries where health care resources and costs are limited. Screen-and treat approach is a method which treatment decision provided immediately after a positive screening test result. The screening tests for cervical cancer vary from visual inspection with acetic acid (VIA), cytology (Pap smear), to a genetic-based test such as HPV test.[6,7] The treatments for positive screening test include ablative and excision procedure. Ablative procedures for precancerous lesions include cryosurgery, mono-polar diathermy, CO2 laser vaporization, or topical application of chemical substances.[7] However, there is no clear evidence that any of surgical procedures are more preferable to treat cervical precancerous lesions.[8]

Trichloroacetic acid (TCA) is widely used as treatment for condylomata acuminata and seems to be a promising option for cervical precancerous lesions treatment because it is simple, cost-effective, can be easily tolerated, zero side effects in systemic, and pregnancy safe.[9–11] TCA using caustic agents to destruct precancerous tissues, preventing it to progress into cancer. It can be used as therapy immediately to patient with positive IVA test. A research stated that after 8 weeks there is high HPV clearance rate and regression of 85% TCA treatment in high-grade CIN.[12]

CERVICAL PRECANCEROUS LESIONS

Cervical lesions associated with HPV infection

HPV infection is the main cause and critical precursor in cervical cancer progress. HPV is one of the most well known sexually transmitted infection which affects basal layer of cervical epithelium in the transformation zone containing HPV-specific receptors. The activation and duplication of HPV in converting epithelium cells affect changes cellularly which commonly in the lower third of the epithelium, distinguished by perinuclear cytoplasmic clearing koilocytotic, nuclear enlargement, hyperchromasia, and atypia. About 90% of the HPV infections eliminated by natural immunity within 12-24 months along with CIN1 (low-grade squamous intraepithelial lesions) changes.[13,14] Lots of studies concluded that steady infection with high-risk HPV (oncogenic type) is the predominant riskifactor for CIN that may ranges from CIN-1 to CIN-3 and invasive cervical cancer.[15–17] A study named VIVIANE study confirmed that HPV-33 and HPV-16 were related with the highest risk of the development of CIN, followed by HPV-18, HPV-31, and HPV-45.[16]

Natural history and classification of cervical precancerous lesions

Each grade of CIN lesions has different natural history. About 70-80% of low-grade squamous intraepithelial lesion (LSIL/CIN1) regress spontaneously without intervention and become undetectable.[18,19] This data suggests that CIN1 is more about a state of infection than a stage of disease development. Successful CIN1 detection does not represent disease progression and inability to detect might be correlated with viral clearance.[16]

There are well-known high-grade dysplasia which are CIN2 and CIN3 or high-grade squamous intraepithelial lesion (HSIL). Although classified as HSIL, CIN2 has better prognosis which less possibility to progress into cancer. CIN2 has two different ways either regression or progression. The annual regression rate of CIN2 is approximately from 15% to 23%, with up to 55% regressing by 4-6 years. Otherwise, about 2% of CIN2 lesions progress to CIN3 within the same period.[19,20] On the other hand, CIN3 is seen as potential true precancer which able to progress to invasive cervical cancer at rate of 0.2-4% within 12 months. Furthermore, it has 30% of probability to progress to invasive cervical cancer in over 30 years if left untreated. Treated CIN3 can become invasive in about 1% cases.[15,19,21,22]

CC BY NC SA

TRICHLOROACETIC ACID 80-90% SOLUTION FOR CERVICAL PRECANCEROUS LESIONS

Mechanism of action

Trichloroacetic acid is classified as keratolytic agents and widely used for treatment of condylomata acuminata.[10,23] A research showed general mechanism of TCA which involved negative-charged trichloro-acetate ions. Those ions disrupt electrostatic interactions that stabilize native conformation of proteins which resulting in protein unfolding and denaturation.[24] This mechanism leads to skin and mucosa disintegration which characterized by white-changing color of ecto-cervix.[12]

