

Research Article

Efficacy of Trichloroacetic Acid (TCA) Compared to Cryotherapy in Treating Patients with Positive IVA Result

Efikasi Trichloroacetic Acid (TCA) Dibandingkan Krioterapi sebagai Terapi Pasien dengan IVA Positif

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Abstract

Objective: To investigate the effectiveness TCA 85% compared to cryotherapy to treat patients with positive IVA result.

Methods: This is a non-inferiority randomized controlled trial study. Patients with positive VIA result referred to Jatinegara Primary Health Center were included in this study. Eligible samples were then treated with either TCA 85% or cryotherapy. The treatment was determined using a random block sampling method. Samples were then followed up 3 months after treatment in order to determine VIA result conversion.

Results: Thirty-six patients were treated with TCA 85% and 36 others were treated with cryotherapy. 35 (97,2%) patients treated with TCA 85% converted to negative VIA, whereas all of the patients that were treated with cryotherapy converted to negative VIA. Bivariate analysis fisher's exact test was then conducted with a result P-value of 1.00 ($p > 0,05$).

Conclusions: There was no statistically significant difference of result between TCA 85% and cryotherapy for treating patients with positive VIA result.

Keywords: cervical cancer, cryotherapy, TCA 85%, VIA test.

Abstrak

Tujuan: Mengetahui efikasi TCA 85% pada tatalaksana IVA positif dibandingkan dengan krioterapi.

Metode: Penelitian ini merupakan penelitian randomized control trial menggunakan metode non-inferiority study. Subyek penelitian ini merupakan pasien dengan hasil IVA positif yang dirujuk ke Puskesmas Kecamatan Jatinegara, Jakarta Timur. Tatalaksana yang diberikan ditentukan menggunakan metode random block sampling. Subyek diikuti selama 3 bulan setelah tindakan untuk menentukan hasil konversi pemeriksaan IVA.

Hasil: Sebanyak 36 subjek diterapi dengan TCA 85% dan 36 lainnya diterapi dengan krioterapi. Sebanyak 35 (97,2%) pasien yang ditatalaksana dengan TCA 85% mengalami konversi menjadi IVA negatif pada follow-up bulan ke-3, sedangkan seluruh pasien yang ditatalaksana dengan krioterapi menjadi konversi menjadi IVA negatif. Dilakukan analisis bivariat fisher's exact test dan didapatkan nilai p sebesar 1,00 ($p > 0,05$).

Kesimpulan: Tidak ada perbedaan bermakna dari efikasi penggunaan TCA 85 % dibandingkan dengan krioterapi pada terapi IVA positif.

Kata kunci: kanker serviks, krioterapi, pemeriksaan IVA, TCA 85%.

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INTRODUCTION

Cervical cancer is the 4th most prevalent cancers in the world. In 2012 the incidence of cervical cancer exceeds 528.000 with an estimated mortality rate of 266.000 death. In Indonesia, the incidence of cervical cancer in 2018 in 90-100 case per 100.000 population each year.¹ The prevalence of cervical cancer in Indonesia is 98.692 case (0.8 cases per 1000 population). Therefore, means to prevent and cure cervical cancer is urgently needed, as it creates a significant health problem specifically in Indonesia.^{2,3}

There are various steps to prevent cervical cancer. The first step is primary prevention by eliminating contact with a carcinogen to prevent initiation and promotion in the carcinogenesis process. Promotion and education are utmost important in this step. The second step is secondary prevention with screening and early detection of cervical cancer. There are various methods for cervical screening, two of which is Pap smear and Visual Inspection with Acetic Acid (VIA).¹ Pap smear (Sensitivity 44-78%, Specificity 91-107%) is generally better than VIA (Sensitivity 37-97%, Specificity 49-98%) but VIA is recommended by World Health Organization (WHO) especially in developing countries such as Indonesia as it is more cost-effective and easy to perform.

Once a patient has been diagnosed with a positive VIA test, medical treatment should be immediately done to eliminate precancerous tissues, preventing it to develop becoming cancer. The treatment of choice is cryotherapy, however, its instrument (CO₂ and NO₂ gas) has limited access in rural places. Trichloroacetic Acid (TCA) is proposed as a potential alternative

therapy for patients with positive VIA result. TCA suppresses keratinocyte proliferation, collagen synthesis, protein synthesis, and fibroblast metalloproteinase activity. It has previously been shown that topical TCA 85% has good efficacy in treating grade I-III precancerous lesion.⁴

METHODS

This is a non-inferiority randomized controlled trial study to determine the efficacy of TCA compared to cryotherapy as a treatment for positive VIA result. Samples are patients with positive VIA result referred to VIA polyclinic Jatinegara Primary Healthcare, East Jakarta from August 2017 until December 2018.

