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Efficacy of inosine pranobex as an adjuvant oral therapy in anogenital warts

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Abstract

Background: Human papillomavirus (HPV) causes the most prevalent sexually transmitted infection and is an important etiological factor in genital cancer. HPV infection manifests in broad spectrum, from genital warts to cervical intraepithelial neoplasia and cancers. Genital warts remain a frequent problem in primary care. Current modalities provide unsatisfactory result in curing genital warts completely. To date, there are many convincing studies encouraging oral inosine pranobex as an adjuvant therapy to improve post-conventional therapy cure-rate.

Aim: To assess the efficacy of inosine pranobex as an adjuvant oral therapy in anogenital warts.

Methods: Literature search was performed using Pubmed, Ebsco and Science Direct database. Inclusion criteria were human subjects, randomized controlled trial on patients with genital warts, and inosine pranobex as adjuvant therapy. The studies were appraised and findings were formulated to find the best evidence for collating recommendations in treating genital warts patients.

Results: There were three articles related to the clinical questions. All articles were found to be valid after selection based on exclusion and inclusion criteria.

Discussion: All articles recommended the addition of oral inosine pranobex as an adjuvant therapy in treating patient with genital warts. Based on the critical appraisal performed previously, addition of oral inosine pranobex may minimize conventional therapy failure.

Conclusion: Based on the best evidence available, we would recommend the addition of oral inosine pranobex as adjuvant for treating genital warts, except in special conditions, such as for patients with financial problem as this therapy was not covered by national health insurance.

Keywords: *effectiveness, genital warts, inosine pranobex*

Background

Human papillomavirus (HPV) are a group of DNA viruses that infect human epithelial cells. It causes the most prevalent sexually-transmitted infection and is an important etiological factor in the development of genital cancer. Up to 79 percent of sexually-active women have a genital HPV infection during their lifetime. The peak prevalence occurs in their early 20s.¹ HPV infection may manifest in broad spectrum, from genital warts to cervical intraepithelial neoplasia and cervical and other type of cancers. It depends on the types of HPV and the viral loads.²

Genital warts caused by HPV infection remains a frequent problem in primary care. There are many modalities to cure genital warts, such as chemical treatments and ablative treatments. None of them gives satisfactory result in totally curing genital warts. To date, there are many convincing studies, which encourage oral inosine pranobex as an adjuvant treatment to improve post-conventional therapy cure-rate.^{2,3} Inosine pranobex could induce differentiation of T-cell and enhance lymphoproliferative responses against virus.⁴

Case Illustration

A 23-year-old female was referred to our division due to vulvar warts. Physical examination showed

multiple vulvar warts and cervical condyloma acuminata. Her vulvar warts and cervical condyloma acuminata had been removed by the doctor. In the doctor's clinical experience, genital warts tend to recur frequently.

The initial treatment plan was a combination of oral immunomodulatory drug, such as inosine pranobex, and conventional therapy to achieve total remission and lower the recurrence rate of the vulvar warts and cervical condyloma acuminata. Medical literature search was performed for the evidence on the efficacy of available immunomodulator (inosine pranobex) to improve the cure rate of condyloma acuminata.

Clinical question

In developing the research question, we use PICO approach, as explained databases, such as Pubmed, Ebsco (including Medline Complete, Cochrane Central Registry of Controlled Trial, and Cochrane Database of Systematic Review) and Science Direct. Literature search was conducted on November 11th, 2016 using condyloma acuminata or genital warts and inosine pranobex or inosiplex or Isoprinosine© as keywords (**Table 1**).

Selection

below.

Based on the case illustrated above, the clinical question formulated will be: in a patient with condyloma acuminata, can inosine pranobex improve the cure rate of warts?

P : Patient with condyloma acuminata

I : Conventional therapy and inosine pranobex

C : Conventional therapy

O : Warts totally cured

Type of clinical question: therapy

Methods

Literature search procedures were performed using several leading

Twenty-three titles were obtained; the selection of literature was conducted based on title/abstract and elimination of duplicates. Further selection was conducted based on inclusion and exclusion criteria as shown in the flowchart (**Appendix 1**). Three articles appropriate for the issue were obtained.