Short-term efficacy of TCA for cervical precancerous lesions

A study conducted in Austria, involved 241 patients with cervical precancerous lesions were treated with a single 85% TCA treatment as first-line therapy and observed after 8 weeks. Out of those 241 patients, there were 179 patients with HSIL (CIN2+) and 62 patients with LSIL (CIN1). The histologic regression rate of patients with HSIL after 8 weeks was 87.7% (95% confidence interval [CI] 82.0-92.1) and the remission rate was 80.3% (95% CI 73.3-85.5). Meanwhile the remission rate of LSIL patients was 82.3% (95% CI 70.5-90.8). Clearance rate of HPV16 and HPV18 were 73.5% (95% CI 62.5-81.3) and 75.0% (95% CI 46.2-95.0), respectively. There were no reported side effects during management and monitoring. This study concluded that high regression, high remission, and high HPV clearance rate after 8 weeks of follow-up were obtained.[12]

TCA vs. Spray monopolar diathermy

A study conducted by Darwish and Zahran (2013), compared the efficacy, tolerability, and safety of 70% TCA versus monopolar spray coagulation for persistent benign cervical lesions treatment. The results were both of 70% TCA that applied topically and monopolar spray coagulation obtained remarkable efficacy, high accomplishment rates, and very little complications. However, 70% TCA has higher tolerability and safety. Moreover, 70% TCA is simple and can be used widely by gynecologists with limited experience. It is recommended for ectopic cervical lesions or cervicitis that are nonspecific, but not for hypertrophic lesion, such as polyps.[7]

TCA vs. Cryotherapy

Cryotherapy becomes treatment of choice to destruct cervical precancerous lesions. However, this procedure has limited access and instrument. TCA has potential to become alternative treatment for precancerous lesions. A research conducted to measure the effectiveness of 85% TCA versus cryotherapy to treat patient with positive IVA result. The conclusion of this study was there is not statistically difference between 85% TCA and cryotherapy.

CONCLUSION

Some studies suggested 70-85% TCA has potential to support 'screen-and-treat' program of the WHO to eradicate cervical precancerous lesions, thus mortality and morbidity risk of cervical cancer could be decreased in the future. Moreover, TCA is simple, well-tolerated, minimal complications, and side effects with high efficacy as available treatment for precancerous lesions.

REFERENCES

1. International Agency for Research on Cancer. Cervical cancer estimated indidence, mortality and prevelence worldwide in 2012. Ministry of Health, Republic of Indonesia. 2017.
2. Andrijono. Sinopsis kanker ginekologi [Synopsis of gynecological cancer]. 4th ed. Jakarta: Balai Penerbit FK UI; 2013. p. 59–129.
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3): 209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.
4. Centers for Disease Control and Prevention. Basic information about HPV and cancer [Internet]. CDC. 2020 [cited 2021 Sep 27]. Available from: https://www.cdc.gov/cancer/hpv/basic_info/index.htm
5. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem and its associated goals and targets for the period 2020 – 2030. Vol. 2, United Nations General Assembly. 2021. Available from: http://apps.who.int/bookorders.
6. World Health Organization. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. World Health Organization; 2013.
7. Darwish AM, Zahran KM. Trichloroacetic acid application versus spray monopolar diathermy for