The minimal required sample is calculated using a comparison of 2 proportion formula. The minimal sample is 36 patient per group. Random block sampling method was selected. Patients were then classified into 2 groups, which are treated by either one of TCA or Cryotherapy.

Collected data was then analyzed using SPSS for Mac Ver. 20. Age, medical history, obstetric history, birth control history, the side effect was then analyzed descriptively. Cryotherapy and TCA 85% treatment result was statistically analyzed using Fisher's Exact Test. This study has a 5% error bound and 95% confidence interval limit.

RESULTS

A total of 107 subjects met the inclusion criteria of this study. VIA test was then re-performed in these subjects. 35 subjects were then excluded as it turns out that they have a negative VIA result. A total of 72 subjects were further analyzed.

Table 1. Sociodemographic and Clinical Characteristic of Positive VIA Result Patient

Characteristic	TCA (n = 36)	Cryotherapy (n = 36)	Total (N=72)	P-value
Age	32.5 (20 – 47)	32 (19–48)	32 (19-48)	0.988
20-29	12 (33.3)	15 (41.6)	27 (40.3)	
30-39	15 (41.6)	11 (30.5)	26 (33.3)	
40-49	7 (19.4)	9 (25)	16 (22.2)	
>49	2 (5.5)	1 (2.7)	3 (4.2)	
Marriage				0.492
Not Married	0	5 (13.8)	5 (6.9)	
1 Time	36 (100)	29 (80.5)	65 (90.2)	
2 Times	0	1 (2.7)	1(1.4)	
3 Times	0	1 (2.7)	1(1.4)	
First Sexual Contact				0.343
< 20	28 (77.8)	4 (11.1)	12 (16.7)	
20-29	0	30 (83.3)	58 (80.0)	
30 – 39	0	1 (2.7)	1 (1.4)	
>30		1 (2.7)	1 (1.4)	

Obstetric History				<0.001
Nullipara	3 (8.3)	13 (36.1)	16 (22.2)	
Primipara	16 (44.1)	13 (36.1)	29 (40.27)	
Multipara	17 (47.2)	10 (27.7)	27 (37.5)	
Abortion History				1.000
0	32 (88.8)	30 (83.3)	62 (86.1)	
1	2 (5.5)	2 (5.5)	4 (5.5)	
>1	2 (5.5)	4 (11.1)	6 (8.3)	
Cervicitis Status				0.326
Yes	25 (69.4)	21 (58.3)	46 (63.8)	
No	11 (30.6)	15 (41.7)	26 (36.2)	
Pap smear History				1.000
Yes	4 (11.1)	2 (5.5)	6 (8.3)	
No	32 (88.8)	34 (94.4)	66 (91.6)	
Contraception History				0.152
Injection	10 (27.8)	11 (30.6)	21 (29.1)	
Combination Pill	3 (8.3)	0	3 (4.2)	
IUD	5 (13.8)	6 (16.7)	11 (15.3)	
Sterile	2 (5.6)	0	2 (2.8)	
No	16 (44.4)	19 (52.7)	35 (48.6)	
Side Effect				0.128
Dizziness	0	4 (11.1)	4 (11.1)	
Nausea	0	13 (36.1)	13 (18.1)	
Abdominal Cramp	0	7 (19.4)	7 (9.7)	
Pain	21 (58.3)	4 (11.1)	25 (34.7)	
None	15 (41.7)	8 (22.2)	23 (39.2)	

Both TCA and Cryotherapy successfully converted VIA result in 3 months follow up. There are 2,78% patients with positive VIA after TCA

treatment, whereas all patients with cryotherapy treatment successfully convert to negative VIA. Fisher's Exact Test was then performed.

Table 2. Comparison of TCA 85% and Cryotherapy to Therapy Success in Three Months Follow up

Therapy		3 Months VIA follow up		Total	P-value
		Negative	Positive		
TCA 85%		35 (97.2)	1 (2.78)	36	1.00
	Cryotherapy	36 (100)	0 (0)		
Total		71	1	72	

Among patients treated with TCA 85%, 41.7% of subjects underwent reapplication of TCA 85% during 1st month follow up due to thick lesion.

In addition, 30.5% of patients had complaints of mild pain, which can be tolerated by patients without the administration of analgesics.