Critical Appraisal

The articles were independently appraised, using standardized criteria. Disagreement between researchers was resolved through a discussion.

Results

Using our searching strategy, three RCT articles were included (Georgala *et al.*;⁵ Davidson-Parker J, *et al.*;⁶ and Mohanty KC, *et al.*⁷). Descriptions of PICO from each article are listed in **Table 2**. Validity, importance, and relevance comparison are explained in **Table 2**.

Discussion

HPV causes the most prevalent sexually-transmitted infection worldwide and is responsible as an etiological factor of cancer development.¹ In our center (Cipto Mangunkusumo Hospital), the prevalence has been increasing in the last three years (20.29%, 24.05%, and 35.16% in 2012, 2013, and 2014, respectively).⁸

There are numerous treatment modalities for genital warts, such as chemical treatments and ablative treatments.¹ Yet despite this fact, all modalities are met with a high recurrence rate.⁹ To date, although conventional therapies for genital warts can remove most warts, no single treatment modality is more superior to the others, both in terms of completely curing the warts and preventing its recurrence.³

Recently, inosine pranobex has been introduced as an orally-consumed non-specific immunostimulant. Inosine pranobex is a synthetic purine derivative with immunomodulatory and antiviral properties.² Inosine pranobex was studied in several diseases including genital warts and other viral infection.⁸ A study conducted by Petrova, *et al.* (2010)³ demonstrated a significant pharmacological activity in subclinical HPV infection of the vulva and should be considered as an alternative treatment for the condition.⁹

Unfortunately, there are not many prospective studies on inosine pranobex treatment in HPV infection which manifests as genital warts. Based on the previous evidence, inosine pranobex may give promising result in improving the cure rate and lowering the recurrence rate of HPV-related genital wart. We found three randomized controlled trials which were conducted to assess whether inosine pranobex improved the efficacy the conventional treatments in patients with genital wart.

Previous study from Davidson-Parker, *et al.* (1988)⁶ showed that there was a significant effect in eradicating the warts by the end of the study period ($p < 0.05$). This study also showed that there was a significant reduction in the extent of the

anogenital and genital warts at the end of the study compared with the classifications on entry which was seen only in patients receiving inosine

pranobex ($p=0.05$). The weakness of this study was a high percentage of loss-to-follow up patients ($>20\%$).⁶

Table 1. Description of PICO from Therapeutic Studies

Authors	Patients	Intervention	Comparison	Outcome
Georgala, <i>et al.</i> ¹	Patients with genital warts who had been resistant to conventional therapies	Oral inosiplex 50mg/kgBW daily for 12 weeks	Placebo	Complete response was defined as the total clearance of cervical lesions.
Davidson-Paker J, <i>et al.</i> ²	Patients who had anogenital warts and history of genital warts in at least one year	Oral inosine pranobex 1 gr, 3 times daily, for 4 weeks	Placebo (lactose)	Clinical improvement (reduction in both the number of warts present and the extent of the lesions)
Mohanty, <i>et al.</i> ³	Patients with anogenital warts	Oral Inosine pranobex treatment 1 gr, 3 times daily with conventional therapy (topical 25% podophyllin, if no response occurred, patients received cryotherapy or electrocautery)	Conventional therapy (topical 25% podophyllin, if no response occurred, patients received cryotherapy or electrocautery) without oral Inosine pranobex	Clinical cure was defined as the disappearance of the warts and the return of skin texture to normal.