treating benign cervical lesions: a randomized controlled clinical trial. J Low Genit Tract Dis. 2013(3):248-54. doi: 10.1097/LGT.0b013e31827527e3. PMID: 23733165.
8. Fader AN. Surgery in cervical cancer. N Engl J Med. 2018;379(20):1955-7. doi: 10.1056/NEJMe1814034. Epub 2018 Oct 31. PMID: 30379600; PMCID: PMC6989030.
9. Wakeham K, Kavanagh K. The burden of HPV-associated anogenital cancers. Curr Oncol Rep. 2014;16(9):402. doi: 10.1007/s11912-014-0402-4. PMID: 25118645.
10. Ratnasari DT. Kondiloma akuminata. J Ilm Kedokt Wijaya Kusuma. 2018;5(2). doi: 10.30742/jikw.v5i2.336
11. Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob Health. 2021;9(2):e161-e169. doi: 10.1016/S2214-109X(20)30459-9. Epub 2020 Nov 16. Erratum in: Lancet Glob Health. 2021 Feb;9(2):e119. PMID: 33212031; PMCID: PMC7815633.
12. Geisler S, Speiser S, Speiser L, et al. Short-term efficacy of trichloroacetic acid in the treatment of cervical intraepithelial neoplasia. Obstet Gynecol. 2016;127(2):353-9. doi: 10.1097/AOG.0000000000001244. PMID: 26942365.
13. Basu P, Taghavi K, Hu S-Y, et al. Management of cervical premalignant lesions. Curr Probl Cancer 2018;42(2):129–36. doi: 10.1016/j.currproblcancer.2018.01.010
14. Liu Y, Sigel K, Gaisa MM. Human papillomavirus genotypes predict progression of anal low-grade squamous intraepithelial lesions. J Infect Dis. 2018;218(11):1746-52. doi: 10.1093/infdis/ jiy463. PMID: 30053247; PMCID: PMC6195660.
15. Kombe Kombe AJ, Li B, Zahid A, et al. Epidemiology and burden of human papillomavirus and related diseases, molecular pathogenesis, and vaccine evaluation. Front Public Health. 2021 ;8:552028. doi: 10.3389/fpubh.2020.552028. PMID: 3355 3082; PMCID: PMC7855977.
16. Skinner SR, Wheeler CM, Romanowski B, et al. Progression of HPV infection to detectable cervical lesions or clearance in adult women: Analysis of the control arm of the VIVIANE study. Int J Cancer. 2016;138(10):2428-38. doi: 10.1002/ijc.29971. PMID: 26685704; PMCID: PMC4787275.
17. Mirabello L, Clarke MA, Nelson CW, et al. The intersection of HPV epidemiology, genomics and mechanistic studies of HPV-mediated carcinogenesis. Viruses. 2018 Feb 13;10(2):80. doi: 10.3390/v10020080. PMID: 29438321; PMCID: PMC5850387.
18. Bowden SJ, Kalliala I, Veroniki AA, et al. The use of human papillomavirus DNA methylation in cervical intraepithelial neoplasia: A systematic review and meta-analysis. EBioMedicine. 2019;50:246-259. doi: 10.1016/j.ebiom.2019.10.053. Epub 2019 Nov 12. PMID: 31732479; PMC ID: PMC6921230.
19. Koeneman MM, van Lint FHM, van Kuijk SMJ, et al. A prediction model for spontaneous regression of cervical intraepithelial neoplasia grade 2, based on simple clinical parameters. Hum Pathol. 2017;59:62-69. doi: 10.1016/j.humpath.2016.09.012. Epub 2016 Sep 30. PMID: 27697590.
20. Rositch AF, Burke AE, Viscidi RP, et al. Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. Cancer Res. 2012;72(23):6183-90. doi: 10.1158/0008-5472.CAN-12-2635. Epub 2012 Sep 27. PMID: 23019223; PMCID: PMC3513486.
21. Gravitt PE, Rositch AF, et al. A cohort effect of the sexual revolution may be masking an increase in human papillomavirus detection at menopause in the United States. J Infect Dis. 2013;207(2):272–80. doi: 10.1093/infdis/jis660
22. Demarco M, Lorey TS, Fetterman B, et al. Risks of CIN 2+, CIN 3+, and cancer by cytology and human papillomavirus status: The foundation of risk-based cervical screening guidelines. J Low Genit Tract Dis. 2017;21(4):261-267. doi: 10.1097/LGT.0000000000000343. PMID: 28953116; PMCID: PMC5625966.
23. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol. 2012;5(6):25-36. PMID: 22768354; PMCID: PMC3390234.
24. Fein LA, Marbin SJ. Condylomata acuminata of the neovagina in a transgender woman treated with trichloroacetic acid. Int J STD AIDS. 20201;31(10) :1011–3. doi: 10.1177/0956462420937161