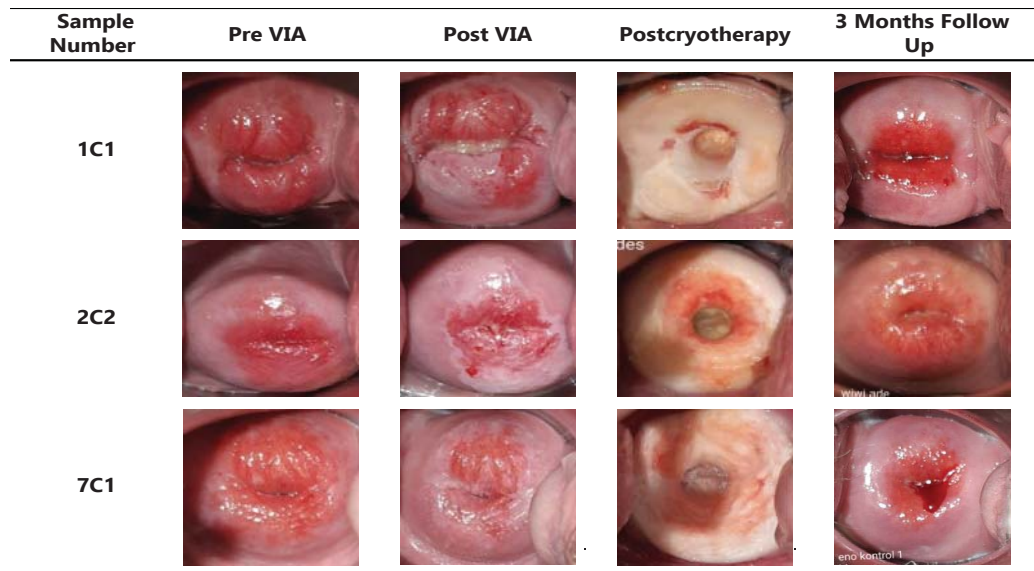


Figure 1. VIA Positive Patients treated with Cryotherapy

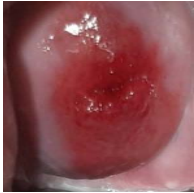
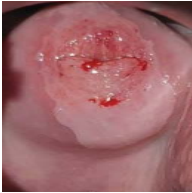
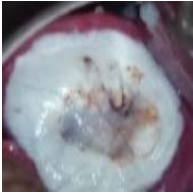
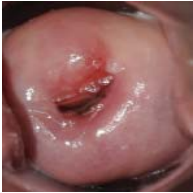








Sample Number	Pre VIA	Post VIA	Post TCA 85%	3 Months Follow Up
13T2				
15T2				
16T1				

Figure 2. VIA Positive Patients Treated with TCA 85%





Sample Number	Pre VIA	Post VIA	Post TCA 85%	3 Months Follow Up Result
12T2				

Figure 3. Three Months Unconverted Positive VIA Follow Up Result

DISCUSSION

TCA is a potential treatment for patients with positive VIA result, as TCA 85% is cost-effective, easily obtained, does not require special tools, does not have systemic side effect, and safe to be used during pregnancy. TCA was also proved to be effective in treating other conditions such as condyloma acuminata, vaginal intraepithelial neoplasia, and anal intraepithelial neoplasia.^{5,6} One study showed that TCA was used to treat anal intraepithelial neoplasia in 98 subjects with high-grade squamous intraepithelial lesions (HSIL).⁷ In this study, the remission or regression rate to low-grade squamous intraepithelial lesions (LSIL) was 79%.⁷ TCA was given in patients with condyloma acuminata 1 time per week for 3 consecutive weeks. The cure rate was 73.4%.⁸

TCA is effective to treat patients with positive VIA result. The application of TCA 85% has a remission rate of 80.3% for HSIL and 82.3% for LSIL in 3 months follow up. Subjects in study has

a similar sociodemographic profile to this study, specifically with the median age of 31 years old and same period of follow up. However, there are some differences as the classification of patients into HSIL and LSIL using biopsy or pap smear (if the patient refuses biopsy). In this study, 97.2% subject successfully converted to negative VIA in 3 months follow up. However, this data was not statistically significant ($p=1.00$)⁴

TCA with a concentration of 85% had also been showing to be effective for the treatment of HPV infected patients without dysplasia. The cure rate was 81.6%. Boothby, et al also studied a different concentration of TCA, that is 50% TCA. The result was there was no significant difference in the application of 50% TCA compared to placebo.⁹ The result of posthoc power analysis in this study is 16.9%. Lower than the estimation before this study began at 80%. This is because of the lower proportion of event than predicted. Therefore, further research is needed with more accurate sample number based on event incidence in this

study.

TCA is tolerated by the patient with a mean VAS score of 3. As a comparison, VAS score of the insertion of IV line is 7.⁶ Patients treated with cryotherapy needed to delay the decision to initiate the therapy because of longer abstinence period in cryotherapy, vaginal discharge for 1 month is uncomfortable to the patient, cryotherapy also requires partner's informed consent.¹⁰

CONCLUSION

Based on this study there was no significant difference between the application of TCA 85% compared with cryotherapy for the therapy of patients with positive VIA result. TCA 85% can be used for the therapy for positive VIA patients. In conclusion, there were no statistically significant difference of result between TCA 85% and cryotherapy for treating patients with positive VIA result.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest in this study.

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