*mg: milligram, kg: kilogram, BW: body weight, gr: gram

Table 2. Critical Appraisal for Therapeutic Studies

	Georgala, et al. (2006) ⁵	Davidson-Parker J, et al. (1988) ⁶	Mohanty KC, et al. (1986) ⁷
VALIDITY			
Was the assignment of patients to treatments randomised? And was the randomisation list concealed?	Yes	Yes	Yes
Were all patients who entered the trial accounted for at its conclusion? – and were they analysed in the groups to which they were randomised?	Yes	Yes	Yes
Were patients and clinicians kept blind to which treatment was being received?	Yes	Yes	Yes
Aside from the experimental treatment, were the groups treated equally?	Yes	Yes	Yes
Were the groups similar at the start of the trial?	Yes	Yes	Yes
IMPORTANCE			
RR	0.76	0.38	0.047
CER	1	0.44	0.56
EER	0.76	0.17	0.027
RRR	0,23	0,625	0,95
ARR	0.23 (0.03–0.43)	0.28 (0.21-0.35)	0.54 (0.42–0.66)
NNT	4.3 (2.3–33) → 5 (rounding)	3.6 (2.9-4.8) → 4 (rounding)	1.86 (1.5–2.4) → 2 (rounding)
APPLICABILITY			
Is your patient so different from those in the trial that its results can't help you?		No	
How great would the potential benefit of therapy actually be for your individual patient? f= 0.35 (based on prevalence in our centre in 2014)	NNT/F =12.2	NNT/F= 10.3	NNT/F= 5.3
Do your patient and you have a clear assessment of their values and preferences?		Yes	
Are they met by this regimen and its consequences?	Yes, they are. If the patients can afford the treatment (inosine pranobex is not covered by public insurance)		

*RR: Risk Ratio, CER: Control event rate, EER: Experimental event rate, RRR: Relative risk reduction, ARR: Absolute risk reduction, NNT: Number needed to treat

Previous study from Mohanty, *et al.* (1986)⁷ demonstrated that supplementation of inosine pranobex to the conventional therapy increased the success rate from 41% to 94%. Inosine pranobex was well-tolerated, and none of the patients reported side effects. Furthermore, immunological studies showed an increased number of B cells in 21% of peripheral blood samples.⁷ This study was considered valid based on the fulfillment of validity criteria

All articles showed us a decent importance. Based on the critical appraisal done previously, addition of oral inosine pranobex may minimize conventional therapy failure (Absolute risk reduction 0.54 (0.42-0.66), 0.28 (0.21-0.35) and 0.23 (0.03 – 0.43) for the first, second, and third article, respectively). Based on the ARR, the NNTs were 2 (1.5-2.4), 4 (2.9-4.8) and 5 (2.3-33) for the first, second, and third article, respectively. This means that 2 – 5 persons need to be treated to get one additional good effect.

Based on their importance, these articles were assessed for their applicability in our clinical practice. Looking at the genital warts' prevalence in our center, the risk of the outcome (treatment failure if inosine pranobex is not given as adjuvant therapy) in our patient, relative to the patients in these trial ranges from 5.3 to 12.2. Our patients did not considerably differ from the patients in the trials, and this fact encourages the addition of inosine pranobex as an adjuvant therapy for improving the cure rate of genital warts.

Due to this validity, importance and applicability assessment, we would like to recommend the addition of inosine pranobex as an adjuvant therapy for genital warts. In Indonesia, there are seven available brands of inosine pranobex, namely: Isoprinosine®, Isprinol®, Laprosin®, Methisoprinol®, Pronovir®, Viridis®, Visoprine®. Unfortunately, the unit costs were IDR 8.000/tablet, IDR 6.380/tablet and IDR 3.000/tablet, for Isoprinosine®, Viridis®, and Methisoprinol®, respectively;¹⁰ and for the standard dosage of 50 mg/kg body weight, an average adult of 60 kgs would require six tablets daily. To date, inosine pranobex hasn't been covered by public health insurance in Indonesia. Hence, the decision of prescribing inosine pranobex as an adjuvant therapy for genital warts should be made by considering its suitability, cost, efficacy, and affordability, as well as the patient's preference.

Conclusion

Based on the best evidence available, we would recommend the addition of oral inosine pranobex as adjuvant to conventional therapy for genital warts, regardless of financial issue. Therefore, we need to conduct another study with a better clinical trial method (double blind, randomized) in the future.

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Appendix 1. Search strategy flowchart

